

TABLE 49
Difference in 12-Month Patient Survival

Weights	Difference in Rates Tacrolimus - CBIR (%)	96.5% Confidence Interval	
		Lower (%)	Upper (%)
Equal	8.3	-0.6	17.2
Unequal	2.1	-4.2	8.4

The two approaches to averaging over centers result in different point estimates of the difference between treatments as well as in different confidence intervals. This suggests that there was variability between centers in terms of the relative response to therapy. Nevertheless, both approaches yield lower bounds which indicate that tacrolimus does not have a rate of survival which is 10 percentage points worse than CBIR. This supports the sponsor's primary conclusion that tacrolimus is effective with respect to patient survival.

8.2.4.2.2 Graft Survival

The sponsor's result for overall cumulative graft survival and the Kaplan-Meier estimates for graft survival rates for the intent-to-treat population are summarized in Table 50 (Source: Vol 1.88, Report Number GHBA-157, Table 27).

TABLE 50
Graft Survival

	Tacrolimus	CBIR
Kaplan-Meier Estimate at 365 Days	76%	70%
95% Confidence Intervals	71%, 82%	64%, 75%

Wilcoxon test for comparison of survival curves, p-value = 0.073.

To assess whether tacrolimus and CBIR were "equivalent" with respect to one year graft survival the sponsor presented 96.5% confidence intervals on the differences between the two treatment group (Table 51, Source: Response to Questions from the FDA dated 11/9/93). As for patient-survival, the analysis took into account stratification by center and used two different weighting schemes (See section 8.2.4.2.1 above).

TABLE 51
Difference in 12 Month Graft Survival

Weights	Difference in Rates Tacrolimus - CBIR (%)	96.5% Confidence Interval	
		Lower (%)	Upper (%)
Equal	9.4	0.1	18.7
Unequal	4.8	-2.6	12.2

The difference between point estimates obtained by the two approaches to averaging over center suggests there was variability among the centers in terms of relative response to therapy. Both approaches yield lower bounds that indicate that tacrolimus does not have a rate of graft survival which is 10 percentage points worse than CBIR. These analyses support the sponsor's conclusion that tacrolimus is effective with respect to graft survival.

8.2.4.2.3 Acute Rejection

The Kaplan-Meier estimates (proportion without event) of six-month acute rejection were 0.42 for the tacrolimus group and 0.58 for the CBIR group with a p-value of 0.001 (Source: Vol 1.88, Report Number GHBA-157, Table 29). 95% confidence intervals were not provided. Based on this analysis the sponsor claims that tacrolimus was superior to CBIR with respect to acute rejection.

This endpoint remains problematic in an open-label study. The diagnosis of acute rejection involved the investigator's interpretation of clinical and laboratory signs suggesting rejection followed by the investigator's decision to perform a confirmatory liver biopsy. A significant proportion of acute rejection episodes occur early and might have been systematically detected by the Day 7 liver biopsy specified by the written protocol. Analysis of the incidence of acute histologic rejection at Day 7 was not performed by the sponsor because the majority of the patients did not have a routine liver biopsy taken on Day 7. No explanation was provided in the study report as why this part of the protocol was not respected.

The sponsor claims that the analysis of acute rejection was conducted to establish the superiority of tacrolimus and not its equivalence to CBIR. The protocol is unclear on this point. In an April 8, 1993 phone conversation, the sponsor confirmed that equivalence (within 10%) was the goal of this clinical trial. No distinction was made between primary and secondary endpoints. Therefore acute rejection should be held to the same standard of proof as the primary endpoints. To demonstrate superiority it is then necessary to show that tacrolimus is at least 10% superior to CBIR at a 95% level of confidence. This translates to having the lower bound for a 95% confidence interval for the difference in incidence rates exceed 10%.

At the request of the FDA the sponsor submitted on 11/9/93 estimates of the 96.5% confidence interval for the difference in rate of acute rejection at 183 days. These analyses take into account stratification by center, and used two weighting schemes as described above (See Section

8.2.4.2.1) and are summarized in Table 52 (Source: Response to Questions from the FDA, dated 11/9/93).

TABLE 52
Free of Acute Rejection at Six Months

Weights	Difference in Rates Tacrolimus - CBIR (%)	96.5% Confidence Interval	
		Lower (%)	Upper (%)
Equal	10.4	-2.6	23.3
Unequal	12.8	3.6	22.1

The lower bounds of the intervals are all greater than -10% which may support a claim for equivalence if the sponsor's definition of acute rejection is acceptable and the ascertainment of this endpoint was reliable and complete. In no case does the lower bound exceed or approach +10%. This rules out a claim for superiority which requires 95% confidence that the difference exceeds +10%.

8.2.4.2.4 Other Efficacy Analyses

Intractable rejection, liver graft histology and steroid use were additional efficacy measures defined in the written protocol.

Intractable rejection was one of the endpoints that was problematic (see Section 8.2.3.3 above). The sponsor presented an analysis of the difference in rates of intractable rejection which is summarized below in Table 53 (Source: 11/9/93 response to questions from the FDA). As for the analysis of acute rejection, this analysis was stratified by center and used two different weighting schemes.

TABLE 53
Free of Intractable Rejection at Six Months

Weights	Difference in Rates Tacrolimus - CBIR (%)	96.5% Confidence Interval	
		Lower (%)	Upper (%)
Equal	9.7	-0.2	19.5
Unequal	7.4	2.8	11.9

Again, the lower bounds of the intervals are greater than -10% which may support the claim for equivalence. In no case does the lower bound exceed +10%. This rules out a claim for superiority which would requires 95% confidence that the difference exceed +10%.

The clinical significance of this endpoint as defined in the written protocol is uncertain. While the protocol required that patients be withdrawn from the study if they were diagnosed with

intractable rejection, some patients with "unresolved chronic rejection" were allowed to continue on study medication. These patients were still included in the diagnostic category of intractable rejection.

Liver histology on the Day 7 biopsy might have provided an objective look at early rejection that could have allowed a valid comparison between groups. However, although detailed in the written protocol, the majority of patients did not have a routine liver biopsy taken on Day 7, and subsequently no analysis was performed.

The sponsor also claimed superiority of tacrolimus over CBIR for use of corticosteroid medication. This endpoint is problematic because of the protocol defined difference in steroid dosing between treatment arms and the fact that tapering of steroids was at the discretion of the investigator who was aware of the patient's treatment assignment. This endpoint could also be influenced by the investigator's choice of anti-rejection therapy.

Four different variables were derived for both IV and oral administration of corticosteroids: total daily dose (mg), total daily dose (mg/kg), cumulative dose (mg), and cumulative dose (mg/kg). The sponsor presented the p values for all four variables (Vol 1.88, Report Number GHBA-157), chose to base the claim on the variable that gave the smallest p-values. For oral administration, 2 of the 4 p-values were not significant or of marginal significance. A third variable was significant ($p=.019$), but had exactly the same median in the two treatment arms. Additionally, as pointed out by the FDA statistician in his review of this study, there was no discussion of how corticosteroid use was adjusted for differential follow-up. Thus, the claims for superiority in steroid use are not adequately supported.

8.2.4.3 Safety outcomes

The sponsor reported all adverse experiences for the first six months of the study. In addition, all serious adverse events (see definition in next paragraph) were reported for the first twelve months of the study. Adverse events were coded according to the COSTART system using the preferred term and body system. The overall incidences of adverse events for both treatment groups, irrespective of causality are listed in Table 41 of Study Report Number: GHBA-157 (Vol 1.88). The sponsor's evaluation of safety is based on the 267 patients randomized to treatment with tacrolimus and the 273 randomized to CBIR.

A serious adverse experience was defined in the written protocol as "one that suggests a significant hazard, contraindication, side effect, or precaution". With respect to human clinical experience, the protocol further specifies "serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or overdose". (Source: Vol 1.94 Appendix 1 to Study Protocol included in Appendix S3 to Report Number GHBA-157).

The protocol also required that the investigators indicate the maximum intensity of each adverse experience (symptoms) as mild, moderate, or severe. Brief definitions were provided for each

of these terms, but no detailed grading guidelines were provided by body system. The term "severe" was specifically a measure of intensity. Thus, a severe reaction was not necessarily considered a serious one. For example, severe alopecia or hirsutism would not be considered a serious event. Conversely, a serious reaction may not necessarily be severe. Laboratory indices of adverse experiences were not graded by maximum intensity but reported as "decreased" or "increased". Study Report Number GHBA-157, does not include any information on the maximum intensity of adverse experiences in its Safety Assessment.

As expected in this clinical setting, adverse events were frequently reported in both treatment groups. This review will focus on those events which were high in incidence (generally greater than 3%), differed between the two treatment arms, or were clinically significant. Because of the study design, one cannot fully evaluate the relative contribution of tacrolimus to adverse events; however, the sponsor attempted to assess the relationship between certain adverse events and measures of drug exposure.

8.2.4.3.1 Discontinuation from Study

Seventy-two patients in the tacrolimus group and 67 patients in the CBIR group discontinued from the study owing to death or adverse events. Adverse events that led to withdrawal from the study are listed in Table 54 by body systems and treatment groups (Source: Vol 1.88, Study Report GHBA-157, Table 58).

TABLE 54
Withdrawals from Study GHBA-157 Owing to Adverse Events

Body System	Tacrolimus N=267 N (%)	CBIR N=273 N (%)
BODY AS A WHOLE [DEATH]	34 (12.7) [32 (12.0)]	42 (15.4) [41 (15.0)]
NERVOUS SYSTEM	16 (6.0)	2 (0.7)
UROGENITAL SYSTEM	12 (4.5)	5 (1.8)
DIGESTIVE SYSTEM	10 (3.7)	17 (6.2)
CARDIOV. SCULAR	10 (3.7)	10 (3.7)
METABOLIC SYSTEM	8 (3.0)	3 (1.1)
RESPIRATORY	5 (1.9)	2 (0.7)
SKIN/ APPENDAGES	2 (0.7)	0 (0.0)
MUSCULOSKELETAL	1 (0.4)	1 (0.4)
HEMIC/LYMPHATIC	1 (0.4)	0 (0.0)
TOTAL	72 (27.0)	67 (24.5)

The most commonly reported groups of adverse experiences which led to withdrawal from the tacrolimus treatment group were death, disorders of the nervous system, and disorders of the urogenital system. Death led to the withdrawal of 32 patients (12.0%) receiving treatment with tacrolimus and 41 (15.0%) patients receiving CBIR therapy. Kidney failure and abnormal kidney function were both reported in five patients receiving treatment with tacrolimus, and in two patients and one patient respectively in the CBIR treatment group. Psychosis and confusion were reported as leading to withdrawal from the study in four tacrolimus treated patients compared to one patient in the CBIR treatment group.

3.2.4.3.2 Deaths

Data continued to be collected on all patients following withdrawal from the study but adverse experiences collected post-withdrawal from the study are not reported in the adverse event tabulations. Twenty-eight patients died following withdrawal from the study. Thus overall, 118 patients died during the one year treatment period: 18.5% of patients in the tacrolimus treatment group and 24.7% of patients in the CBIR group. Tabulations of deaths and capsule summaries for these are included in Appendices 11 and 39 of Study Report Number GHBA-157 (Vol 1.91 and 1.93). The causes of death resembled those observed in study FPC-FK506-7, and were largely dominated by infection, sepsis and multiorgan failure. In addition, 5 subjects died of

recurrent hepatocellular carcinoma.

Examination of individual summaries of patients who died (Vol. 1.93, Appendix 39) reveals that manifestations of multisystem failure, sepsis, cardiovascular events and central nervous system events were often present in the same patient prior to death. Most of the deaths occurred early during the first 28 days post-transplant. While immunosuppression may have contributed to some of these deaths, tacrolimus-based immunosuppression does not appear to have been associated with an excess of deaths compared to CBIR.

8.2.4.3.3 Adverse Events by Body System

8.2.4.3.3.1 Overall

The number of patients experiencing a particular adverse experience, irrespective of causality in relation to the study drug, is listed in Table 41 of Study Report Number: GHBA-157 (Vol 1.88). The ten most commonly reported COSTART categories of adverse experiences are listed here in Table 55A in decreasing order of frequency.

TABLE 55A
Most Commonly Reported Adverse Experiences

Adverse Experience	Tacrolimus N=267	CBIR N=273
	N (%)	N (%)
Tremor *	116 (43.5)	81 (29.7)
Infection	103 (38.6)	121 (44.3)
Pleural Effusion	90 (33.7)	92 (33.7)
Hypertension	88 (33.0)	103 (37.7)
Kidney Function Abnormal *	88 (33.0)	58 (21.3)
Diarrhea *	87 (32.6)	61 (22.3)
Headache *	84 (31.5)	58 (21.3)
Hyperglycemia *	82 (30.7)	56 (20.5)
Nausea	79 (29.6)	60 (22.0)
Insomnia	78 (29.2)	55 (20.2)

* p-value <0.01 using Fisher's Exact test.

The ten most commonly reported groups of serious adverse experiences are listed in Table 55B

in decreasing order of frequency (Source: Vol 1.88, Report Number GHBA-157, Table 49. The most commonly reported groups of serious adverse experiences in the tacrolimus group were, death, sepsis, kidney failure, abnormal kidney function, pneumonia and hemorrhage.

TABLE 55B
Most Frequent Serious Adverse Experiences

Serious Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Death	32 (12.0)	41 (15.0)
Sepsis	24 (9.0)	22 (8.1)
Kidney Failure	19 (7.1)	11 (4.0)
Kidney Function Abnormal	15 (5.6)	9 (3.3)
Pneumonia	14 (5.24)	21 (7.7)
Hemorrhage	14 (5.2)	7 (2.6)
Hepatitis	13 (4.9)	15 (5.5)
Diabetes Mellitus **	13 (4.9)	2 (0.7)
Infection	9 (3.4)	18 (6.6)
Gastrointestinal Disorder	9 (3.4)	14 (5.1)

** $p < 0.05$ using the Fisher's Exact test.

8.2.4.3.3.2 Nervous System

Selected adverse events related to neurotoxicity are shown in Table 56 (Source: Vol 1.88, Study Report Number: GHBA-157, Table 41). Tremor was the most commonly occurring adverse event in both treatment groups, but occurred more frequently in the tacrolimus group (43.4% tacrolimus treated patients vs 29.7% patients treated with CBIR therapy [$p < 0.01$]). Headaches were also common and were reported more frequently in the tacrolimus group than in the CBIR group (31.5% versus 21.2%, $p < 0.01$) as were paresthesia (15.7% versus 13.6%).

TABLE 56
Overall Adverse Experiences Relative to Neurotoxicity

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Tremor *	111 (43.5)	89 (29.7)
Headache *	84 (31.3)	58 (21.2)
Paresthesia	61 (15.7)	37 (13.6)
Convulsion	13 (4.9)	8 (2.9)
Neuropathy	10 (3.5)	14 (5.1)
Dizziness	9 (3.4)	4 (1.5)
Grand Mal Convulsion	4 (1.5)	3 (1.1)
Encephalopathy	2 (0.8)	4 (1.5)

* $p < 0.01$ using Fisher's Exact test.

Selected adverse events that were considered serious (grade 3 or 4 or requiring an IND Safety Report) are listed in Table 57 (Source: Vol 1.88, Report Number GFBA-157, Table S). Overall, serious nervous system adverse events were more frequently reported in patients treated with tacrolimus than in those treated with CBIR. Coma and psychosis were reported in 1.9% of the patients in the tacrolimus group. Grand mal convulsion, serious paresthesia and tremor were reported in 1.1% of patients receiving tacrolimus.

TABLE 57
Serious Nervous System Adverse Experiences

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Coma	5 (1.9)	3 (1.1)
Psychosis	5 (1.9)	1 (0.4)
Neuropathy	4 (1.5)	1 (0.4)
Grand Mal Convulsion	3 (1.1)	1 (0.4)
Paresthesia	3 (1.1)	0 (0.0)
Tremor	3 (1.1)	0 (0.0)
Total	23 (9.0)	6 (2.3)

Selected nervous system adverse experiences related to cognitive function are shown in Table 58 (Source: Vol 1.88, Report Number GHBA-157, Table M). Insomnia, agitation and confusion were more frequently reported in the tacrolimus group than in the CBIR group.

TABLE 58
Nervous System Adverse Experiences Related to Cognitive Function

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Insomnia **	78 (29.2)	55 (20.2)
Confusion **	23 (8.6)	11 (4.0)
Agitation	14 (5.2)	12 (4.4)
Depression	11 (4.1)	13 (4.8)
Somnolence	10 (3.8)	6 (2.2)

** $p < 0.05$ using Fisher's Exact test.

8.2.4.3.3 Urogenital System

The nephrotoxic potential of cyclosporine used in the active control regimen is well recognized (See official Package Insert for Sandimmune[®] in effect on August 1, 1992). However, events involving impairment of renal function were reported more frequently in the tacrolimus group than in the CBIR group (Table 59, Source: Vol 1.88, Report Number GHBA-157, Table N). In particular, "kidney function abnormal" was the most frequently reported COSTART term in this category, 33.0% for the tacrolimus treatment group compared to 21.2% in the CBIR treatment group ($p < 0.01$). Other commonly occurring adverse experiences with an incidence greater than 5% included urinary tract infection, oliguria and kidney failure. Oliguria was reported for significantly more patients in the tacrolimus treatment group ($p < 0.05$).

TABLE 59
Overall Adverse Experiences Relative to Nephrotoxicity

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Kidney Function Abnormal *	88 (33.0)	58 (21.2)
Creatinine Increased	51 (19.1)	46 (16.9)
Oliguria **	49 (18.4)	30 (11.0)
Hyperkalemia	28 (10.5)	22 (8.0)
Kidney Failure	25 (9.4)	20 (7.3)
BUN Increased	22 (8.2)	20 (7.3)

* $p < 0.01$, ** $p < 0.05$ using Fisher's Exact test.

Kidney failure was also the most frequently reported serious (grade 3 or 4) adverse event in this category. It was reported for 7.1% of patients in the tacrolimus treatment group and 4% of patients in the CBIR group. Abnormal kidney function which was judged to be serious was reported for 5.6% of patients in the tacrolimus group and 3.3% of patients receiving CBIR.

Thirty-seven patients (13.8%) in the tacrolimus group and 35 (12.8%) in the CBIR group required hemodialysis during the study (Source: Vol 1.97, Appendix S28). Dialysis was initiated prior to transplantation in four patients from each group. Among patients who required dialysis, mean number of days of hemodialysis treatment on study was 11.5 in the tacrolimus group (range 1-46) and 13.9 in the CBIR group (range 1-41). As might be expected, hemodialysis on study was associated with a high mortality rate on study at six months, 51.3% in the tacrolimus group and 48.7% in the CBIR group.

8.2.4.3.3.4 Cardiovascular System

Hypertension, a well known adverse experience associated with the use of cyclosporine-based immunosuppression, was the most frequently reported event in this category. It was reported in 88 (33.0%) patients treated with tacrolimus and 103 (37.7%) patients treated with CBIR (Source: Vol 1.88, Report Number GHBA-157, Table 41). Other adverse events experienced by more than 5% of patients in either treatment group included, hemorrhage, hypotension, tachycardia, heart failure and bradycardia.

Hemorrhage was the most frequently reported serious adverse experience occurring in 14 (5.2%) patients in the tacrolimus treatment group compared with 7 (2.6%) patients in the CBIR treatment group (Source: Vol 1.88, Report Number GHBA-157, Table 49). Shock and heart failure were both experienced by 8 (3.0%) patients receiving treatment with tacrolimus and by 9 (3.3%) and 3 (1.1%) patients, respectively, in the CBIR treatment group. Other serious events reported for more than 1% of patients in either treatment group included arterial

thrombosis, cardiac arrest, vascular disorder and thrombophlebitis.

8.2.4.3.3.5 Digestive System

The most frequently reported adverse events related to the gastrointestinal system are displayed in Table 60 (Source: Vol 1.88, Study Report Number GHBA-157, Table I). Diarrhea, nausea and/or vomiting anorexia and dyspepsia were more frequently reported in the tacrolimus group.

TABLE 60
Selected Overall Adverse Experiences Related to the Digestive System

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Diarrhea	87 (32.6)	61 (22.3)
Nausea	79 (29.6)	60 (22.0)
Constipation	52 (19.5)	53 (19.4)
Vomiting	31 (11.6)	25 (9.2)
Dyspepsia	22 (8.2)	18 (6.6)
Anorexia	17 (6.4)	13 (4.8)
Liver Function Test Abnormal	14 (5.2)	9 (3.3)

The incidence of serious (grade 3 or 4) adverse events related to the gastrointestinal system were similar in frequency between the two treatment groups. Hepatitis, the most frequently occurring serious event, was reported for 4.9% and 5.5% of patients, in the tacrolimus and CBIR treatment groups, respectively.

8.2.4.3.3.6 Metabolic and Nutritional Disorders

The most commonly occurring adverse event in this category was hyperglycemia, which was reported more frequently in the tacrolimus treatment group than in the CBIR group, 30.7% compared with 20.5%, respectively ($p < 0.01$) (Source: Vol 1.88, Report Number GHBA-157, Table 41). Diabetes mellitus was also reported more frequently in the tacrolimus treatment group than in the CBIR group, 17.2% compared with 9.5%, respectively ($p < 0.05$). Finally, hypomagnesemia was more frequently reported in the tacrolimus group than in the CBIR group, 15.0% compared with 8.4%, respectively.

Other common adverse experiences in the tacrolimus treatment group with an incidence greater than 5% were: increased creatinine concentrations, hypokalemia, increased alanine aminotransferase concentrations (AST), hyperkalemia, peripheral edema, increased alkaline phosphatase concentrations, increased whole blood urea nitrogen levels, hyperbilirubinemia,

hypocalcemia, hyperlipemia, hyponatremia, and hypocholesterolemia. The incidence rates of these events were similar between the two treatment groups.

Twelve percent of patients in the tacrolimus treatment group, and 8.4% of patients in the CBIR group experienced events judged to be serious (grade 3 or 4) by the investigator and falling in the "metabolic and nutritional disorder" body system. Serious diabetes was diagnosed in 4.7% of patients receiving tacrolimus compared with 0.7% of patients in the CBIR treatment group (Source: Vol 1.88, Report Number GHBA-157, Table 41).

8.2.4.3.3.7 Hemic and Lymphatic System

Anemia, thrombocytopenia and coagulation disorders occurred frequently in both treatment groups. These are considered expected consequences of liver transplantation surgery. The most frequently occurring event was thrombocytopenia (Table 61, Source: Vol 1.88, Report Number GHBA-157, Table 41). Other events that were reported at a frequency of greater than 5% of patients in either treatment group were hypochromic anemia, leukocytosis and leukopenia. Anemia was reported for more patients receiving treatment with tacrolimus (4.5%) compared with CBIR (0.7%) ($p < 0.05$). Leukopenia was reported in 2.6% tacrolimus treated patients and 10.6% CBIR treated patients ($p < 0.01$).

TABLE 61
Selected Hemic and Lymphatic Adverse Experiences

Adverse Experience	Tacrolimus N (%)	CBIR N (%)
Thrombocytopenia	31 (11.6)	48 (17.6)
Leukocytosis	22 (8.2)	19 (7.0)
Coagulation Disorder	13 (4.9)	10 (3.7)
Anemia **	12 (4.5)	2 (0.7)
Leukopenia *	7 (2.6)	29 (10.6)

* $p < 0.01$, ** $p < 0.05$ using Fisher's Exact test.

Serious (grade 3 or 4) hemic and lymphatic disorders were reported for 4.1% of patients in the tacrolimus treatment group and 5.9% of patients receiving CBIR therapy. The most frequently occurring event was thrombocytopenia reported for 1.5% of patients in the tacrolimus treatment group and 3.7% of patients receiving CBIR therapy. Serious coagulation disorders and leukopenia were diagnosed in less than 2% of patients in each treatment group. (Source: Vol 1.88, Report Number GHBA-157, Table 49)

8.2.4.3.3.8 Respiratory System

The most frequently occurring event was pleural effusion reported for 90 tacrolimus treated patients (33.7%) and 92 (33.7%) patients in the CBIR treatment group (Source: Vol 1.88, Report Number GHBA-157, Table 41). Other adverse events experienced by more than 5% of patients in either treatment group included pneumonia, pharyngitis, rhinitis, and bronchitis. All adverse events categorized under this body system were experienced by a similar proportion of patients in both treatment groups.

Serious (grade 3 or 4) adverse respiratory events were reported for 37 patients (13.9%) and 35 patients (12.8%) in the tacrolimus and CBIR treatment groups, respectively (Source: Vol 1.88, Report Number GHBA-157, Table 49). The most frequently reported serious adverse event was pneumonia; this was experienced by 14 tacrolimus -treated patients (5.2%) and 21 patients (7.7%) in the CBIR treatment group.

8.2.4.3.3.9 Skin and Appendages

As might be expected in the clinical setting of systemic immunosuppression, herpes simplex was the most frequently occurring event, reported for 34 (12.7%) of patients receiving tacrolimus and 31 (11.4%) of patients receiving CBIR (Table 62, Source: Vol 1.88 Report Number GHBA-157, Table 42). Hirsutism, a well recognized adverse event associated with the use of cyclosporine, was reported in 23 (8.4%) patients treated with CBIR and in one of the patients treated with tacrolimus. Pruritus, rash and alopecia were more frequently reported in patients treated with tacrolimus than in those treated with CBIR (Table 62).

TABLE 62
Selected Adverse Experiences Related to Skin and Appendages

Adverse Experiences	Tacrolimus N (%)	CBIR N (%)
Herpes simplex	34 (12.7)	31 (11.4)
Pruritus *	32 (12.0)	14 (5.1)
Hirsutism *	0 (0.0)	23 (8.4)
Rash **	21 (7.9)	9 (3.3)
Alopecia	12 (4.5)	4 (1.5)

* $p < 0.01$, ** $p < 0.05$ using Fisher's Exact test.

8.2.4.3.3.10 Infections

The sponsor presented analyses of total reported infections and of confirmed infections. An

infection was deemed to be present if, in response to clinical signs and symptoms the investigator prescribed appropriate medication, even if the infection was not confirmed by appropriate microbiology and/or virology techniques. Table 63 shows the number of patients who had infections treated with antimicrobial medication during the study (Source: Vol 1.88, Report Number GHBA-157, Table 36).

TABLE 63
Number of Patients who had Infections
Treated with Antimicrobial Medication during the Study

	Tacrolimus (N=267) N (%)	CBIR (N=273) N (%)
Patients with at least One Infection	207 (77.5)*	220 (80.6)*
Patients with 1 Episode of Infection **	70 (33.8)	71 (32.3)
Patients with 2 Episodes of Infection **	63 (30.4)	64 (29.1)
Patients with 3 Episodes of Infection **	38 (18.4)	31 (14.1)
Patients with 4 Episodes of Infection **	23 (11.1)	24 (10.9)
Patients with 5 Episodes of Infection **	3 (1.4)	16 (7.3)
Patients with >5 Episodes of Infection **	10 (4.9)	14 (6.9)
Number of Episodes of Infection	484	567

* (% of efficacy population)

** (% of patients with at least one infection)

As expected in the setting of systemic immunosuppression, infections were commonly reported in both treatment groups. A total of 484 infections were reported for 207 patients (77.5%) in the tacrolimus treatment group compared with a total of 567 infections in 220 patients (80.6%) in the group receiving CBIR therapy (p-value = 0.443, by sponsor's analysis using the continuity adjusted Chi-Square statistic). The sponsor's analysis using the Cochran-Mantel-Haenszel mean score test did not find a significant difference in the distribution of episodes of treated infections between the two treatment groups (p= 0.079). A total of 69 COSTART terms relating to infection were used to categorize these events. Out of these 69 only two terms showed a statistically significant difference between treatment groups (sponsor's analysis; Source: Vol 1.88, Report Number GHBA-157, Table 36). Treated herpes zoster was reported in 12 patients treated with CBIR and 2 treated with tacrolimus therapy (p<0.05). The term "infection" was reported for 80 patients (30.0%) treated with tacrolimus and 110 patients (40.3%) receiving CBIR (p<0.05). The latter difference is difficult to interpret in light of the numbers of treated infections which were similar between the two groups.

Confirmed infection was defined as a treated infection confirmed by microbial cultures, smears, serology or other appropriate techniques. A total of 287 treated infections were confirmed in

156 patients (58.4%) in the tacrolimus treatment group compared with 355 episodes in 172 patients (63.0%) in the group receiving CBIR therapy ($p=0.317$, by sponsor's analysis using the continuity-adjusted Chi-Square statistic; Source: Vol 1.88 Report Number GHBA-157, Table 38). No significant difference was found between treatment groups with respect to the frequency of the ten most common pathogens isolated (Source: 1.88, Report Number GHBA-157, Table 40).

Overall, there is insufficient evidence to support the sponsor's claim that tacrolimus therapy was associated with a significantly lower incidence of infection compared to the cyclosporine-based immunosuppressive regimens used in this study.

8.2.5 Conclusions Regarding Efficacy and Safety Data

The following conclusions reflect discussion with the FDA's Primary Statistical Reviewer for this study. Please see the FDA's Statistical Review and Evaluation of this study for additional details.

Tacrolimus-based immunosuppressive therapy and CBIR appear "equivalent" with respect to 12 month patient and graft survival. The results of the analyses stratified by investigator were consistent with the unstratified analyses. With 96.5% confidence, the 12 month rate of patient survival could be as much as 8.4% higher or as much as 4.2% lower among patients randomized to tacrolimus than among patients randomized to CBIR; the 12 month rate of graft survival could be as much as 12.2% higher or as much as 2.6% lower among patients randomized to tacrolimus.

There is insufficient evidence to support the sponsor's contention that tacrolimus-based immunosuppression is therapeutically superior to CBIR with respect to six-month incidence of acute rejection. The 96.5% confidence intervals for both the sponsor's stratified and unstratified analyses of the difference between treatment groups in six-month rates of acute rejection fell well within the $\pm 10\%$ zone of equivalence.

A strength of this study is the complete ascertainment of patient and graft survival at one year. The major weakness remains the open-label design. Analyses performed by the sponsor and the FDA to assess the influence of bias suggest that the impact was probably minimal on the estimates of the treatment effects reflected in the primary efficacy endpoints (12 month patient and graft survival).

The pattern of adverse events observed in the tacrolimus group was similar overall to that observed in the CBIR treatment group; however, at the dose used in this study the tacrolimus-based regimen was associated with a greater incidence of neurological, renal and gastrointestinal adverse experiences than was CBIR. Infection was the most common adverse experience observed.

There is insufficient evidence to support the sponsor's claim that tacrolimus-based

immunosuppression was safer than cyclosporine-based therapy when used to prevent organ rejection in patients who received liver transplants.

9 Overview of Efficacy

Both Study FPC-FK506-7 and Study GHBA-157 were characterized by similar design, size and duration. Both studies support the conclusion that tacrolimus-based immunosuppression and CBIR appear "equivalent" with respect to patient and graft survival. The evidence was insufficient to support the claim that a tacrolimus-based immunosuppressive regimen was therapeutically superior to CBIR with respect to acute rejection. Because it is assumed that the active control cyclosporine-based regimens are representative of current clinical practice and are effective in preventing graft rejection in patients who have received a liver transplant, we are allowed to conclude that these two clinical studies support that tacrolimus-based immunosuppression is equally effective.

Patient survival and graft survival in the two studies are compared in the table below (source: Vol 1.49, Integrated Summary of Effectiveness, Table 8).

TABLE 64
One-Year Patient and Graft Survival

Protocol	One-Year Patient Survival		One-Year Graft Survival	
	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	88%	88%	82%	79%
GHBA-157	81%	75%	76%	70%

A lower rate of one-year patient and graft survival was observed in study GHBA-157 compared to study FPC-FK506-7. One of the possible reasons for the difference in survival rates between the two studies is the differential inclusion of patients at greater risk for graft loss. Table 65 summarizes the principal differences in inclusion criteria between the two studies.

TABLE 65
Differing Entry Criteria

Study	Renal Dysfunction	Fulminant Hepatic Failure	Malignancies	Pediatrics
FPC-FK506-7	Excluded *	Excluded FHF patients in stage IV hepatic encephalopathy	Excluded	Included
GHBA-157	Included	Included	Excluded primary liver cancer with metastases	Excluded

* FPC-FK506-7 definition of renal dysfunction: <30 mL/min (GFR), or >2.0 mg/dL (SCr), or dialysis dependent.

Patients ≤ 3 years old and those ≥ 60 years old have lower one-year survival rates than patients in any other age category. Fulminant hepatic failure (FHF) patients, often with severe encephalopathy, have low short term post-transplantation survival rates, approximately 62% at one year. Malignancies are associated with one-year patient survival rate of 60%, but due to tumor recurrence in at least 70% of patients, long-term survival is poor (28% at three years). The sponsor presented a subset analysis excluding patients in Study GHBA-157 who did not meet eligibility criteria for protocol FPC-FK506-7 and comparing this subset to the adult subset of Study FPC-FK506-7. Results of these analyses are summarized in Table 66 (Source: Vol 1.49, Integrated Summary of Effectiveness, Table 16).

TABLE 66
Patient and Graft Survival Rates in Comparable Study Group Subsets

Protocol	One-Year Patient Survival		One-Year Graft Survival	
	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	89%	88%	83%	80%
GHBA-157	85%	79%	80%	72%

The differences in tacrolimus survival rates between the two studies are less pronounced in the analysis of comparable study group subsets. Thus, the difference in tacrolimus survival rates between the two studies may be due in part to the inclusion of higher risk patients in Study GHBA-157.

Another possible reason for the differences in survival rates between the two studies may have been the differential use of anti-rejection therapy. The acute rejection rates at six months were greater in Study FPC-FK506-7 than in Study GHBA-157 (Table 67; Source: Vol 1.49, Integrated

Summary of Efficacy, Table 17). This could have led to a greater use of concomitant immunosuppressive therapy in Study FPC-FK506-7. In addition, the standard treatment for acute rejection recommended in protocol FPC-FK506-7 appeared greater in intensity than most of the regimens used in Study GHBA-157.

TABLE 67
Rate of Acute Rejection and OKT3 Use at Six Months

Study	Acute Rejection Rate		OKT3 Use	
	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	66%	73%	19%	36%
GHBA-157	41%	54%	8%	10%

The differing rejection rates observed in these two studies may be related to the number and timing of protocol-mandated biopsies. Additionally, Study FPC-FK506-7 stipulated that histologic evidence of rejection alone was sufficient to initiate anti-rejection treatment, while Study GHBA-157 required that clinical symptoms or biologic evidence suggesting rejection also be present. While Study FPC-FK506-7 required a repeat biopsy seven days after completion of rejection treatment to assess rejection state, no post-rejection-treatment graft assessment was specified in GHBA-157.

Both protocols underwent several amendments reflecting changes to the starting doses of tacrolimus and duration of IV infusion. The impact of these changes on the efficacy evaluations is unknown.

The daily doses of tacrolimus were also modified by the investigators according to the patients status and measured drug levels. A broad range of daily doses and drug whole blood or plasma concentrations were represented in both studies. Although the ranges of oral drug doses (measured as mg/kg/day) and of drug concentrations overlapped considerably between the two studies, mean daily oral doses and whole blood concentrations were approximately 30% and 45% lower, respectively, in Study GHBA-157 compared to Study FPC-FK506-7.

Although there is evidence from two controlled studies that tacrolimus-based immunosuppressive therapy, as used in these studies, was effective in preventing graft rejection in patients who have received a liver transplant, the optimal dose of tacrolimus remains uncertain and will require additional phase 4 investigations.

10 Overview of Safety

The overview of safety is based primarily on the combined safety data from the two large controlled trials in liver transplantation, FPC-FK506-7 and GHBA-157. A total of 533 liver transplant recipients were treated with tacrolimus in these two studies. Detailed safety information from these studies (12 month and six month data from studies FPC-FK506 and

GHBA-157, respectively) has been submitted for our review. Additional supportive information is available in the published literature submitted with this NDA. The supportive material will be referred to as necessary. It should be noted that the supportive literature did not identify any serious adverse experiences associated with the use of tacrolimus that were not identified in the two large controlled studies.

When interpreting differences between studies in crude incidences of an adverse event thought to be related to tacrolimus, one must keep in mind that the initial tacrolimus dose varied between studies and over time. The initial doses used in published reports from the University of Pittsburgh (included as supportive information to this NDA) were higher than those used in study FPC-FK506-7, which in turn were higher than those in study GHBA-157. These differences reflect the order in which these studies were initiated and conducted. During this period of time the proposed recommended doses were decreased, in an attempt to minimize early adverse events which were thought to be related to tacrolimus.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

Deaths were not necessarily unexpected adverse events in the setting of liver transplantation. Among patients who were assigned to tacrolimus in study FPC-FK506-7 and GHBA-157 there were 31 and 50 deaths respectively. Attribution of any of these deaths to treatment with tacrolimus is problematic in this complicated setting, where co-morbid conditions related to end-stage-liver-disease, surgical complications and the use of multiple medications may have contributed to the fatal outcome. Most deaths were not reasonably attributable to treatment with tacrolimus.

Infection and sepsis are well recognized hazards of immunosuppressive therapy and a leading cause of death in liver transplant recipients. In study FPC-FK506-7, 18 of the 31 deaths in tacrolimus-treated patients involved infection/and or sepsis (Source: Vol 1.87, 1.88, Study Report: FPC-FK506-7, Appendix F). In 16 of these an infection or sepsis was reported as the primary cause of death. In study GHBA-157, 24 out of the 50 deaths in tacrolimus-treated patients were associated with infection and/or sepsis (Source: Vol 1.93 and 1.94, Study Report GHBA-157, Appendix 39). In 14 of these, infection or sepsis was reported as the primary cause of death.

The proportion of deaths in patients treated with CBIR that were associated with or attributed to infection and/or sepsis was similar to what was reported in tacrolimus-treated patients. In study FPC-FK506-7, 15 of 33 deaths in patients treated with CBIR involved infection (Source: Vol 1.87, 1.88, Study Report: FPC-FK506-7, Appendix F). In 13 of these infection and/or sepsis was reported as the primary cause of death. In study GHBA-157, 27 out of 68 deaths in patients treated with CBIR involved infection and/or sepsis (Source: Vol 1.93 and 1.94, Study Report GHBA-157, Appendix 39). For 21 of these, infection/sepsis was reported as the primary cause of death.

Renal function impairment is associated with the use of tacrolimus and was often reported in the string of events that lead to deaths in patients treated with tacrolimus. In study FPC-FK506-7, renal failure was part of the clinical course of 12 out of 31 patients who died in the tacrolimus arm (Source: Vol 1.87, 1.88, Study Report: FPC-FK506-7, Appendix F). In study GHBA-157, renal failure was reported in 22 out of the 50 who died in the tacrolimus arm (Source: Vol 1.93 and 1.94, Study Report GHBA-157, Appendix 39). In none of these cases was renal failure reported as the primary cause of death.

Renal failure was reported in a smaller proportion of CBlR-treated patients who died within 12 months post transplantation.

Hyperkalemia is also associated with the use of tacrolimus and may have contributed to the death in one patient (Patient) enrolled in study GHBA-157. This 57 year old woman underwent liver transplantation for presumed non-A, non-B fulminant hepatitis. At the time of surgery she displayed grade IV encephalopathy and her WHO score was 4.

Tacrolimus was started post operatively at an initial dose of 0.076 mg/kg. On the following day (Day 1), she developed renal insufficiency (prior to transplant renal function was normal). Serum creatinine was elevated to 270 $\mu\text{mol/L}$ on day 2. The tacrolimus dose was not reduced by 50% until day 3. A review of medications reveal that amphotericin (for generalized candidiasis) was a relevant concomitant therapy. Plasma levels of tacrolimus were determined to be 4.6 $\mu\text{g/L}$. This was high compared to the upper limits of the range recommended in the clinical protocol (ng/mL). It is not certain on which day this piece of information was available to the investigator.

The patient's condition deteriorated as she developed respiratory distress requiring mechanical ventilation. Despite reduction of the tacrolimus dose, her renal function deteriorated further. Serum creatinine was elevated to 402 $\mu\text{mol/L}$ on day 9. Serum potassium was elevated to 6.3 mmol/L. It was considered by the investigators that this contributed to two cardiac arrests that the patient had at this stage, but from which she was successfully resuscitated. Tacrolimus was interrupted and hemodialysis was initiated on day 9. A review of medications revealed that vancomycin had been administered on that day.

The patient's condition continued to deteriorate and on day 13 the patient was found to have a flat electroencephalogram. Consequently, active treatment was withdrawn and on day 14 after transplantation the patient expired. A postmortem examination was performed and documented the following abnormalities: 1) cerebral hypoxia following cardiac arrest; 2) hepatorenal failure; 3) Liver transplantation for non-A, non-B hepatitis; 4) rejection of liver transplant; 5) bronchopneumonia; 6) acute duodenal ulcer.

Multiple serious co-morbid conditions contributed to this patient's death. The relative contribution of tacrolimus is difficult to measure here in what began as life threatening fulminant hepatitis. One other patient death attributed to hyperkalemia occurred in the setting of acute liver allograft rejection with massive tissue necrosis, which was believed to be the cause of the

hyperkalemia.

10.1.2 Other Significant/Potentially Significant Events

10.1.2.1 Neurotoxicity

TABLE 68
Selected Overall Adverse Events Related to Neurotoxicity

	GHBA-157	GHBA-157	FPC-FK506-7	FPC-FK506-7
	Tacrolimus N (%)	CBIR N (%)	Tacrolimus N (%)	CBIR N (%)
Tremor	116 (43.5)	81 (29.7)	139 (54.5)	116 (45.8)
Headache	84 (31.5)	58 (21.2)	160 (62.7)	149 (58.9)
Paresthesia	42 (15.7)	37 (13.6)	99 (38.8)	77 (30.4)
Convulsion	13 (4.9)	8 (2.9)	16 (6.3)	17 (6.7)
Neuropathy	10 (3.8)	14 (5.1)	23 (9.0)	24 (9.5)
Encephalopathy	2 (0.8)	4 (1.5)	13 (5.1)	15 (5.9)

TABLE 69
Selected Overall Adverse Events Relative to Cognitive Function

	GHBA-157	GHBA-157	FPC-FK506-7	FPC-FK506-7
	Tacrolimus N (%)	CBIR N (%)	Tacrolimus N (%)	CBIR N (%)
Insomnia	78 (29.2)	55 (20.2)	161 (63.1)	171 (67.6)
Confusion	23 (8.6)	11 (4.0)	42 (16.5)	25 (9.9)
Agitation	14 (5.2)	12 (4.4)	39 (15.3)	32 (12.6)
Nervousness	4 (1.5)	1 (0.4)	32 (12.5)	13 (5.1)

Tremor and headache were the most commonly reported adverse events relative to neurotoxicity and were more frequent in the tacrolimus groups in both studies. In the majority of the cases, episodes of tremor and headache were reversible.

In their analysis of study FPC-FK506-7 the sponsor has reported that tremor correlated ($p < 0.10$) using a step-wise logistic regression with high whole blood trough levels of FK506 during days 1-7 (Study Report: FPC-FK506-7, Appendix B, Table B.11.13). Headache and

tremor correlated ($p < 0.10$), using the Cox proportional hazards method with high whole blood levels of FK506 over the first 90 days (Study Report: FPC-FK506-7, Appendix B, Table B.11.14).

Insomnia, confusion, agitation and nervousness were the most commonly reported adverse events relative to cognitive function and were more frequent in the tacrolimus groups.

In the sponsor's analysis of Study FPC-FK506-7, agitation correlated ($p < 0.10$) with plasma trough levels of tacrolimus during the first 90 days. In addition, there were strong correlations between intraoperative hypotension and confusion, neuropathy, and abnormal thinking. Confusion, insomnia, and somnolence correlated ($p < 0.10$) with high whole blood trough levels of tacrolimus (Source: Vol. 1.67, Study Report: FPC-FK506-7, Appendix B, Tables B.11.3 and Tables B.11.4).

Headache was reported as a serious adverse event in 1.1% and 5.9% of tacrolimus treated patients in studies GHBA-157 and FPC-FK506-7, respectively. Tremor was reported as a serious adverse event in 1.1% and 2.4% of tacrolimus treated patients in studies GHBA-157 and FPC-FK506-7, respectively.

Other serious adverse events related to neurotoxicity reported in study GHBA-157 included coma (5), Psychosis (5), neuropathy (4), grand mal convulsion (3), and paresthesia (3) (Source: Vol 1.88, Report Number GHBA-157, Table S). In particular, one patient developed a multiple symptom complex of severe headache, tremor, dizziness and abnormal vision that resolved following a reduction in the dose of tacrolimus.

Other serious adverse events related to neurotoxicity or impaired cognitive function reported in study FPC-FK506-7 included convulsion (11), encephalopathy (8), grand mal convulsion (5), neuropathy (8), confusion (9), agitation (5), and psychosis (1) (Source: Vol 1.67, Study Report FPC-FK506-7, Table 32 and Table 33).

Overall, more than twice as many serious adverse events relative to neurotoxicity or cognitive function were reported in tacrolimus-treated patients compared to patients treated with CBIR.

Supportive information submitted as publications reporting the experience at the University of Pittsburgh with the use of tacrolimus in liver transplantation also suggest that serious neurotoxicity may be associated with high trough plasma levels of tacrolimus [Alessiani M, Cillo U, Fung JJ et al: *Transplant Proc* 25:628-634, 1993].

Although the exact mechanism is unknown, neurotoxicity (primarily tremors) appears related to the use of tacrolimus. A better understanding of the clinical pharmacodynamics of tacrolimus in liver transplant recipients may help reduce the incidence of serious neurotoxicity.

10.1.2.2 Nephrotoxicity

TABLE 70
Selected Overall Adverse Events Relative to Nephrotoxicity

	GHBA-157	GHBA-157	FPC-FK506-7	FPC-FK506-7
	Tacrolimus N (%)	CBIR N (%)	Tacrolimus N (%)	CBIR N (%)
Kidney Function Abnormal	88 (33.0)	58 (21.2)	101 (39.6)	69 (27.3)
BUN Increased	22 (8.2)	20 (7.3)	75 (29.4)	55 (21.7)
Creatinine Increased	51 (19.1)	46 (16.9)	100 (39.2)	62 (24.5)
Oliguria	49 (18.4)	30 (11.0)	45 (17.6)	37 (14.6)
Kidney Failure	25 (9.4)	20 (7.3)	10 (3.9)	10 (4.0)

Adverse events involving impairment of renal function were commonly reported in both tacrolimus and CBIR patients. In four areas, however, (kidney function abnormal, BUN increased, creatinine increased, and oliguria) there were more reported events in the tacrolimus treatment groups. Kidney function abnormal was the most frequently reported event.

Kidney failure and abnormal kidney function were the most frequently reported serious adverse events related to toxicity. Kidney function abnormal was reported as a serious adverse event in 5.6% and 5.5% of tacrolimus treated patients in studies GHBA-157 and FPC-FK506-7, respectively. Kidney failure was reported as a serious adverse event in 7.1% and 3.5% of tacrolimus treated patients in studies GHBA-157 and FPC-FK506-7, respectively.

TABLE 71
Serious Adverse Events Related to Nephrotoxicity

	GHBA-157	GHBA-157	FPC-FK506-7	FPC-FK506-7
	Tacrolimus N (%)	CBIR N (%)	Tacrolimus N (%)	CBIR N (%)
Kidney Function Abnormal	15 (5.6)	9 (3.3)	14 (5.5)	12 (4.7)
Kidney Failure	19 (7.1)	11 (4.0)	9 (3.5)	7 (2.8)
Creatinine Increased	7 (2.6)	2 (0.7)	10 (3.9)	4 (1.6)
Oliguria	2 (0.8)	1 (0.4)	8 (3.1)	3 (1.2)
Anuria	2 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)

Renal impairment was serious enough to require dialysis or ultrafiltration in 33 and 25 of tacrolimus treated patients in studies GHBA-157 and FPC-FK506-7, respectively. Fewer CBIR treated patients required dialysis or ultrafiltration, 31 in study GHBA-157 and 15 in study FPC-FK506-7.

A higher incidence of death was associated with renal function impairment dialysis or ultrafiltration post-transplantation.

TABLE 72
Patients Requiring Dialysis

Study	GHBA-157	GHBA-157	FPC-FK506-7	FPC-FK506-7
Treatment Group	Tacrolimus N (%)	CBIR N (%)	Tacrolimus N (%)	CBIR N (%)
Required dialysis after transplantation *	33 (12.6%)	31 (11.9%)	25 (10.0%)	15 (5.9%)
Died *	17/33 (51.5%)	16/31 (51.6%)	10/25% (40%)	5/15 (33%)

* Six month data for study GHBA-157 and twelve month data for study FPC-FK506-7.

(Source: Vol 1.97, Appendix S28 to Report GHBA-157; Vol 1.69, Study Report: FPC-FK506-7, Appendix B, Table B.11.10.)

The sponsor has also presented an analysis of the incidence of increased BUN or serum creatinine in study by IV dose of tacrolimus and by whole trough levels (Source: Slides for

Sponsor's presentation to the Advisory Committee, November 22, 1993). Higher IV doses were associated with a higher incidence of increased BUN or serum creatinine. Higher whole blood trough levels were also associated with a higher incidence of these adverse events.

Although the exact mechanism is unknown, impairment of renal function appears related to the use of tacrolimus. The use of tacrolimus should require monitoring of renal function and avoidance of concomitant medications associated with nephrotoxicity. A better understanding of the pharmacodynamics of tacrolimus may help minimize this type of toxicity.

10.1.2.3 Hyperkalemia

Hyperkalemia was associated with the use of tacrolimus and was reported more frequently in study FPC-FK506-7 than in study GHBA-157 (See Table below). This may be explained in part by the use of spironolactone (an aldosterone antagonist used as a potassium sparing diuretic) in study FPC-FK506-7 while it was prohibited in study GHBA-157. However, the incidence of hyperkalemia reported among patients in study FPC-FK506 who received spironolactone was similar to the incidence in those who did not.

In study FPC-FK506-7 hyperkalemia was reported more frequently in tacrolimus treated patients than in CBIR patients. Spironolactone was used more frequently in tacrolimus-treated patients than in CBIR patients (10.3% vs. 6.0%). The differential use of spironolactone is unlikely to explain the difference in incidence of hyperkalemia between the two treatment groups, since less than 10% of the total patients who experienced hyperkalemia while on study drug and on spironolactone. (Source: Vol 1.69, Study Report: FPC-FK506-7, Appendix B, Table B.11.7)

TABLE 73
Incidence of Hyperkalemia

STUDY	Tacrolimus	CBIR
FPC-FK506-7 (12 month data)	112 (43.9%)	66 (26.1%)
GHBA-157 (6 month data)	25 (9.4%)	22 (8.0%)

The sponsor presented an analysis of the number of patients with hyperkalemia (serum potassium > 5.0 mEq) over time, broken down by treatment group and degree of severity. This analysis is summarized in the table below, which combines data on the first six months post-transplantation from studies FPC-FK506-7 and GHBA-157 (Source: Slide to Sponsor's Presentation before the Advisory Committee, November 22, 1994). Over time, hyperkalemia remained more frequently reported in tacrolimus-treated patients than in cyclosporine treated patients. The peak incidence of hyperkalemia occurred at Week 2, when 41 tacrolimus-treated patients were reported to have a serum potassium greater than 5.5 mEq/L compared to 12 in the CBIR group.

TABLE 74
Studies FPC-FK506-7 and GHBA-157 Combined
Serum Potassium (mEq/L)

DAY	>5.0 - 5.5		>5.5 - 6.0		>6.0	
	Tacrolimus	CBIR	Tacrolimus	CBIR	Tacrolimus	CBIR
Week 1	42	23	13	10	4	2
Week 2	63	50	28	10	13	2
Week 4	54	44	10	12	2	1
Month 3	30	23	15	7	2	3
Month 6	46	27	16	10	8	5

Hyperkalemia was judged serious enough by the investigators to lead to the use of mineralocorticoids. In Study FPC-FK506-7, Florinef[®] Acetate (a synthetic mineralocorticoid which increases urinary excretion of K⁺ and H⁺ and urinary reabsorption of Na⁺ from the distal tubular fluid) was used to treat hyperkalemia in 39 (14.8%) of patients in the tacrolimus group compared to 17 (6.4%) of patients in the CBIR group (Source: Vol 1.68, Study Report FPC-FK506-7, Appendix B, Table B.5.4).

Hyperkalemia was also commonly reported in a cohort of 370 consecutive liver transplant recipients treated with tacrolimus at the University of Pittsburgh [Alessiani M, Cilio U, Fung JJ et al: Transplant Proc 25:628-634, 1993]. Hyperkalemia, defined as a serum potassium level >5.3 mEq/L or the need for a potassium-reducing agent occurred in 239 (64.6%) of these patients. Florinef[®] was administered in 46% of the affected population. Although these investigators did not find an association between tacrolimus plasma trough levels and hyperkalemia, spontaneous recovery, which was reported to occur in 27% of the cases, was associated with a reduction in the tacrolimus dose. Median time to occurrence of hyperkalemia was reported by Alessiani et al. to be 23 days. After a median follow-up of 12.2 months post transplantation (range: 6 to 23 months), hyperkalemia was still present in 169, or 70.7% of the affected population.

Although the exact mechanism is unknown, tacrolimus appears to cause hyperkalemia which should require monitoring of serum potassium levels, and the avoidance of potassium-sparing diuretics during treatment with tacrolimus.

10.1.2.4 Lymphoproliferative Disease

A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. It occurs in 1 - 10% of transplant recipients, and is a well recognized complication of solid organ transplantation. The

population most at risk appears to be those receiving potent antilymphocyte preparations in the setting of primary EBV infection. These include mostly young children (age \leq 2 years), who are at risk for primary EBV infection. The risk also appears related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

A total of 4 cases of LPD were reported in studies FPC-FK506-7 and GHBA-157 combined. Two occurred in patients treated with tacrolimus and two in patients treated with CBIR. The crude incidence of this adverse event was less than 1%. Lymphoproliferative disease was a cause of death in one patient treated with CBIR in study FPC-FK506-7.

10.1.2.5 Hypertension

Hypertension was commonly associated with the use of tacrolimus in studies FPC-FK506-7 and GHBA-157 (see table below) and often required treatment. Mild or moderate hypertension was more common than severe hypertension.

TABLE 75
Incidence of Hypertension

STUDY	Tacrolimus	CBIR
FPC-FK506-7 (12 month data)	47%	56%
GHBA-157 (6 month data)	33%	38%

Hypertension was also commonly reported in a cohort of 370 consecutive liver transplant recipients treated with tacrolimus at the University of Pittsburgh [Alessiani M, Cillo U, Fung JJ et al: Transplant Proc 25:628-634, 1993]. Hypertension, defined as an arterial blood pressure elevation above 160 mm Hg systolic or 100 mm Hg diastolic for more than 2 months in a previously normotensive patient, or a need for antihypertensive drugs for any 60-day period to control hypertension, occurred in 122 (32.9%) of 356 patients who were not hypertensive before transplantation. Median time to occurrence of hypertension was reported by Alessiani et al. to be 52 days post transplant and was transient in only 10.7%. After a median follow-up of 12.2 months post transplantation (range 6 to 23 months), hypertension requiring treatment was still present in 103, or 84.5% of the affected population. Although these investigators did not find an association between tacrolimus trough plasma concentrations and hypertension, recovery, when it occurred, was associated with a reduction in tacrolimus dose.

A comparison by Alessani et al. between the hypertensive and non-hypertensive patients failed to show a significant difference in their steroid requirement at day 30 post-transplant, but a tendency for a higher steroid dosage at day 180 appeared to be present, suggesting a role for steroids in the pathogenesis of the hypertension.

Although the exact mechanism is unknown, hypertension requiring treatment appears to be

associated with the use of tacrolimus. The control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since the interference with tacrolimus metabolism may require dosage reduction.

10.1.2.6 Hyperglycemia

Preclinical studies have indicated that pancreatic islets are targets of tacrolimus toxicity. Glucose intolerance and impairment of insulin secretion in animals were observed to be both duration and dose related. These events were associated with histopathological changes in the Langerhans islets. After withdrawal of tacrolimus, these changes in pancreatic function and morphology returned to normal.

Hyperglycemia was commonly associated with the use of tacrolimus and was reported more frequently in study FPC-FK506-7 than in study GHBA-157. The relative role of concomitant corticosteroids use in the pathogenesis is recognized but difficult to evaluate in these studies. However, despite greater use of corticosteroids in the CBIR arms of both studies, in part by protocol design, hyperglycemia and diabetes mellitus were more frequently reported in the tacrolimus-treated group.

TABLE 76
Incidence of Selected Adverse Events Related
to Impaired Glucose Metabolism

	GHBA-157 (6 month data)		FPC-FK506-7 (12 month data)	
	Tacrolimus	CBIR	Tacrolimus	CBIR
Hyperglycemia	30.7%	20.5%	46.3%	39.5%
Diabetes Mellitus	17.2%	9.5%	5.5%	1.2%

The sponsor's analysis of the use of insulin over time in study FPC-FK506-7, reveals that although the use of insulin prior to liver transplantation was more frequent in the CBIR-treated patients than in tacrolimus-treated patients, a greater proportion of tacrolimus treated patients required insulin during the first six months post transplant. The requirement for insulin was most frequent during the first 27 days post liver transplantation. The first 4 weeks after liver transplantation are also the period of greatest use of corticosteroids.

TABLE 77
Use of Insulin in Study FPC-FK506-7

Treatment Period	Tacrolimus	CBIR
Pre-Study	46/263 (17%)	70/266 (26%)
Day 1-27	144/255 (56%)	133/253 (53%)
Day 28-179	68/213 (32%)	55/187 (26%)
Day 180-360	29/187 (16%)	28/178 (16%)

Hyperglycemia was also commonly reported in a cohort of 370 consecutive liver transplant recipients treated with tacrolimus at the University of Pittsburgh [Alessiani M, Cillo U, Fung JJ et al: Transplant Proc 25:628-634, 1993]. In their analysis glucose intolerance was defined as the requirement of for insulin therapy for more than 30 days to maintain fasting blood sugar levels in the normal range. Among the 345 patients who were not diabetic prior to transplantation (early onset diabetes), 61 (17.7%) experienced glucose intolerance requiring insulin within 30 days after liver transplantation. Twenty-three (37.7%) of these developed permanent diabetes mellitus. Early onset diabetes was associated with higher tacrolimus plasma concentrations. Recovery, when it occurred, was associated with a reduction in tacrolimus dose.

Late onset diabetes, after 30 days post liver transplantation, occurred at a median of 152 days in 18 (5.2%) of the 345 patients studied. Of these 18, 11 remained insulin-dependent, 3 recovered and 4 died on insulin therapy. Late onset glucose intolerance was associated with elevated tacrolimus plasma levels. With reduction in the tacrolimus dose, the requirement for insulin therapy was reduced.

Thus, the use of tacrolimus in liver transplant recipients appears to cause hyperglycemia that may require insulin therapy. Tacrolimus-associated diabetes mellitus may regress with dose reduction. However, some liver transplant recipients treated with tacrolimus may permanently require insulin therapy.

10.1.3 Overdosage exposure

No data concerning overdosage exposure has been submitted by the sponsor to the NDA. Adverse events one would expect to observe with overdosage should be similar to those associated with high plasma concentrations of tacrolimus. These include, but are not limited to, acute renal failure, severe neurotoxicity and diabetes mellitus. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent.

As part of the Phase 4 commitments, the sponsor has agreed to create a registry to collect

data on overdosage exposure.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

The sponsor has used the COSTART dictionary of terms to classify and tabulate adverse events in the two large controlled studies. Precautions must be taken when comparing the incidence of adverse events in one study to that in the other. Only adverse events occurring up to 12 months post-transplant in Study FPC-FK506-7 and up to 6 months in Study GHBA-157 are presented. The two studies also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in > 15% of tacrolimus treated patients (combined study results) are presented below for studies FPC-FK506-7 and GHBA-157.

TABLE 78

ADVERSE REACTIONS

	FPC-FK506-7 (%)		GHBA-157 (%)	
	Tacrolimus (N=250)	CBIR (N=250)	Tacrolimus (N=262)	CBIR (N=261)
<u>Nervous System</u>				
Headache	64	60	31	20
Tremor	56	46	44	30
Insomnia	64	68	29	21
Paresthesia	40	30	15	13
<u>Digestive System</u>				
Diarrhea	72	47	32	23
Nausea	46	37	30	22
Constipation	24	27	19	20
LFT Abnormal	36	30	5	2
Anorexia	34	24	6	4
Vomiting	27	15	12	9
<u>Cardiovascular System</u>				
Hypertension	47	56	31	35
<u>Urogenital System</u>				
Kidney Function Abnormal	40	27	33	18
Creatinine Increased	39	25	19	16
Bun Increased	30	22	8	7
Urinary Tract Infection	16	18	19	18
Oliguria	18	15	16	8
<u>Metabolic and Nutritional Disorders</u>				
Hyperglycemia	47	38	29	16
Hypomagnesemia	48	45	15	8
Hyperkalemia	45	26	10	7
Hypokalemia	29	34	11	14
Bun Increased	30	22	8	7
<u>Hemic and Lymphatic System</u>				
Anemia	47	38	4	1
Leukocytosis	32	26	8	7
Thrombocytopenia	24	20	10	14

ADVERSE REACTIONS

	FPC-FK506-7 (%)		GH/A-157 (%)	
	Tacrolimus (N=250)	CBIR (N=250)	Tacrolimus (N=262)	CBIR (N=261)
<u>Body As A Whole</u>				
Abdominal Pain	59	54	26	20
Pain	63	57	19	14
Fever	48	56	15	18
Asthenia	52	48	7	4
Back Pain	30	29	13	14
Ascites	27	22	5	6
Peripheral Edema	26	26	10	11
<u>Respiratory System</u>				
Pleural Effusion	30	32	32	29
Atelectasis	28	30	5	4
Dyspnea	29	23	3	2
<u>Skin and Appendages</u>				
Pruritus	36	20	11	5
Rash	24	19	8	3

The following adverse events, not mentioned above, were reported with greater than 3% incidence in tacrolimus-treated patients. NERVOUS SYSTEM: abnormal dreams, agitation, anxiety, confusion, convulsion, depression, dizziness, emotional lability, hallucinations, hypertonia, incoordination, myoclonus nervousness, neuropathy, psychosis, somnolence, thinking abnormal; SPECIAL SENSES: abnormal vision, amblyopia, tinnitus; DIGESTIVE SYSTEM: cholangitis, cholestatic jaundice, dyspepsia, dysphasia, flatulence, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased appetite, jaundice, liver damage, oral moniliasis; CARDIOVASCULAR: chest pain, abnormal ECG, hemorrhage, hypotension, tachycardia; UROGENITAL SYSTEM: hematuria, kidney failure; METABOLIC NUTRITIONAL: acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, edema, healing abnormal, hyperlipemia, hyperphosphatemia, hyperuricemia, hypocalcemia, hypophosphatemia, hyponatremia, hypoproteinemia, SGOT increased, SGPT increased; ENDOCRINE SYSTEM: diabetes mellitus; HEMIC/LYMPHATIC: coagulation disorder, ecchymosis, hypochromic anemia, leukopenia, prothrombin decreased; BODY AS A WHOLE: abdomen enlarged, abscess, chills, hernia, peritonitis, photosensitivity reaction; MUSCULOSKELETAL: arthralgia, generalized spasm, leg cramps, myalgia, myasthenia, osteoporosis; RESPIRATORY: asthma, bronchitis, cough increased, lung disorder, lung edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration; SKIN & APPENDAGES: alopecia, herpes simplex, hirsutism, skin disorder, sweating.

10.2.2 Drug-Demographic Interactions

Study FPC-FK506-7 enrolled both pediatric and adult recipients of primary orthotopic liver

transplants. Subset analyses of the pediatric patient population reveal safety and efficacy results comparable to those in the adult population. Of note was the increased tacrolimus dose requirements in pediatric patients compared to the adult population in order to maintain similar plasma concentrations. Among the principal adverse events associated with the use of tacrolimus, headache, tremor and renal failure were more frequently reported in adults.

The overall incidence of adverse events was comparable in males and females, despite higher incidences of some in males and of others in females. Of note was the increased incidence of several indices of renal dysfunction in males, and the increased incidence of nausea, with and without vomiting, in females. No differences in dosing based on gender can be recommended.

The number of noncaucasians in the controlled studies was too low to perform detailed analyses of individual adverse events. Among the common adverse events, no differences were seen by race, although caucasians appeared to have a lower incidence in most body systems. The overall incidence of adverse effects were comparable across racial groups. No differences in dosing based on race can be recommended.

10.2.3 Drug-Disease Interactions

Because tacrolimus is metabolized mainly by the liver, tacrolimus pharmacokinetics are markedly affected by hepatic dysfunction. In liver transplant recipients with significant perioperative graft dysfunction plasma tacrolimus may rise and remain elevated despite dose reduction or even discontinuance. These patients are at greater risk for the development of renal dysfunction. As part of the Phase 4 commitments the sponsor has agreed to conduct a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.

10.2.4 Drug-Drug Interactions

Drug interaction studies with tacrolimus have not been conducted. Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. In addition, since tacrolimus may cause hyperkalemia, the use of potassium-sparing diuretics should be avoided.

Initial clinical experience with the co-administration of tacrolimus and cyclosporine resulted in additive/synergistic nephrotoxicity. Tacrolimus should not be used simultaneously with cyclosporine. When converting from one immunosuppressive regimen to another, tacrolimus or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated tacrolimus or cyclosporine blood or plasma concentrations, dosing with the other drugs should be further delayed.

Since tacrolimus is metabolized mainly by the cytochrome P-450 IIIA enzyme systems,

substances known to inhibit these enzymes may decrease the metabolism of tacrolimus with resultant increases in whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus and decreased whole blood or plasma concentrations.

TABLE 79
Drugs That May Increase Tacrolimus Blood Concentrations

Calcium Channel Blockers	Antifungal Agents	Other Drugs
diltiazem nicardipine verapamil	clotrimazole fluconazole itraconazole ketoconazole	bromocriptine cimetidine clarithromycin cyclosporine danazol erythromycin methylprednisolone metoclopramide

TABLE 80
Drugs That May Decrease Tacrolimus Blood Levels

Anticonvulsants	Antibiotics
carbamazepine phenobarbital phenytoin	rifabutin rifampin

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus, vaccination may be less effective. The use of live vaccines should be avoided. Live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid [CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993; 42(RR-4):1-18].

10.2.5 Human Reproduction Data

The overall potential risks of tacrolimus use during pregnancy have not been evaluated in clinical trials. In experience reported by the University of Pittsburgh, eleven female transplant recipients maintained on tacrolimus therapy throughout pregnancy delivered twelve babies, with one patient conceiving twice [Jain A, Venkataramanan R, Fung J, Warty V, Tzakis, A, Starzl T. Pregnancy in liver transplant patients under FK506. Am Soc Transplant Physicians 1993, abstract]. These patients received tacrolimus from week one to 20 months prior to conception. A 34-year-old woman with hypertension and diabetes mellitus developed

proteinuria and worsening hypertension during the second trimester. Elective cesarean section was performed at 24 weeks and the baby died. Another patient who conceived within 4 weeks after transplantation, developed a CMV infection, which was treated with ganciclovir. The baby was born at 22 weeks and died immediately after birth. Ten pregnancies were successful, four with cesarean sections. The neonates showed no growth retardation or congenital anomalies. Long term follow-up is not yet available on these children. Of note, moderate to severe hyperkalemia was observed in the majority of the infants, but resolved within 24-48 hours. Acute renal failure was present also in one infant, but resolved within 48 hours. Elevated tacrolimus plasma and blood concentrations were measured in some of the infants. Thus, tacrolimus appears to cross the placental blood barrier.

11 Labeling Review

The proposed Package Insert, included in the original NDA submission, was substantially revised after discussion between the FDA and the sponsor. Revision, "J", dated April 8, 1994 is the final version agreed upon, and incorporates all the successive changes requested by the FDA.

Important changes included removal of any wording that could infer superiority rather than therapeutic equivalence between tacrolimus and cyclosporine-based immunosuppressive regimens in liver transplantation. Adequate precautions and warnings sections concerning the risk of hyperkalemia associated with the use of tacrolimus were included. Precautions concerning the concomitant use of tacrolimus and cyclosporine have also been included. Tabulations of the adverse reactions were broken down by study, instead of pooling events by treatment arm. This is felt to be necessary because of the differences between Study FPC-FK506-7 and GHBA-157 in duration of safety observations, patient populations, type of cyclosporine-based immunosuppression in the control arm, and intensity of the immunosuppressive regimens used to prevent or to treat rejection.

12 Conclusions

The sponsor has demonstrated that tacrolimus-based therapy is equivalent to cyclosporine-based therapy in preventing allograft rejection in liver transplant recipients. Because it is established that cyclosporine is effective for the prophylaxis of organ rejection in liver transplantation, it can be concluded that the data supporting equivalence has established that tacrolimus is effective for this same indication.

There is insufficient evidence to support that tacrolimus is superior to cyclosporine with respect to the prevention of acute rejection.

The safety profile of tacrolimus in liver transplant recipients is similar to that of cyclosporine. Notable differences were that use of tacrolimus was not associated with

gingival hyperplasia and hirsutism, two well characterized adverse events associated with the use of cyclosporine. Tacrolimus also demonstrated more nephrotoxicity, neurotoxicity (tremors, headache), and gastrointestinal toxicity (nausea, vomiting and diarrhea) than cyclosporine based therapy in two large controlled clinical trials of primary liver transplantation.

There is preliminary evidence that these adverse events were related to drug levels, and that clinical monitoring or laboratory safety parameters, symptoms and tacrolimus blood levels may help minimize these adverse experiences. However, there is insufficient data to support specific recommendations for therapeutic drug level monitoring. A better understanding of the human pharmacokinetics and pharmacodynamics of tacrolimus may improve its safety margin when used to prevent graft rejection in liver transplant recipients.

There is insufficient evidence to support that tacrolimus is safer than cyclosporine with respect to development of post-transplant hypertension and infection.

The risks associated with the use of tacrolimus must be weighed in the light of the life-threatening diagnoses that lead to liver transplantation, and the serious consequences of uncontrolled allograft rejection. Overall, there is a reasonable balance between the risks and benefits of tacrolimus-based immunosuppressive therapy when used for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants.

13 Recommendations

Tacrolimus should be approved for the prophylaxis of organ rejection in liver allograft recipients. The sponsor should be notified that they may not claim superiority to Sandimmune™ (cyclosporine) in this indication.

In addition to the labelling recommendations previously made to the sponsor, the label should be changed to list adverse experiences by study with a description of the principal differences between studies FPC-FK506-7 and GHRA-157 regarding patient population, entry criteria, active control regimen and tacrolimus dosing.

The following Phase IV commitments should be recommended to the sponsor in addition to those recommended by the other reviewing specialties.:

1. The sponsor should commit to conduct pediatric studies to better characterize the pharmacokinetics, safety and efficacy in children.
2. The sponsor should be encouraged to commit to the development of an oral liquid formulation which might be more suitable for use in small children than the proposed capsules.
3. The sponsor should commit to creating a registry for collecting safety data on

pregnancies occurring during the use of tacrolimus.

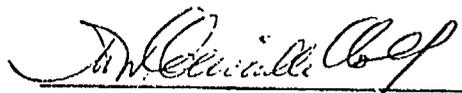
4. The sponsor should commit to collecting data concerning overdosage with tacrolimus.
5. The sponsor should commit to collecting long-term safety and efficacy data from the ongoing portion of study GHBA-157 (up to 24 months post-transplant) and patients who received tacrolimus in Study FPC-FK506-7.
6. The sponsor should commit to conducting a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.

In letters dated January 31, 1994, February 7, 1994, and April 8, 1994, the sponsor committed to perform additional clinical, pharmacological/toxicological and pharmacokinetic studies, to collect certain data and develop new drug forms.

14 Pertinent Advisory Committee Minutes

The Antiviral Drugs Advisory Committee's Subcommittee on Immunosuppressant Drugs met on November 22, 1993 to discuss data on the safety and efficacy of NDAs 50-708 and 50-709 for tacrolimus. The committee voted 10 - 0 to answer yes to the first question posed by the Agency: "Has tacrolimus been shown to be safe and effective by adequate and well-controlled trials for the prophylaxis of organ rejection in adult patients receiving allogeneic liver transplants?". A motion was made to vote on whether tacrolimus had been shown to be superior to cyclosporine with respect to secondary endpoints (such as acute and refractory rejections) and they voted 10 - 0 that superiority had not been shown.

The remaining questions from the Agency were answered by discussion, and not by a formal vote. Please see the summary minutes dated December 29, 1993 for additional details.



Marc Cavallé-Coll, M.D., Ph.D.
Medical Officer

DRAFT.

NDA 50,708

95

Concurrences:

HFD-530/DivDir/DFeigal

HFD-530/DepDir/DFreeman(6-20-94)

HFD-530/MO/Drafter/MCavaillé-Coll

cc:

HFD-530 Orig. NDA 50-708

HFD-530 Orig. NDA 50-709

HFD-340

HFD-530/MO/MCavaillé-Coll

HFD-530/Pharm/LBlack

HFD-530/Chem/MSeggel

HFD-715/SBiostat/LKammerman

HFD-715/Biostat/PFlyer

HFD-426/Biopharm/ADorantes

HFD-426/Biopharm/KMiller

PATENT AND EXCLUSIVITY INFORMATION

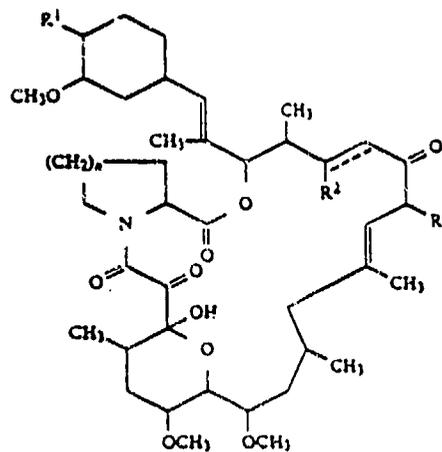
There are three current US patents on FK506, also known as FR-900506, tacrolimus, or PROGRAF™ brand of tacrolimus (Table 1). The assignee of the patents is Fujisawa Pharmaceutical Company, Ltd., Osaka, Japan. The Sponsor (Fujisawa Pharmaceutical Company, a division of Fujisawa USA, Inc., Deerfield, Illinois) of this application has exclusive marketing rights for PROGRAF in the USA.

Table 1: US PATENTS FOR FK506 (FR-900506)

Patent Number	Date of Patent	Title
4,894,366	Jan 16, 1990	Tricyclo Compounds: A Process for Their Production and a Pharmaceutical Composition Containing the Same.
4,916,138	Apr 10, 1990	Solid Dispersion Composition of FR-900506 Substance.
4,929,611	May 29, 1990	Method for Immunosuppression.

FK506 qualifies as a new chemical entity based on US Patent 4,894,366, which covers the tricyclo compounds per se (Figure 1), including FK506 ($R^1 = \text{OH}$, $R^2 = \text{OH}$, $R^3 = \text{CH}_2\text{-CH=CH}_2$) and a pharmaceutical formulation containing such compounds.

Figure 1: Structure of Tricyclo Compounds, Including FK506.



US Patent 4,916,138 covers the solid dispersion formulation of FK506.

US Patent 4,929,611 covers the method of treatment and prevention of resistance by transplantation, graft-versus-host disease by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like by administering these compounds.

Therefore, the Sponsor of this application requests full exclusivity of this compound for the indications named in this application. This is based on the evidence that FK506 is a new chemical entity, the indications sought are covered in the patents, and the solid dispersion formulation of FK506 will be marketed in the USA by the Sponsor.

Dennis Drehkoff October 15, 1992

Dennis Drehkoff
Patent Counsel

Date

EXCLUSIVITY SUMMARY FOR NDA # 50-708 SUPPL # _____

Trade Name PROGRAF Generic Name tacrolimus

Applicant Name Fujisawa USA HFD # 530

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Revised 5-90

d) Did the applicant request exclusivity?

YES / /

NO / /

*Patent
override
if desired*

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS; GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / /

NO / /

If yes, NDA # _____

Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

to meet AP prior to 78

YES / /

NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / /

NO / /

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

CB
1493

Dr. Cavalli, Jeffrey D
Signature
Title: Medical Officer

1/25/94
Date

Signature of
Division Director

Date

EXCLUSIVITY SUMMARY FOR NDA # 50-709 SUPPL # _____

Trade Name PROGRAF Generic Name tacrolimus
Applicant Name Fujisawa USA HFD # 530
Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Revised 5-90

d) Did the applicant request exclusivity?

YES / /

NO / /

*Patent
override
exclusivity*

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / /

NO / /

If yes, NDA # _____

Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / /

NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / /

NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III. ✓

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE #.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent, or more of the cost of the study.

1) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!	
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	_____
Investigation #2		!	
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!	
YES /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____
Investigation #2		!	
YES /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

B
12-14-93

[Handwritten Signature]
Signature
Title: *Medical Officer*

1/25/94
Date

Signature of
Division Director

Date



Fujisawa USA, Inc.
 Parkway North Center, Three Parkway North
 Deerfield, Illinois 60015-2548
 Tel. (708) 317-8800 • Telefax (708) 317-7296

Fujisawa

SUBMISSION CERTIFICATION

I certify that, with respect to the New Drug Application for tacrolimus capsules, NDA #20-362, Fujisawa USA, Inc. (the applicant) and Fujisawa Pharmaceutical Co., Ltd. (discoverer of tacrolimus and developer of the drug product) ⁵⁰⁻⁷⁰⁸

- did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)];
- did not use the facilities and/or personnel formerly known as Lyphomed in the research and development (i.e., generation of chemistry, manufacturing and control data) of tacrolimus capsules; and
- will not use the facilities and/or personnel formerly known as Lyphomed in the manufacturing, packaging, or testing of tacrolimus capsules to be marketed.

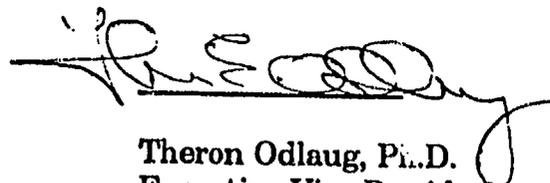
Theron Odlaug, Ph.D.
 Executive Vice-President,
 Operations
 Fujisawa USA, Inc.

Hatsuo Aoki, Ph.D.
 Chairman and Chief Executive Officer
 Fujisawa USA, Inc. and
 Managing Director
 Fujisawa Pharmaceutical Co., Ltd.

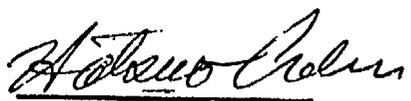
SUBMISSION CERTIFICATION

I certify that, with respect to the New Drug Application for tacrolimus ampules, Fujisawa USA, Inc. (the applicant) and Fujisawa Pharmaceutical Co., Ltd. (discoverer of tacrolimus and developer of the drug product)

- did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)];
- did not use the facilities and/or personnel formerly known as Lyphomed in the research and development (i.e., generation of chemistry, manufacturing and control data) of tacrolimus ampules; and
- will not use the facilities and/or personnel formerly known as Lyphomed in the manufacturing, packaging, or testing of tacrolimus ampules to be marketed.



Theron Odlaug, Ph.D.
Executive Vice-President,
Operations
Fujisawa USA, Inc.



Hatsuo Aoki, Ph.D.
Chairman and Chief Executive Officer
Fujisawa USA, Inc. and
Managing Director
Fujisawa Pharmaceutical Co., Ltd.

MEMORANDUM

DATE: January 24, 1994

TO: David W. Feigal, M.D., M.P.H.

FROM: Donna J. Freeman, M.D. *DSF* 1/24/94

SUBJECT: NDA 50-708 and NDA 50-709 - Tacrolimus for the prophylaxis of organ rejection in primary hepatic transplantation.

The major issues in the review of these NDA's have been thoroughly discussed in Marc Cavaillé-Coll's Medical Officer's Review. This memorandum will briefly comment on a few major points that have been discussed at some length during the review process.

1. **Scope of the indication.** The indication sought in these NDA's is for primary liver transplant rejection prophylaxis. A wider indication was discussed with the sponsor on several occasions, including the possibility of review of data to support "liver rescue", i.e. use of tacrolimus to resolve rejection episodes following transplantation in patients being treated with other immunosuppressive regimens (cyclosporine-based). However, it was ultimately agreed that the database to support this expanded indication was not available or included in the NDA, hence the indication sought is limited to primary liver allograft immunosuppression.
2. **Comparisons with "standard" immunosuppressive regimens.** The sponsor has provided adequate data to demonstrate immunosuppressive activity comparable to that of the active control used in the randomized controlled trials, a cyclosporine-based immunosuppressive regimen. In some of the secondary endpoints examined the sponsor believed that the tacrolimus-based regimen was superior to the cyclosporine-based regimen, but these claims were not supported by careful and critical review of the data. The open-label nature of the studies made determination of acute rejection and decisions to escalate immunosuppressive treatments unavoidably biased. The advisory committee agreed after presentation of the results of these studies that the two treatments were equivalent in efficacy, but claims of superiority were not supportable for the secondary endpoints. It should also be made clear to the sponsor that marketing campaigns should not contain comparisons with cyclosporine referring to these secondary endpoints.
3. **Differences between the two major studies.** While similar enough to allow the results of one to support the conclusions of the other, the two major studies do have some striking differences, and these differences have led to a separate description of adverse events for each study in the package insert. The two protocols differed in several design elements, including the degree of immunosuppression used and in the definition and management of rejection episodes. There were also differences in drug dosing, and the apparent differences in incidence of certain AE's may be due in part to different exposures to drug in the two patient populations.
4. **Pharmacokinetic-pharmacodynamic relationships.** An attempt was made during the clinical studies to ascertain blood levels of tacrolimus at various time points during treatment, but the relationships between these observed levels and either immunosuppressive efficacy or systemic

toxicity are not understood. In addition, various assay methodologies were used so that comparing results from one center or time with another is problematic. Hence, the guidance in the package insert on blood level monitoring is necessarily very general. Assay methods are under continuing development and should be standardized and more readily available in the early post-marketing phase. With better understanding of the PK/PD relationships, AE's may be fewer and more easily managed.

5. **Pediatric usage.** There is some experience with pediatric patients contained in the US study, and the labeling reflects this experience as accurately as possible given the limitations of the database. The sponsor has been requested to address the pediatric use of tacrolimus by rapidly developing a suspension dosage form for use in children and by conducting further clinical studies to expand the pediatric safety and PK database.

cc: NDA 50-708
NDA 50-709

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 50708

Trade (generic) names PrografTM (tacrolimus capsules)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

The drug product has some potential for use in children, but there is no reason to expect widespread pediatric use because liver transplantation is uncommon in children less than 16 years old (394 recipients in 1991) and because an alternative drug, cyclosporine, is available for this condition. The sponsor has not submitted a request under 21 CFR 210.58 or 314.126 (c) for a waiver of the requirement at 21 CFR 201.57 (f) for adequate and well controlled studies in children.

FUSA has not requested that information on pediatric dosing be included under **INDICATIONS AND USAGE**. However, the sponsor has included information under *Pediatric Patients* that is not supported by adequate and well controlled trials. In the section on **PRECAUTIONS** the sponsor has included the following information under *Pediatric Patients*:

Successful liver transplants have been performed in pediatric patients (age less than 12 years) using Prograf. One of the two randomized active-controlled trials of Prograf in primary liver transplantation included 51 pediatric patients. Thirty patients were randomized to Prograf and 21 to cyclosporine-based therapies. Additionally, 22 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough levels of tacrolimus similar to adult patients. (See **DOSAGE AND ADMINISTRATION**).

Additional information has been included in the section on **DOSAGE AND ADMINISTRATION** under *Pediatric Patients*:

Pediatric patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations. Therefore, it is recommended that therapy be initiated in pediatric patients at the high end of the recommended adult intravenous and oral dosing ranges (0.1 mg/kg/day intravenous and 0.3 mg/kg/day oral). Dose adjustments may be required.

As part of Phase 4 commitments the sponsor has been encouraged to conduct additional pediatric studies to better characterize the pharmacokinetics, pharmacodynamics, safety and efficacy in children.


Signature of Preparer

2-2-94
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package