Name of Sponsor/Company: Astellas Pharma Global Development		
Name of Finished Product: NA		
Name of Active Ingredient: Tacrolimus Granules		

SYNOPSIS

Title of Study: A Two Centre Clinical Pilot Study in Children With Tacrolimus (FK506) Fine Granule Formulation As Immunosuppressive Therapy in Liver Allograft Transplantation

Investigators/Coordinating Investigator: [redacted]

Study Center(s): This 2-center study was conducted at 2 contracted sites, 1 site each in France and Belgium.

Publication Based on the Study: Not applicable

Study Period: 12 months

Study Initiation Date (Date of First Enrollment): 21 Mar 1996

Study Completion Date (Date of Last Evaluation): 02 Jul 1998

Phase of Development: Phase 2

Objectives: To assess the safety and efficacy of tacrolimus granules in children undergoing liver allograft transplantation, to refine the current dosing schedule in children and to compare dosing based on weight with dosing based on body surface area. A pharmacokinetics assessment was undertaken to help evaluate the dosing regimen for tacrolimus granules, data for which are presented in a separate pharmacokinetic report.

Methodology: This was a 12-month, open-label, phase 2, noncomparative, pilot study conducted at 2 European sites to assess the safety and efficacy of tacrolimus granules in pediatric patients undergoing liver transplantation.

Patients aged 15 and under undergoing a primary liver allograft transplantation were enrolled into the study. No randomization was performed since this was an open-label study. Treatment was to begin within 6 h of skin closure and consisted of tacrolimus, corticosteroids and azathioprine.

After the initial screening on day 0 (baseline or screening visit; day of skin closure), patients were observed for efficacy and safety variables over a period of 12 months. Study visits were scheduled on days 1, 5, 9, 14, 21 and 28; weeks 6, 8 and 10; and months 3, 6, 9 and 12.

During the study, patients were observed for rejection episodes, patient and graft survival and adverse events (AEs). Changes in study drug dosing and concomitant medication (including immunosuppressive medication) were recorded at each visit and the whole blood trough levels of tacrolimus were measured. The microbiological status and incidence of infection were also assessed. The findings from the pharmacokinetic analysis are presented in a separate report.

Number of Patients (Planned, Enrolled and Analyzed): A total of 20 patients were planned to be recruited; 28 patients were enrolled in the study and all were included in the intent-to-treat (ITT) population.

Diagnosis and Main Criteria for Inclusion: Patients were eligible to enter the study if they fulfilled the following criteria:

1. The patient had undergone primary liver allograft transplantation.
2. The patient was 15 years of age or younger.
3. The patient's parent or legal representative had given written informed consent to participate in the study. The patient had given assent where applicable.

Patients were excluded from participation if they had undergone any previous organ transplantation or were to receive a multi-organ transplant, exhibited symptoms or had a history of malignancy, had gross renal impairment, had severe hepatic infection or had human immunodeficiency virus (HIV) or hepatitis B virus (HBV) positive serology along with other exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Numbers: Tacrolimus therapy was to commence as soon as possible after surgery but no later than 6 h after closure of the skin. An initial dose of 0.045 mg/kg per 24-h was to be administered as a continuous 24-h intravenous infusion for 12 h to 4 days.

After the initial period of intravenous therapy, tacrolimus was to be administered orally for a duration of 12 months. Oral dosing was to commence no sooner than 12 h after stopping intravenous infusion. The planned starting dose was 0.3 mg/kg per day divided into a twice-daily dose regimen. The maximum initial dose was 0.5 mg/kg per day. Recommended target whole blood levels of tacrolimus were 5 to 15 ng/mL during the first month after transplantation and 5 to l0 ng/mL thereafter. Dose adjustments were to be made on the basis of the patient's overall clinical status and trough concentrations. An immediate dose reduction or discontinuation was to be carried out in the case of postoperative neurological dysfunction (e.g., severe tremor or motor aphasia). Patients with postoperative renal impairment were not to commence tacrolimus therapy or to begin at a lower dose. Patients with early poor graft function were not to commence therapy with tacrolimus until a significant improvement in liver function had been observed: anti-thymocyte globulin (ATG) was used for induction in this case.

Study drug batch numbers included both intravenous and oral formulations of tacrolimus.

- Tacrolimus ampoules (5mg/mL): [redacted], [redacted], [redacted] and [redacted]
- Tacrolimus capsules (1 mg): [redacted], [redacted], [redacted], [redacted] and [redacted]
- Tacrolimus granules (0.2 mg): [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]
- Tacrolimus granules (1 mg): [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]

Duration of Treatment (or Duration of Study, if applicable): 12 months

Reference Product, Dose and Mode of Administration: Patients were to be administered azathioprine and corticosteroid immunosuppressive therapy according to standard practice at each participating site, as well as antirejection therapy with corticosteroids or ATG/ murine monoclonal anti-CD3 antibody (OKT3).

Criteria for Evaluation: Efficacy assessments during the study included patient survival, graft survival, rejection, histological grade of rejection and liver function tests.

Safety assessments included overall incidence of AEs during the study period, with specific emphasis on the development of lymphoproliferative disease, nephrological and neurological events, as well as diabetes and hypertension.

Statistical Methods:

Population for Analysis: An intent-to-treat (ITT) population, which included all patients who were enrolled in the study who received at least 1 dose of tacrolimus, was used for analysis.

Efficacy: Efficacy was to be analyzed by the incidence of first acute rejection, time to first acute rejection and patient and graft survival. Time-based analyses for patient and graft survival and acute rejection were not performed by the Kaplan-Meier method due to the small number of patients and events. Refractory acute rejections were not identified or summarized. No analyses were performed for chronic rejection or histological grade of rejection. Cumulative patient and graft survival were analyzed up to and including month 12 data irrespective of study drug discontinuation.

For key efficacy and safety variables, subgroup analysis by age was performed for ≥ 5 years, < 5 years and < 1 year rather than ≥ 3 years and < 3 years as originally planned. The analyses with age cutoff of 5 years were conducted to comply with a US regulatory requirement. The results of these analyses are considered descriptive. Subgroup analysis by site and by patients who received a partial organ of a living related donor were not performed.

Safety: AEs were coded using the sponsor-modified Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) coding system. Incidence of AEs, serious AEs (SAEs), AEs causally related to study drug (considered by the investigator to be possibly or probably related to study drug or if relationship is missing) and AEs leading to discontinuation of study drug or death were summarized.

Acute rejection episodes were recorded on both the AE case report forms (CRF) page and rejection CRF page. However, acute rejection events were not counted as an AE/SAE and were excluded from the safety analyses. The same was done for graft loss events.

The designation of AEs as infections by the investigator was captured on the CRF. In addition to this designation, the following COSTART terms were used to identify infections for analyses: bronchitis, oral moniliasis, fever, infection, flu syndrome, pharyngitis, otitis media, cholangitis and esophagitis. Infections as well as AE terms belonging to the following groups of special interest were summarized by group regardless of severity, relationship to study drug, change in dosage due to event or treatment required for event: nephrological disorders, glucose metabolism disorders, neurological disorders, cardiovascular events and malignancy events.

Summary statistics and changes from baseline were presented for laboratory parameters (hematology and biochemistry) and vital signs (heart rate and systolic and diastolic blood pressure). Local laboratory values were to be converted to SI units.

Blood pressure was summarized over time and not compared to age-specific 5^{th} and 95^{th} percentiles of blood pressure measurements as originally planned. Growth performance was monitored by routine evaluation of height and weight. Echocardiography and electrocardiogram (ECG) were not performed at all scheduled visits and changes from baseline were listed and not summarized.

Summary of Results/Conclusions:

Subject Disposition: A total of 28 patients were enrolled in the study, received study drug (either intravenous or oral administration) and were included in the ITT population [Table 1].

Demographics: A majority of the 28 patients were ≥ 1 year of age (75.0%) and most were < 5 years (64.3%). A majority of the patients were Caucasian (85.7%). Most donors were male (63.0%) [Table 2].

Efficacy Results: The findings from this study support the efficacy of tacrolimus granules in pediatric liver transplantation.

At 12 months posttransplantation, 6 (21.4%) patients had experienced acute rejection; no chronic rejection was reported [Table 3]. Three rejections each were noted in patients ≥ 5 years and < 5 years of age, corresponding to 30.0% and 16.7% of patients, respectively. One (14.3%) patient experiencing a rejection was < 1 year of age.

Graft and patient survival was 89.3% at 12 months [Table 3]. Three (10.7%) patient deaths occurred as a result of AEs and were considered as graft losses. Two (20.0%) of these deaths were in patients ≥ 5 years of age and 1 (5.6%) was in a patient < 5 years. No deaths or graft losses were reported in patients < 1 year of age.

Safety Results: The high rate of AEs reported during this study was to be expected considering the study population and the radical nature of surgery. Three deaths were reported, 2 during study drug treatment and 1 following study drug discontinuation. The 2 patients who died while on study drug were ≥ 5 years of age while the patient who died after study drug discontinuation was < 5 years. None of the patients who died were < 1 year of age.

The most frequently reported AEs were fever and infection in 16 (57.1%) patients each, diarrhea in 15 (53.6%) patients and hypertension and bile duct disorder in 13 (46.4%) patients each [Table 4].

A total of 22 (78.6%) patients reported SAEs [Table 5]. Infection reported in 5 patients (17.9%) and hemoperitoneum, hemorrhage and bile duct disorder reported in 3 patients each (10.7%) were the most commonly reported SAEs, followed by fever, thrombosis and increased levels of γ-glutamyl transferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 2 patients each (7.1%). Three patients reported AEs that led to discontinuation of study drug, 1 of whom subsequently died and all 3 were < 5 years of age. No AEs leading to discontinuation were reported in patients < 1 year of age.

AEs classified as infection were reported in 25 (89.3%) patients overall. Fever and infection were the most common AEs, reported in 16 (57.1%) patients each, followed by diarrhea reported in 11 (39.3%) patients and pharyngitis in 8 (28.6%) patients. SAEs classified as infection were reported in 5 (17.9%) patients overall and CMV and EBV infections reported in 1 (3.6%) patient each were considered to be SAEs.

Nephrological disorders were reported in 15 (53.6%) patients. Oliguria was the most commonly reported AE, observed in 7 (25.0%) patients. SAEs classified as nephrological disorders were reported in 2 patients, with kidney function abnormal and toxic nephropathy reported in 1 (3.6%) patient each.

Glucose metabolism disorders were reported in 2 (7.1%) patients. A single (3.6%) patient was diagnosed with an AE of hyperglycemia and there were no reports of diabetes mellitus.

Neurological disorders were reported in 10 (35.7%) patients. Agitation, headache and insomnia were the most common AEs, reported in 5 (17.9%), 3 (10.7%) and 2 (7.1%) patients, respectively. Agitation and encephalopathy reported in 1 (3.6%) patient were considered to be SAEs.

A total of 17 (60.7%) patients experienced a cardiovascular event, and hypertension reported in 13 (46.4%) patients was the most common AE, followed by cardiomegaly reported in 4 (14.3%) patients. SAEs classified as cardiovascular events were reported in a total of 9 (32.1%) patients, and included hemorrhage reported in 3 (10.7%) patients and thrombosis in 2 (7.1%) patients overall.

A single (3.6%) patient experienced an SAE of lymphoma like reaction that [redacted]

Laboratory evaluations (hematology and biochemistry), vital signs, ECG and echocardiography did not show any clinically relevant changes. Growth measurements showed steady increases in patient height and weight during the course of the study.

CONCLUSIONS: Based on the results of this study tacrolimus granules were found to be efficacious and well tolerated as a primary immunosuppressant in pediatric liver transplantation. There were few rejection episodes reported during the study, and patient and graft survival rates were approximately 90% in the treated patients. The oral tacrolimus dose measured by both body weight and body surface area decreased by approximately 2-fold by the end of the study compared to the dose administered at the start of the study. Overall, the efficacy results and safety profiles were comparable among patients ≥ 5 years and < 5years or < 1 year of age in this pilot study.

Date of Report: 24 Apr 2017

Table 1 Disposition of Patients (ITT Population)

Parameter	Tacrolimus, n (%)
Enrolled	28 (100)
Completed	22 (78.6)
Total deaths	3 (10.7)
During study	2 (7.1)
After withdrawal	1 (3.6)
Withdrawn†	4 (14.3)
AEs	3 (10.7)
Lost to follow-up	1 (3.6)

AE: adverse event; ITT: intent-to-treat

† Discontinued study drug for reasons other than death.

Source: Table 12.1.1.3.1

Table 2 Summary of Recipient and Donor Demographics and Baseline Characteristics (ITT Population)

Parameter Category/Statistics	Tacrolimus n = 28
Sex, n (%) (Recipient)	
Male	13 (46.4)
Female	15 (53.6)
Sex, n (%) (Donor)	
Male	17 (63.0)
Female	10 (37.0)
Missing	1
Race, n (%) (Recipient)	
Black	1 (3.6)
Caucasian	24 (85.7)
Oriental	1 (3.6)
Other	2 (7.1)
Race, n (%) (Donor)	
White	17 (100.0)
Missing	11
Age, Years (Recipient)	
Mean (SD)	4.4 (4.2)
Age, Years (Donor)	
Mean (SD)	18.4 (13.3)
Age Group, n (%) (Recipient)	
< 5 years	18 (64.3)
≥ 5 years	10 (35.7)
< 1 year	7 (25.0)
≥ 1 year	21 (75.0)
Weight, kg (Recipient)	
Mean (SD)	15.7 (9.0)
Height, cm (Recipient)	
Mean (SD)	94.5 (27.6)

ITT: intent-to-treat

Source: Tables 12.1.2.1.1, 12.1.2.4.1

Table 3 Efficacy Outcomes (Incidence) During the First Year Posttransplant (ITT population)

Outcome	Tacrolimus, n (%)			
	Total n = 28	**≥ 5 Years n = 10**	**< 5 Years n = 18**	**< 1 Year n = 7**
Acute Rejection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Biopsy Proven Acute Rejection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Death	3 (10.7)	2 (20.0)	1 (5.6)	0
Graft Loss	3 (10.7)	2 (20.0)	1 (5.6)	0

ITT: intent-to-treat

Source: Tables 12.3.1, 12.3.2, 12.3.3

Table 4 Summary of Common (≥ 2 Patients Overall) AEs (ITT population)

COSTART System Organ Class Preferred Term	Tacrolimus, n (%)			
	Total n = 28	**≥ 5 Years n = 10**	**< 5 Years n = 18**	**< 1 Year n = 7**
Any AE	**28 (100.0)**	**10 (100.0)**	**18 (100.0)**	**7 (100.0)**
Body as a Whole	**25 (89.3)**	**9 (90.0)**	**16 (88.9)**	**7 (100.0)**
Fever	16 (57.1)	3 (30.0)	13 (72.2)	5 (71.4)
Infection	16 (57.1)	6 (60.0)	10 (55.6)	6 (85.7)
Pain	10 (35.7)	4 (40.0)	6 (33.3)	5 (71.4)
Ascites	8 (28.6)	3 (30.0)	5 (27.8)	1 (14.3)
CMV infection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
EBV infection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Abdominal pain	4 (14.3)	2 (20.0)	2 (11.1)	1 (14.3)
Sepsis	4 (14.3)	3 (30.0)	1 (5.6)	1 (14.3)
Hemoperitoneum	3 (10.7)	1 (10.0)	2 (11.1)	1 (14.3)
Allergic reaction	2 (7.1)	0	2 (11.1)	2 (28.6)
Cardiovascular System	**20 (71.4)**	**6 (60.0)**	**14 (77.8)**	**6 (85.7)**
Hypertension	13 (46.4)	3 (30.0)	10 (55.6)	6 (85.7)
Cardiomegaly	4 (14.3)	1 (10.0)	3 (16.7)	2 (28.6)
Hemorrhage	4 (14.3)	0	4 (22.2)	2 (28.6)
Hypotension	3 (10.7)	2 (20.0)	1 (5.6)	1 (14.3)
Vascular disorder	3 (10.7)	0	3 (16.7)	0
Pericardial effusion	2 (7.1)	0	2 (11.1)	0
Thrombosis	2 (7.1)	2 (20.0)	0	0
Digestive System	**26 (92.9)**	**9 (90.0)**	**17 (94.4)**	**7 (100.0)**
Diarrhea	15 (53.6)	2 (20.0)	13 (72.2)	5 (71.4)
Bile duct disorder	13 (46.4)	5 (50.0)	8 (44.4)	2 (28.6)
Vomiting	6 (21.4)	2 (20.0)	4 (22.2)	2 (28.6)
Gastroenteritis	4 (14.3)	0	4 (22.2)	2 (28.6)
Liver function tests abnormal	4 (14.3)	0	4 (22.2)	4 (57.1)
Oral moniliasis	4 (14.3)	3 (30.0)	1 (5.6)	1 (14.3)
Esophagitis	3 (10.7)	0	3 (16.7)	2 (28.6)
Cholangitis	2 (7.1)	2 (20.0)	0	0
GI hemorrhage	2 (7.1)	1 (10.0)	1 (5.6)	0
GI moniliasis	2 (7.1)	0	2 (11.1)	2 (28.6)

Table continued on next page

COSTART System Organ Class Preferred Term	Tacrolimus, n (%)			
	Total n = 28	≥ 5 Years n = 10	< 5 Years n = 18	< 1 Year n = 7
Hemic and Lymphatic System	**10 (35.7)**	**3 (30.0)**	**7 (38.9)**	**4 (57.1)**
Anemia	9 (32.1)	3 (30.0)	6 (33.3)	4 (57.1)
Metabolic and Nutritional Disorder	**15 (53.6)**	**4 (40.0)**	**11 (61.1)**	**6 (85.7)**
Hyperuricemia	6 (21.4)	2 (20.0)	4 (22.2)	0
Hypocalcemia	5 (17.9)	1 (10.0)	4 (22.2)	4 (57.1)
Acidosis	4 (14.3)	1 (10.0)	3 (16.7)	3 (42.9)
GGT increased	3 (10.7)	1 (10.0)	2 (11.1)	1 (14.3)
SGOT increased	3 (10.7)	0	3 (16.7)	2 (28.6)
SGPT increased	3 (10.7)	0	3 (16.7)	2 (28.6)
BUN increased	2 (7.1)	0	2 (11.1)	1 (14.3)
Hypoproteinemia	2 (7.1)	0	2 (11.1)	1 (14.3)
Musculoskeletal System	**2 (7.1)**	**1 (10.0)**	**1 (5.6)**	**0**
Cramps	2 (7.1)	1 (10.0)	1 (5.6)	0
Nervous System	**9 (32.1)**	**6 (60.0)**	**3 (16.7)**	**3 (42.9)**
Agitation	5 (17.9)	2 (20.0)	3 (16.7)	3 (42.9)
Headache	3 (10.7)	3 (30.0)	0	0
Insomnia	2 (7.1)	2 (20.0)	0	0
Respiratory System	**18 (64.3)**	**4 (40.0)**	**14 (77.8)**	**6 (85.7)**
Pharyngitis	8 (28.6)	1 (10.0)	7 (38.9)	3 (42.9)
Bronchitis	7 (25.0)	2 (20.0)	5 (27.8)	3 (42.9)
Rhinitis	7 (25.0)	1 (10.0)	6 (33.3)	4 (57.1)
Pleural effusion	4 (14.3)	1 (10.0)	3 (16.7)	1 (14.3)
Asthma	3 (10.7)	1 (10.0)	2 (11.1)	2 (28.6)
Cough increased	2 (7.1)	1 (10.0)	1 (5.6)	0
Pneumonia	2 (7.1)	0	2 (11.1)	0
Skin and Appendages	**7 (25.0)**	**3 (30.0)**	**4 (22.2)**	**2 (28.6)**
Pruritis	4 (14.3)	2 (20.0)	2 (11.1)	1 (14.3)
Herpes simplex	3 (10.7)	2 (20.0)	1 (5.6)	0
Special Senses	**4 (14.3)**	**0**	**4 (22.2)**	**1 (14.3)**
Otitis media	3 (10.7)	0	3 (16.7)	1 (14.3)
Urogenital System	**12 (42.9)**	**5 (50.0)**	**7 (38.9)**	**5 (71.4)**
Oliguria	7 (25.0)	3 (30.0)	4 (22.2)	4 (57.1)
Urinary tract infection	2 (7.1)	0	2 (11.1)	1 (14.3)
Kidney function abnormal	2 (7.1)	1 (10.0)	1 (5.6)	0

AE: adverse event; BUN: blood urea nitrogen; CMV: cytomegalovirus;
COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms; EBV: Epstein-Barr virus;
GGT: γ-glutamyl transferase; GI: gastrointestinal; ITT: intent-to-treat;
SGOT: Serum glutamic-oxaloacetic transaminase (also referred to as aspartate aminotransferase [AST]);
SGPT: Serum glutamic-pyruvic transaminase (also referred to as alanine aminotransferase [ALT])

Source: Table 12.6.1.2.1, 12.6.1.2.2, 12.6.1.2.3

Table 5 Summary of Common (≥ 2 Patients Overall) SAEs (ITT population)

COSTART System Organ Class Preferred Term	Tacrolimus, n (%)			
	Total n = 28	≥ 5 Years n = 10	< 5 Years n = 18	< 1 Year n = 7
Any SAE	**22 (78.6)**	**7 (70.0)**	**15 (83.3)**	**6 (85.7)**
Body as a Whole	**13 (46.4)**	**4 (40.0)**	**9 (50.0)**	**4 (57.1)**
Infection	5 (17.9)	1 (10.0)	4 (22.2)	3 (42.9)
Hemoperitoneum	3 (10.7)	1 (10.0)	2 (11.1)	1 (14.3)
Fever	2 (7.1)	0	2 (11.1)	0
Cardiovascular System	**9 (32.1)**	**3 (30.0)**	**6 (33.3)**	**1 (14.3)**
Hemorrhage	3 (10.7)	0	3 (16.7)	1 (14.3)
Thrombosis	2 (7.1)	2 (20.0)	0	0
Digestive System	**11 (39.3)**	**5 (50.0)**	**6 (33.3)**	**2 (28.6)**
Bile duct disorder	3 (10.7)	1 (10.0)	2 (11.1)	2 (28.6)
Metabolic and Nutritional Disorder	**4 (14.3)**	**1 (10.0)**	**3 (16.7)**	**2 (28.6)**
GGT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
SGOT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
SGPT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
Respiratory System	**2 (7.1)**	**0**	**2 (11.1)**	**1 (14.3)**
Skin and Appendages	**2 (7.1)**	**1 (10.0)**	**1 (5.6)**	**0**
Urogenital System	**2 (7.1)**	**2 (20.0)**	**0**	**0**

COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms; GGT: γ-glutamyl transferase;
GI: gastrointestinal; ITT: intent-to-treat; SAE: serious adverse event;
SGOT: Serum glutamic-oxaloacetic transaminase (also referred to as aspartate aminotransferase [AST]);
SGPT: Serum glutamic-pyruvic transaminase (also referred to as alanine aminotransferase [ALT])

Source: Table 12.6.1.4.1, 12.6.1.4.2, 12.6.1.4.3