8.H.5.9. *Incidence of Common (≥3%) Adverse Events by Duration of IV Treatment*

The incidence of common (≥3% incidence) adverse events was tabulated according to the duration of tacrolimus or cyclosporine IV dosing (Table 18A, Appendix C). The subsets examined were ≤1, 2-4, 5-7, and ≥8 days. However, few patients were treated with IV tacrolimus after day 4, so only the first two subsets will be discussed. Overall and in most body systems, the incidence of adverse events was highest in the ≤1 day subsets of tacrolimus and cyclosporine patients. The exceptions were the Digestive System for both treatment groups, due largely to increases in constipation and diarrhea after day 2, and the Nervous System for cyclosporine patients, due to an increase in headache and insomnia during days 2-4. The high incidences of hypertension (10.0%), hyperglycemia (16.0%), insomnia (11.0%), and kidney function abnormal (11.6%) in the ≤1 day subset of tacrolimus patients represent the earliest post transplant period. These incidences were reduced to 5.5%, 4.2%, 6.6%, and 5.5%, respectively, on days 2-4.

In the nonrandomized trials, the adverse events with the highest incidence on day ≤1 were diarrhea (5.2%), nausea (5.2%), hyperglycemia (3.9%), headache (9.1%), and pruritus (9.1%). The incidence of tremor was highest on days 2-4 (11.8%) (Table 19, Appendix C).

8.H.5.10. *Incidence of Common (≥3%) Adverse Events by Tacrolimus Plasma Trough Levels*

The incidence of common adverse events was tabulated by plasma trough levels (≤1, >1-2, >2-3, or >3 ng/mL) over the 7 days preceding the event for the FPC-FK506-7 and FPC-FK506-9 studies, which used a similar enzyme immunoassay (Table 20, Appendix C). Because of differences in the temperature of separation of plasma from whole blood in the two procedures, this stratification was made separately for the Japanese liver transplantation trial (Table 21, Appendix C).

This analysis reveals no increase of adverse events with plasma trough levels. In fact, several adverse events showed negative correlations with trough levels. The most prominent of these (>10% incidence in the lowest plasma level group) were asthenia, back pain, fever, infection, pain, anorexia, LFT's abnormal, nausea, leukocytosis, hypomagnesemia, headache, paresthesia, and tremor. This apparent negative correlation is probably related to the number of observations available for each trough level. Since the number of observations

decreased several-fold for higher trough levels, a larger number of adverse events fell by chance into the lower trough level group. Only increased serum creatinine showed a trend toward increasing incidence with plasma trough levels (8.0%, 9.3%, 9.1%, 13.1%).

In the FPC-FK506-7 study,[40] the Cox proportional hazards model was used to estimate the relative risk of several adverse events based on the tacrolimus plasma or whole blood trough level. Increased serum creatinine, nausea and vomiting, anorexia, agitation, and hyperkalemia showed positive correlations with the plasma trough levels over the first 90 days. Adverse events which correlated with whole blood trough levels included increased serum creatinine, confusion, insomnia, tremor, somnolence, headache, rash, and pruritus. Thus, there is evidence that some adverse events are correlated with plasma or whole blood trough levels.

8.H.5.11. Incidence of Adverse Events by Tacrolimus Blood Trough Levels in a Controlled Kidney Trial

The incidence of adverse events by body system for the FPC-FK506-10 primary kidney transplant trial (amended sequential therapy) is presented in Table 77 for low, medium, and high tacrolimus target whole blood trough concentrations and for CBIR.[52]

Table 77: Incidence of Adverse Events by Whole Blood Trough Levels in Tacrolimus Patients and Comparative Incidence in CBIR patients in a Controlled Kidney Transplant Trial[a]

Body System	Incidence (%)			
	Tacrolimus			CBIR N = 28
	Low N = 33	Medium N = 30	High N = 29	
Body as a Whole	12 (36.4)	10 (33.0)	13 (44.8)	12 (42.9)
Cardiovascular	8 (24.2)	9 (30.0)	10 (34.5)	7 (25.0)
Digestive	18 (54.5)	12 (40.0)	18 (62.1)	12 (42.9)
Endocrine	0 (0.0)	4 (13.3)	1 (3.4)	1 (3.6)
Hemic/Lymphatic	5 (15.2)	5 (16.7)	4 (13.8)	5 (17.9)
Metabolic/Nutritional	24 (72.7)	25 (83.3)	24 (82.8)	26 (92.9)
Musculoskeletal	2 (6.1)	5 (16.7)	2 (6.9)	3 (10.7)
Nervous	16 (48.5)	18 (60.0)	15 (51.7)	8 (28.6)
Respiratory	5 (15.2)	5 (16.7)	3 (10.3)	2 (7.1)
Skin/Appendages	7 (21.2)	8 (26.7)	10 (34.5)	6 (21.4)
Special Senses	1 (3.0)	1 (3.3)	0 (0.0)	1 (3.6)
Urogenital	16 (48.5)	8 (26.7)	16 (55.2)	9 (32.1)
TOTAL	32 (97.0)	29 (96.7)	29 (100)	27 (96.4)

The incidence of adverse events involving the skin and appendages increased with increasing tacrolimus target trough concentration. The incidence of adverse events in the low and medium target trough concentrations was generally comparable to that in the CBIR patients. The exceptions were metabolic and nutritional disorders, which were higher in the CBIR, and nervous system events, which were higher in the tacrolimus groups.

8.H.6. Incidence of Serious Adverse Events

As discussed above, there were differences in the two primary liver transplantation trials with respect to the duration of data accumulation. In the FPC-FK506-7 study, all adverse events were collected over 12 months,

while in the GHBA-157 study, all adverse events were collected for 6 months and serious adverse events over 12 months. Adverse events in the former trial were characterized as mild, moderate, or severe or life threatening. To define a serious (FDA definition) adverse events category, all severe or life-threatening events, neoplasms, and adverse events leading to hospitalization were combined. In the finalized 6-month GHBA-157 study database, serious, as well as mild, moderate, or severe, adverse events were available. For these integrated tabulations, serious and severe adverse events were combined for the first 6 months, and serious adverse events are presented between months 6 and 12.

For the FPC-FK506-9 study, severe adverse events are presented as serious. For the FPC-FK506-10 (primary kidney) study, severe or life-threatening and serious adverse events are pooled for these tabulations. Because few patients are involved in the kidney study and there was a very low incidence of serious events, these results, while available for review in Appendix C, will not be discussed further.

The overall incidence of serious adverse events over the first six months in the controlled liver transplant trials and 12 months in the nonrandomized trials are shown by body system in Table 78 (Tables 22A and 22B, Appendix C).

Table 78: Incidence of Serious Adverse Events by Body System: Comparison of Tacrolimus and CBIR Patients in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Body System	Incidence (%)			
	Controlled		Nonrandomized	Total
	Tacrolimus N = 512	CBIR N = 511	Tacrolimus N = 141	Tacrolimus N = 653
Body as a Whole	124 (24.2)	141 (27.6)	24 (17.0)	148 (22.7)
Cardiovascular	101 (19.7)	83 (16.2)	12 (8.5)	113 (17.3)
Digestive	134 (26.2)	134 (26.2)	20 (14.2)	154 (23.6)
Endocrine	15 (2.9)	1 (0.2)	0 (0.0)	15 (2.3)
Hemic/Lymphatic	34 (6.6)	35 (6.8)	7 (5.0)	41 (6.3)
Metabolic/Nutritional	62 (12.1)	48 (9.4)	17 (12.1)	79 (12.1)
Musculoskeletal	6 (1.2)	8 (1.6)	3 (2.1)	9 (1.4)
Nervous	94 (18.4)	56 (11.0)	22 (15.6)	116 (17.8)
Respiratory	67 (13.1)	54 (10.6)	15 (10.6)	82 (12.6)
Skin/Appendages	13 (2.5)	4 (0.8)	5 (3.5)	18 (2.8)
Special Senses	3 (0.6)	3 (0.6)	0 (0.0)	3 (0.5)
Urogenital	69 (13.5)	44 (8.6)	14 (9.9)	83 (12.7)
TOTAL	338 (66.0)	308 (60.3)	68 (48.2)	406 (62.2)

Table 79 compares the overall and serious incidence figures for the most common adverse events in tacrolimus or CBIR patients in the comparative liver transplant trials.

Table 79: Total and Serious Incidence of the Overall Most Frequently Reported Adverse Events in Controlled Liver Transplant Trials

Adverse Event	Overall Incidence (%)		Serious (%)	
	Tacrolimus	CBIR	Tacrolimus	CBIR
Abdominal Pain	42.0	36.8	4.1	3.9
Asthenia	29.1	25.6	1.0	0.6
Fever	31.3	36.8	5.1	4.5
Infection	33.6	39.1	3.3	7.0
Pain	40.6	35.2	1.2	1.8
Hypertension	38.9	44.8	0.6	2.0
Anorexia	19.7	13.7	1.0	0.0
Constipation	21.7	23.5	0.2	0.0
Diarrhea	51.6	34.6	1.8	1.2
LFT Abnormal	20.1	15.9	3.3	3.5
Nausea	37.9	29.4	1.8	0.6
Vomiting	18.9	11.7	1.0	0.6
Anemia	25.2	19.0	2.0	1.6
Creatinine Increased	28.9	20.4	3.3	1.2
Hyperglycemia	37.9	26.8	1.6	0.8
Hyperkalemia	26.8	16.4	1.2	1.4
Hypomagnesemia	31.1	26.4	0.2	0.4
Peripheral Edema	17.8	18.0	0.4	0.2
Headache	46.9	39.1	2.1	1.4
Insomnia	46.5	43.6	0.6	0.0
Paresthesia	27.0	21.3	1.0	0.0
Tremor	49.6	37.6	1.4	0.2
Pleural Effusion	31.1	30.3	2.5	1.0
Hirsutism	3.3	19.4	0.0	0.0
Pruritus	23.2	12.3	0.2	0.0
Kidney Function Abnormal	36.5	22.5	5.5	3.1

See Tables 6A and 22B, Appendix C.

Although these adverse events were common overall and showed differences between the treatment groups, when serious events were considered, the incidence was lower and many events showed less or no differences between treatment groups.

An alternative approach is followed in Table 80, where serious adverse events with an incidence of ≥2% are presented, along with their overall incidences.

Table 80: Total and Serious Incidence of the Most Frequently Reported Serious Adverse Events in Controlled Liver Transplant Trials

Adverse Event	Overall Incidence (%)		Serious (%)	
	Tacrolimus N = 512	CBIR N = 511	Tacrolimus N = 512	CBIR N = 511
Abscess	8.8	7.6	2.1	2.5
Peritonitis	3.5	3.7	2.0	2.5
Sepsis	12.9	17.4	6.1	6.8
Arterial Thrombosis	2.7	3.5	2.5	2.9
Heart Arrest	2.3	1.6	2.1	1.6
Hemorrhage	12.1	9.6	3.9	1.8
Hypotension	10.9	10.0	2.9	2.7
Cholangitis	11.5	13.9	1.0	2.3
GI Disorder	7.6	10.4	2.7	4.1
GI Hemorrhage	7.0	6.5	1.8	2.5
GI Perforation	7.8	5.3	3.9	2.2
Hepatitis	9.4	7.8	3.5	4.7
Liver Damage	3.9	3.7	2.0	1.2
Diabetes Mellitus	10.2	4.7	2.7	0.2
Thrombocytopenia	16.4	16.8	2.3	2.5
SGOT Increased	6.3	6.1	1.4	2.0
Confusion	12.7	7.0	2.0	0.2
Convulsion	5.5	4.9	2.0	2.9
Neuropathy	6.4	6.7	2.1	0.4
Dyspnea	15.6	12.3	2.7	2.2
Pneumonia	11.5	12.3	3.7	4.1
Respiratory Disorder	5.3	5.7	2.3	2.0
Kidney Failure	6.1	4.7	4.9	2.7

See Tables 6A and 22B, Appendix C.

In this tabulation, approximately half of the serious adverse events were higher in incidence in the CBIR and half in the tacrolimus patients. Most of the differences between the two treatment groups were small.

Tables 22C and 22D (Appendix C) tabulate the incidence of serious adverse events over 0-180 days and 0-360 days for the FPC-FK506-7 and 0-183 and 0-360 days for the GHBA study. Further discussion of serious adverse events will include the complete databases of these trials and nonrandomized trials.

8.H.6.1. Incidence of Serious Adverse Events by Gender

The overall incidences of serious adverse events in male (N = 325) and female (N = 328) tacrolimus patients enrolled in liver transplant studies were comparable at 63.4% and 63.1%. However, within the COSTART body systems, some differences (≥2% reported here) were notable (Table 23, Appendix C). Infection (5.5% vs. 3.0%), sepsis (7.7% vs. 4.0%), and shock (2.5% vs. 0.0%) were higher in males than females. Hypotension (5.5% vs. 1.8%) was higher in males, but the incidence of serious hypertension was comparable (0.9% vs. 0.3%) and low.

GI perforation (4.0% vs. 2.1%) and hepatitis (4.3% vs. 1.8%) were also more common in males, as were apnea (3.1% vs. 0.3%), dyspnea (3.7% vs. 1.8%), and pneumonia (5.5% vs. 3.0%).

The incidence of Nervous System serious adverse events was low, except for headache (4.3% vs. 4.6%), which was comparable by gender.

Serious adverse events related to nephrotoxicity which were higher in males were kidney failure (6.5% vs. 4.0%) and kidney function abnormal (6.2% vs. 4.0%). Other serious events were comparable in incidence: BUN increased (1.2% vs. 1.2%), creatinine increased (3.4% vs. 2.4%), and oliguria (1.5% vs. 1.5%).

Overall, serious adverse events with a disparate incidence were more common in males than females.

8.H.6.2. Incidence of Serious Adverse Events by Age

The comparative incidence of serious adverse events in pediatric (≤12 years) and adult (>12 years) tacrolimus patients was tabulated (Table 22E, Appendix

C). A further tabulation was made stratified by age groups (Table 24, Appendix C), but the small numbers prevent many conclusions.

In the Body as a Whole, abdominal pain (1.4% vs. 5.4%) was more common in adults. Fever (9.5% vs. 4.3%) was more common in pediatric patients and infection (5.4% vs. 4.1%) and sepsis (5.4% vs. 5.9%) were comparable in incidence.

In the Cardiovascular System, arterial thrombosis (4.1% vs. 1.7%), heart arrest (4.1% vs. 2.1%), hypotension (5.4% vs. 3.5%), and thrombophlebitis (2.7% vs. 0.5%) were more common in pediatric patients. In addition GI hemorrhage (6.8% vs. 1.4%) was more common in pediatric patients. These serious adverse events are likely to be related to the difficult nature of liver transplantation in pediatric patients.

GI disorder (0.0% vs. 2.6%) and GI perforation (0.0% vs. 3.5%) were more common in adults and intestinal perforation (2.7% vs. 0.0%) and liver function tests abnormal (5.4% vs. 3.5%) in pediatric patients. Diabetes mellitus (0.0% vs. 2.4%) was more common in adults, whereas hyperglycemia (2.7% vs. 1.7%) was comparable in incidence. Coagulation disorder (4.1% vs. 0.7%) was more common in pediatric patients. Lymphoma-like reactions were seen in two pediatric (2.7%) and four adult (0.7%) patients. Acidosis (4.1% vs. 0.7%) and hypomagnesemia (2.7% vs. 0.0%) were more common in pediatric patients.

Of serious events possibly related to neurotoxicity, convulsion (4.1% vs. 1.9%) was more common in pediatric and headache (0.0% vs. 5.0%) in adult patients. Paresthesia (0.0% vs. 0.9%) and tremor (0.0% vs. 1.7%) were only seen in adults.

Of serious events possibly related to nephrotoxicity, hyperkalemia (0.0% vs. 2.2%), kidney failure (2.7% vs. 5.5%), and kidney function abnormal (2.7% vs. 5.4%) were more common in adults. Oliguria (4.1% vs. 1.2%) was more common in pediatric patients.

An examination of serious adverse events in pediatric patients aged 1-3 years versus the overall population revealed a higher incidence of certain adverse events in these young patients (Table 24, Appendix C). These included fever (13.3% vs. 4.9%), sepsis (8.9% vs. 5.8%), heart arrest (6.7% vs. 2.3%), hypotension (8.9% vs. 3.7%), GI hemorrhage (8.9% vs. 2.0%), liver function tests abnormal (8.9% vs. 3.7%), and coagulation disorder (6.7% vs. 1.1%). These are likely to reflect the very complicated liver transplantation operation

in these young patients and the underlying multiorgan dysfunction which led to the requirement for liver transplantation. Notably, nephrotoxicity appears to be lower in these patients than in the overall population.

Overall, these tabulations support the relative safety of tacrolimus in pediatric liver transplant patients.

8.H.6.3. Incidence of Serious Adverse Events by Race

One or more serious adverse events were reported in 340/528 (64.4%) of caucasian, 19/32 (59.4%) of black, 17/40 (42.5%) of oriental, and 31/45 (68.9%) of hispanic tacrolimus patients (Table 25A, Appendix C). Because of low numbers of noncaucasians in these studies, no definitive conclusions could be reached.

8.H.6.4. Incidence of Serious Adverse Events by Daily IV Dose at Onset

Serious adverse events were tabulated, stratified by the daily tacrolimus IV dose at onset of the events (Table 27, Appendix C). There was no correlation between dose and serious adverse events overall or in any body system. Only kidney function abnormal showed an apparent increase with IV dose (1.1%, 1.4%, 3.1%), but the numbers of patients involved were 4, 5, and 5 at the three dose levels examined.

8.H.6.5. Incidence of Serious Adverse Events by 3-Day Average Oral Dose at Onset in Adult Patients

The incidence of serious adverse events was tabulated, stratified by the 3-day average daily tacrolimus oral dose at onset of the events (Table 28, Appendix C). This stratification was only made in adult patients, as the number of pediatric patients was too low to allow for any definitive conclusions and oral dosing was higher in pediatric patients. In this analysis in adult patients, no correlations with oral tacrolimus dose were noted. The overall serious adverse events incidence showed a negative correlation with dose.

8.H.6.6. Incidence of Serious Adverse Events by Route of Administration

The incidence of serious adverse events was tabulated by the route of tacrolimus administration at onset of the events in patients in liver

transplantation trials (Table 29, Appendix C). Serious adverse events which occurred with a ≥2% frequency between the two groups (oral vs. IV) were abdominal pain (4.5% vs. 0.5%), fever (5.1% vs. 0.0%), infection (3.8% vs. 0.7%), sepsis (4.6%, 1.8%), GI perforation (2.7% vs. 0.5%), hepatitis (3.2% vs. 0.0%), hyperkalemia (2.1% vs. 0.0%), headache (4.1% vs. 0.5%), and pneumonia (4.3% vs. 0.2%). None of these differences is unexpected as IV dosing duration was generally limited to 4 days or less in these tacrolimus patients. Serious infections and other complications such as those described above are expected to manifest themselves several days after surgery.

Serious adverse events related to nephrotoxicity [e.g., kidney failure (3.5% vs. 2.0%) and kidney function abnormal (3.0% vs. 2.5%)] were reported in a disproportionate percentage of patients during IV tacrolimus dosing. This finding, along with a concern that patients early post transplant might be more susceptible to nephrotoxic insult, led to the recommendation for lower initial IV tacrolimus dosing in clinical trials and in the proposed tacrolimus labeling.

8.H.6.7. Incidence of Serious Adverse Events by Duration of Oral Dosing

The incidence of serious adverse events was tabulated by the duration of oral dosing of tacrolimus or CBIR at onset of the events in patients in controlled liver transplantation trials (Table 30A, Appendix C).

In keeping with the findings in the discussion above, fever, infection, and sepsis of a serious nature appeared predominantly in the days 15-28 and 29-90 subgroups. These serious infections or possible infection were higher in incidence in the CBIR groups compared to tacrolimus-treated patients. Serious pneumonia increased in incidence in the day 29-90 and 91-180 subgroups, and was slightly higher in incidence in the tacrolimus than the CBIR patients.

Severe hepatitis was reported in both treatment groups in the intervals 15-28, 29-90, and 91-180 days. This incidence two weeks or later after transplantation is not unexpected and could be due to recurrent hepatitis that necessitated transplantation or hepatitis acquired as a result of the donor organ.

Serious GI disorder and GI perforation also increased in incidence between days 15 and 180. However, the COSTART designation GI perforation encompasses a wide number of surgically related events; within the limitations of COSTART coding, biliary leaks were categorized as GI perforations.

Serious abnormal liver function tests were reported with increased incidence in patients in both treatment groups between days 29 and 180. However, this adverse event is probably related to rejection episodes, and was higher in incidence in the CBIR group.

Kidney failure and kidney function abnormal were reported with a higher incidence in tacrolimus patients compared with CBIR patients in the first week after oral treatment.

8.H.6.8. *Incidence of Serious Adverse Events by Duration of IV Dosing*

The incidence of serious adverse events was stratified by treatment group and the duration of IV dosing at the onset of the events (Table 31A, Appendix C). Because of the low incidence seen, few definitive conclusions could be made. The incidence of serious sepsis was highest (15.2%) in patients treated with IV tacrolimus on day ≥8. Serious kidney function abnormal was highest (2.1%) on day ≤1 in tacrolimus patients.

8.H.6.9. *Incidence of Serious Adverse Events by Plasma Trough Levels*

The incidence of serious adverse events was stratified by the tacrolimus plasma trough level for the 7 days preceding the events (Table 32A, Appendix C). The highest incidence of adverse events was seen at the lowest trough level. Because of low incidence across stratifications, no conclusions were possible.

8.H.7. Deaths and/or Discontinuations Due to Adverse Events

A total of 107 tacrolimus patients discontinued the controlled studies and 23 discontinued the nonrandomized studies because of adverse events. In the controlled trials, 63 CBIR patients discontinued because of adverse events. The reasons patients discontinued the studies is shown by body system in Table 81 (Table 35, Appendix C). Capsule summaries of each of these patients are contained in the individual Clinical Study Reports.

Table 81: Incidence of Adverse Events Leading to Discontinuation

Body System	Controlled Tacrolimus N = 618	Nonrandomized Tacrolimus N = 141	Controlled CBIR N = 545
Body as a Whole	20 (3.2)	5 (3.5)	20 (3.7)
Cardiovascular	37 (6.0)	2 (1.4)	28 (5.1)
Digestive	29 (4.7)	6 (4.3)	32 (5.9)
Endocrine	2 (0.3)	0 (0.0)	0 (0.0)
Hemic/Lymphatic	12 (1.9)	3 (2.1)	9 (1.7)
Metabolic/Nutritional	23 (3.7)	5 (3.5)	16 (2.9)
Musculoskeletal	2 (0.3)	1 (0.7)	4 (0.7)
Nervous	37 (6.0)	4 (2.8)	16 (2.9)
Respiratory	20 (3.2)	3 (2.1)	12 (2.2)
Skin/Appendages	4 (0.6)	1 (0.7)	1 (0.2)
Urogenital	28 (4.5)	7 (5.0)	13 (2.4)

The incidence of discontinuations due to adverse events involving the Body as a Whole was slightly higher for the CBIR patients. Fever resulted in the discontinuation of 4 tacrolimus controlled, 0 tacrolimus nonrandomized, and 8 CBIR patients. Infections led to discontinuation of 3 tacrolimus controlled, 1 tacrolimus nonrandomized, and 1 CBIR patients. Sepsis resulted in the discontinuation of 8 tacrolimus controlled, 2 tacrolimus nonrandomized, and 10 CBIR patients. Other adverse events were noted in 1 or 2 patients in any group, except abdominal pain, which resulted in discontinuation of 2 tacrolimus controlled, 2 tacrolimus nonrandomized, and 3 CBIR patients.

The major reasons for discontinuation involving the cardiovascular system were arterial thrombosis (9 tacrolimus controlled, 0 tacrolimus nonrandomized, and 12 CBIR patients), heart arrest (8, 1, 3), hypotension (13, 1, 7), and tachycardia (4, 0, 2). Overall, more tacrolimus patients than CBIR patients discontinued because of such adverse events.

Discontinuation because of Digestive Tract adverse events was higher for CBIR patients than tacrolimus patients. GI hemorrhage, led to discontinuation of

no tacrolimus and 7 CBIR patients. Other adverse events which led to numerous discontinuations were cholangitis (0, 0, 3) hepatic failure (8, 0, 5), hepatitis (1, 0, 4), and liver function tests abnormal (7, 0, 5).

Two tacrolimus patients in controlled studies discontinued because of diabetes mellitus. Adverse events involving the Hemic/Lymphatic systems which led to multiple discontinuations were anemia (3, 0, 3), lymphoma-like reaction (0, 3, 0), and thrombocytopenia (4, 0, 1).

Metabolic and Nutritional adverse events related to liver dysfunction which led to multiple discontinuations were bilirubinemia (3, 2, 2) and SGOT increased (3, 0, 2). One incidence each of myopathy and twitching in controlled tacrolimus patients, arthralgia in a nonrandomized patient, and bone disorder, bone neoplasm, osteoporosis, and twitching in CBIR patients led to discontinuation.

Nervous system adverse events leading to discontinuation were more common in tacrolimus patients than CBIR patients in the controlled studies. Adverse events which led to multiple discontinuations were coma (6, 1, 3), convulsion (7, 1, 2), encephalopathy (4, 0, 1), grand mal convulsion (3, 1, 1), psychosis (4, 0, 1), and thinking abnormal (4, 0, 1). Respiratory adverse events which led to multiple discontinuations included apnea (5, 0, 3), dyspnea (8, 0, 4), pneumonia (6, 2, 4), and respiratory disorder (4, 1, 2). Single cases of epidermal necrolysis and rash in controlled tacrolimus patients and pruritus in a nonrandomized patient led to discontinuation.

Adverse events related to nephrotoxicity which led to multiple discontinuations were increased serum creatinine (6, 2, 3), hyperkalemia (2, 0, 3), kidney failure (9, 3, 5), kidney function abnormal (8, 3, 3), and oliguria (6, 0, 2).

Overall, 73 of 512 tacrolimus (14.3%) patients and 83 of 511 CBIR (16.2%) patients enrolled in controlled liver studies died. In the nonrandomized liver studies, 32 of 141 (22.7%) patients died. In the controlled kidney trials, 1 of 106 tacrolimus (0.9%) and 2 of 34 CBIR (5.9%) patients died (Table 36, Appendix C).

The specific causes of death are given in Table 37, Appendix C. The main causes were cardiac arrest, infections or sepsis, multiorgan failure, and hepatic failure or hepatitis. Infections or sepsis were contributing causes of death in a number of patients.

8.H.8. Clinical Laboratory Assessments

Clinical laboratory data are presented in Tables L001 through L115 in Appendix C. The data are presented according to the type of study: controlled or nonrandomized and by organ. The following discussion will address the laboratory data according to the issues of nephrotoxicity, impaired glucose metabolism, liver function tests, and hematology in liver and kidney transplant patients.

8.H.8.1. Laboratory Parameters Relative to Potential Nephrotoxicity

The following clinical laboratory parameters were evaluated for potential drug-related nephrotoxic effects:

- Glomerular filtration rate (GFR)
- Serum creatinine
- Serum potassium
- Serum uric acid
- Blood urea nitrogen (BUN)

In controlled liver transplantation trials, the mean GFR showed a decrease from baseline to days 21-35 in both tacrolimus and CBIR patients. In tacrolimus patients, the GFR decreased from 84.6 to 55.1 mL/min and that in CBIR patients decreased from 89.2 to 63.6 mL/min. On days 330-390, the mean GFR was 58.8 mL/min in tacrolimus (N = 85) and 62.6 mL/min in CBIR (N = 72) patients (Table L001 Appendix C).

BUN values increased in both treatment groups in controlled liver transplantation trials, reached a maximum during week 1 post transplantation, and remained elevated over the first two weeks post transplantation (Table L002, Appendix C). The numbers of patients with values greater than the upper limit of the normal range (ULN), >2 times ULN, and >3 times ULN were higher in the tacrolimus group than in the CBIR group. In the nonrandomized liver trials, BUN increased initially, then decreased to values just above baseline (Table L004, Appendix C).

The mean serum creatinine, potassium, and uric acid over time in tacrolimus- and CBIR-treated patients in FPC controlled liver transplant trials is shown in Table 82 (Tables L010, L024, and L032, Appendix C).

Table 82: Mean (± SD) Serum Creatinine, Potassium, and Uric Acid (mg/dL) in Tacrolimus and CBIR Patients in FPC Controlled Trials in Liver Transplantation

Day	Creatinine		Potassium		Uric Acid	
	Tacrolimus	CBIR	Tacrolimus	CBIR	Tacrolimus	CBIR
0	1.3 ± 0.8	1.3 ± 0.8	4.2 ± 0.6	4.2 ± 0.6	4.8 ± 2.0	5.2 ± 4.7
Wk 1	1.4 ± 1.0	1.3 ± 0.9	4.3 ± 0.4	4.1 ± 0.6	7.1 ± 3.1	5.8 ± 3.1
Wk 2	1.4 ± 0.8	1.3 ± 0.9	4.6 ± 0.7	4.4 ± 0.6	6.7 ± 2.7	5.8 ± 2.8
Wk 4	1.3 ± 0.8	1.3 ± 0.7	4.4 ± 0.6	4.4 ± 0.6	6.4 ± 2.1	6.0 ± 2.5
Mo 3	1.4 ± 0.6	1.3 ± 0.5	4.4 ± 0.6	4.3 ± 0.6	7.1 ± 2.3	7.1 ± 2.7
Mo 6	1.4 ± 0.6	1.3 ± 0.5	4.5 ± 0.7	4.3 ± 0.6	6.8 ± 1.9	7.0 ± 1.9
Mo 12	1.5 ± 0.6	1.5 ± 0.5	4.6 ± 0.5	4.3 ± 0.5	6.9 ± 1.7	7.0 ± 1.9

Serum creatinine concentrations increased to a similar degree from baseline in patients treated with tacrolimus or CBIR in controlled FPC liver transplant trials. The mean increase from baseline was 0.1 to 0.3 mg/dL at any time point and highest at months 6 and 12 post transplant in both treatment groups. While more tacrolimus patients had serum creatinine greater than the (ULN) or >2 times the ULN during the first two weeks of the study, comparable numbers of patients in the two groups had values >3 times the ULN.

Mean serum potassium values increased in both treatment groups. Overall, more tacrolimus patients had values greater than ULN during the study than CBIR patients.

Mean serum uric acid values also increased in both tacrolimus and CBIR patients. More tacrolimus than CBIR patients had values greater than the ULN, especially early post transplant.

Mean serum creatinine levels increased from baseline in tacrolimus-treated liver transplant patients in nonrandomized studies (Table L034, Appendix C). The increase was comparable to that seen in tacrolimus patients in controlled trials, reaching a maximum mean value of 1.91 mg/dL. A few patients had values >2 or >3 times ULN. A high mean value of 5.1 mg/dL at month 12 appears to be due to a single outlier, as the median is 1.6 mg/dL.

Mean serum potassium in the nonrandomized tacrolimus patients increased from baseline to a slightly higher degree than noted in the controlled trials; mean values remained <4.9 mg/dL (Table L009, Appendix C). Mean serum uric acid levels increased from baseline in these patients. The increase was also slightly higher than that in controlled liver transplant patients. Mean BUN values were also noted to increase initially, reaching a maximum in week 2 in these liver transplant patients.

Thus, the above parameters indicate a nephrotoxic potential for both tacrolimus and CBIR in liver transplant and rescue patients.

In kidney transplant patients, serum creatinine levels are more a measure of efficacy than safety. As expected in such patients, serum creatinine fell from a high of 4.15 mg/dL on day 0 to 2.10 mg/dL on day 42 in tacrolimus-treated patients (Table L033, Appendix C).

Serum potassium showed an increase from baseline (4.07 mEq/L) to day 42 (4.77 mEq/L) in the kidney transplant patients (Table L008, Appendix C).

8.H.8.2. Laboratory Parameters Relative to Impaired Glucose Metabolism

Mean blood glucose was highest at baseline in both tacrolimus and CBIR groups in the controlled liver transplant trials. Thereafter, it decreased in both groups. The mean values at most time points were slightly lower in the CBIR patients, except at month 12 where it was lower in tacrolimus patients. In parallel, the number of patients with values 1-3-fold the ULN was slightly higher in the tacrolimus group through month 6 (Table L105, Appendix C). In the nonrandomized liver transplant patients, blood glucose showed an initial increase over the first 4 weeks, then decreased through month 12 (Table L107, Appendix C). The mean values in these patients were comparable to those in the controlled trials.

8.H.8.3. Laboratory Parameters Relative to Liver Function

The following laboratory parameters relative to liver function and toxicity were examined:

- SGPT/ALT
- SGOT/AST
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- GGTP

Mean SGPT/ALT were elevated at baseline in both treatment groups in the controlled liver transplant trials. Thereafter, the levels decreased over time. Mean values after about week 2 were within or near the normal range and were comparable in tacrolimus- and CBIR-treated patients. Mean SGOT/AST showed a similar pattern of increased baseline, but normal or near normal mean values were achieved within week 1 of transplantation and maintained throughout the study. A few patients at each time point post transplantation had SGPT and/or SGOT values 1-3 times the ULN. In the nonrandomized trials, mean SGPT/ALT and SGOT/AST were elevated at baseline, but decreased steadily throughout the study. These mean values, however, generally remained just above the normal range.

Mean direct bilirubin showed an initial increase during week 1 in the tacrolimus and weeks 1 and 2 in the CBIR group in the controlled liver transplant studies. Following this, the mean values in both treatment groups decreased, with a faster decrease in the tacrolimus patients. In the nonrandomized trials, mean direct bilirubin was elevated at baseline (several-fold higher than in the controlled patients) and showed a steady decrease throughout the study. Although the number of patients followed after 90 days was small, normalization of the mean value occurred in these patients. A similar pattern was seen with total bilirubin in controlled and nonrandomized studies.

Alkaline phosphatase and GGTP increased from baseline over the first weeks post transplantation in both treatment groups in the controlled liver transplant trials, then slowly decreased, but generally remained higher than baseline. Alkaline phosphatase decreased from baseline within 1 week in the nonrandomized studies and remained stable thereafter, whereas GGTP values decreased throughout the trial. The baseline values in the nonrandomized study were several-fold higher than those in the controlled trials.

In the kidney transplant studies, SGOT and SGPT were normal at baseline and day 42. No patients had values >ULN at either of these time points. This was also the case with total and direct bilirubin.

8.H.8.4. Laboratory Parameters Relative to Hematology

Mean platelet counts decreased initially in the controlled and nonrandomized liver transplantation studies (Tables L038A, L038B, L040A, and L040B, Appendix C). In tacrolimus and CBIR patients in the controlled trials, mean platelet counts were <100,000/µL at baseline, <150,000/µL during the first week, and generally >200,000/µL during the remainder of the study. The mean in the nonrandomized patients was >200,000/µL, except at months 6 and 12. The platelet count increased rapidly in the controlled trials, but remained below baseline in the nonrandomized trials. This decrease in platelet count, probably reflects effects related to surgery in the controlled patients. The reason for a sustained decrease in the nonrandomized trials is unclear.

The erythrocyte count generally showed a mild decrease or little change in the first weeks after transplantation in both tacrolimus and CBIR patients in the controlled liver transplantation trials and a mild decrease in the nonrandomized trials (Tables L041A, L041B, L043A, and L043B, Appendix C). Following this the erythrocyte count increased and stabilized for the remainder of the study in both controlled and nonrandomized trials. However, at every time point examined, about half of the patients had counts below the lower limit of the normal range. Mean changes in hemoglobin and hematocrit paralleled the changes in the erythrocyte count.

In kidney transplant patients, the mean platelet count increased post transplantation and was >250,000/µL on day 42 (Tables L039A,B, Appendix C). The mean erythrocyte count increased slightly post transplantation (Tables L042A,B, Appendix C). Mean changes in the hemoglobin and hematocrit paralleled these changes in the erythrocyte count.

The lymphocyte count increased post transplantation in controlled liver and kidney transplant patients and in patients in the nonrandomized liver trials. The leukocyte count decreased after week 2 in tacrolimus and CBIR patients in controlled trials and tacrolimus patients in nonrandomized liver trials. In contrast, the leukocyte count increased from baseline to day 42 in the kidney transplant patients.

8.H.8.5. Laboratory Parameters Relative to Lipid Metabolism

Low-density lipoprotein values decreased initially from baseline (105-107 mg/dL) in tacrolimus and CBIR patients in controlled liver transplant trials. By month 12, values in the tacrolimus patients were just below baseline levels (99.5 mg/dL), whereas those in CBIR patients were greater than baseline (138.5 mg/dL) (Table L078A, Appendix C). High-density lipoprotein levels increased over time in both treatment groups, with values at month 12 of 45.0 and 49.2 mg/dL, respectively.

Mean serum cholesterol increased from baseline in both treatment groups in controlled liver transplant trials. However, mean cholesterol increased from 148.6 to 161.6 mg/dL in tacrolimus and from 147.0 to 222.5 mg/dL in the CBIR patients from baseline to month 12 (Table L089, Appendix C). Serum triglycerides also increased from baseline to month 12 in both groups: from 90.8 to 156.2 mg/dL in tacrolimus and from 102.4 to 215.9 mg/dL in CBIR patients (Table L096, Appendix C).

From these laboratory parameters, it is evident that tacrolimus has less adverse effects on lipid metabolism than CBIR. The long-term effects of lower LDL, triglycerides, and cholesterol values may translate into less cardiovascular complications associated with these parameters in tacrolimus patients.

8.H.9. Safety Data From Published Clinical Trials

Since tacrolimus has not been marketed in any country until the June 7, 1993 launch in Japan, safety data are largely limited to the database previously described and to published literature, largely from the University of Pittsburgh. The world literature is searched regularly for publications relevant to tacrolimus. (The scope of this effort was described in Section 8.F.)

These literature-derived safety data are presented as supportive evidence of the relative safety of tacrolimus, primarily in liver transplantation. There were no additional adverse events reported from the University of Pittsburgh in liver transplantation that did not appear in the ISS database. The major categories of adverse events reported by this center involve neurotoxicity, nephrotoxicity, GI disturbances, glucose metabolism disorders, infectious complications, and neoplasms. The incidence of adverse events contained in the various publications from this single center generally show an advantage for tacrolimus over CBIR (randomized or historical). The published results

from the University of Pittsburgh in liver and kidney transplantation (the second largest experience at this center) will be presented.

The incidence of adverse events or deaths from studies of tacrolimus in other indications will be summarized briefly. Adverse events reported in all of these individual studies were summarized in Sections 8.D. through 8.F. The cited literature is contained in Section 8.N. in the order of citation. All clinical literature is contained in alphabetical order, by author, in Section 8.O.

8.H.9.1. Safety Data From Liver Transplantation Trials Reported in the Literature

The University of Pittsburgh has published the results of a number of studies in liver transplantation. The overall incidence of adverse events in such trials is extremely difficult to determine from the publications from this center, as only significant or key adverse events are summarized. Safety data from these studies are summarized below. Differences reported between publications on the same patient population are presented.

Table 83. Incidence (%) of Adverse Events in a Non-FPC Controlled Liver Transplant Trial[43]

Adverse Event	Tacrolimus N = 41	CBIR N = 40
Blurred Vision	(13.2)	(13.1)
Chest Pain	(3.7)	(2.2)
Decreased Appetite	(9.9)	(8.8)
Diarrhea	(11.7)	(12.8)
Dizziness	(4.6)	(5.9)
Fatigue	(12.0)	(8.8)
Gas Pain	(16.2)	(16.3)
Hair Growth	(5.2)	(14.1)
Hair Loss	(10.1)	(7.5)
Headache	(23.7)	(16.3)
Hyperesthesia	(21.3)	(28.5)
Musculoskeletal	(20.6)	(26.7)
Increased Appetite	(8.3)	(7.2)
Insomnia	(41.0)	(28.5)
Nausea	(8.3)	(6.7)
Nightmares	(5.0)	(2.8)
Photophobia	(10.7)	(11.7)
Pruritus	(10.4)	(10.7)
Shortness of Breath	(5.5)	(5.0)
Sweating	(7.7)	(6.1)
Tinnitus	(6.4)	(11.2)
Tremors	(24.0)	(24.0)

While the reported terms differ from the COSTART dictionary used by FUSA, all of these adverse events are also present in the ISS database at incidence

levels comparable to or higher than those reported in this single-center experience.

The University of Pittsburgh investigators have published reviews of the safety of tacrolimus in all transplantation patients (Fung *et al.*[93]) and in primary liver transplantation (Alessiani *et al.*[97]). Results reported for 370 primary liver transplant patients (417 grafts) are presented in Table 84.

Table 84: Number of Patients with Adverse Events Reported in Primary Liver Transplantation (N = 370 Patients; N = 417 Grafts)

Adverse Event	Pre-existing	During Study		Total	Recovered
		Early	Late		
Nephrotoxicity	31			200	92
Hypertension	14			122	13
Hyperkalemia				239	64
Diabetes	25	61[a]	18[a]	151[b]	106[b]
Neurotoxicity				31	29
Dialysis				75	51
Lymphoproliferative Disorder				16[b]	3[b]
CMV Infection				20%[b]	

a: Alessiani *et al.*, 1993[97]
b: Fung *et al.*, 1991[93]

The specific incidence of adverse events defined as neurotoxicity was further tabulated (Table 85).

Table 85: Incidence of Reported Adverse Events Related to Neurotoxicity (N = 31 Incidences)

Adverse Event	Fung *et al.*, 1991[96]	Alessiani *et al.*, 1993[97]
Seizure	10	12
Delirium		11
Dysarthria	5	5
Coma	4	4
Confusion	12	

The reasons for the discrepancies in these two reports are unknown, although characterization as confusion or delirium appears to be a choice of terms. Assuming that the number of seizures is indeed 12, the percentage in all patients (12/370) is 3.2%. This is lower than the incidence reported in FPC-sponsored studies.

CMV (cytomegalovirus) infections were not specifically collected in sponsored studies. The University of Pittsburgh focused on such infections, as CMV was considered the most common opportunistic infection in transplant patients.[93] However, the incidence of infections in which CMV might be the primary pathogen in sponsored studies is in-line with the reported incidence of CMV infections reported in primary liver transplantation patients at this single center.

While lymphoproliferative disorders are discussed in one publication,[98] only an overall incidence of 16 patients (of 1057 total) is presented.

Reported causes of death in a study of 210 primary liver transplantation patients were sepsis (3.3%), intraoperative (0.8%), heart failure (0.8%), stroke (0.8%), and fulminant failure (0.8%).[98] Adverse events in these patients included expressive aphasia (N = 2), tremors, paresthesias, increased sensitivity to light, insomnia, mood changes, and new-onset diabetes. Hirsutism, gingival hyperplasia, and gynecomastia were not reported, although a few cases of alopecia were reported. When a group of 125 patients was considered (110 adult and 15 pediatric; same population with a few added patients), an additional death due to hepatic coma was noted.[99]

Reported causes of death (N = 14) in a study of 173 patients converted to tacrolimus were sepsis (N = 4), hemorrhagic complications (N = 3), metastatic

carcinoma (N = 3), liver allograft failure (N = 2), technical complications of retransplant (N =1), and unknown (N = 1).[99]

One of the earliest clinical publications on tacrolimus was reported from the University of Pittsburgh.[11] They reported on adverse events in 40 patients converted from cyclosporine-based therapy to tacrolimus. A higher rate of adverse events was reported in these patients than seen in later studies, but the types of events were comparable to those reported later.

In this study, headaches were reported in 70% of patients treated with IV tacrolimus, but these were less with oral tacrolimus. Anorexia was reported in all but 2 of the patients who received IV tacrolimus. The incidence of other reported adverse events is shown in Table 86.

Table 86: Incidence of Adverse Events in Patients Converted From Cyclosporine-Based Therapy to Tacrolimus

Adverse Event	Incidence (%)
Nausea	65%
Vomiting	35%
Warmth	61%
Flushing	16%
Rash	10%
Chest Pain	10%
Anxiety	10%
Abdominal Cramping	<5%
Night Sweats	
Fatigue	
Photophobia	
Blurred Vision	
Hyperkalemia	35%

Therefore, examination of these published results reveals no adverse events not captured in the ISS database and supports the relative safety of tacrolimus in liver transplantation and rescue.

8.H.9.2. Safety Data From Kidney Transplantation Trials Reported in the Literature

Phase II early and late kidney transplantation trials conducted by Fujisawa Pharmaceutical Co, Ltd. (Osaka, Japan) were reported in the literature, but an audited database was not available for this submission. The reported safety data from these trials and primary and rescue trials conducted by the University of Pittsburgh are presented below.

Adverse events described in the early and late kidney Phase II transplantation trials conducted in Japan[30,57,58] are shown in the Table 87.

Table 87: Incidence of Adverse Events in Early and Late Phase II Kidney Transplant Trials in Japan

Adverse Event	Incidence (%)			
	Late Phase II Study N = 70		Early Phase II Study N = 36	
Tremor	7	(10.0)	10	(27.8)
Headache	4	(5.7)	7	(19.4)
Numbness	2	(2.9)	1	(2.8)
Peripheral Sensory Abnormality	1	(1.4)		
Agitation, Unconsciousness			1	(2.8)
Disorientation			1	(2.8)
Chest Pain	7	(10.0)	5	(13.9)
Abnormal ECG	4	(5.7)	2	(5.6)
Chest Discomfort	2	(2.9)	2	(5.6)
Distressed Feeling of Chest	1	(1.4)		
Palpitations	1	(1.4)	2	(5.6)
Decreased Cardiac Function	1	(1.4)		
Decreased Ejection Fraction			1	(2.8)
Tachycardia at Exercise			1	(2.8)
Abdominal Distention	10	(14.3)	11	(30.6)
Nausea, Vomiting	6	(8.6)	4	(11.6)
Diarrhea	4	(5.7)	1	(2.8)
Abdominal Pain	1	(1.4)		
Gastric Ulcer			2	(5.6)
Renal Impairment	19	(27.1)	16	(44.4)
Polyuria			2	(5.6)
Hyperglycemia	22	(31.4)	9	(25.0)
Acute Pancreatitis	1	(1.4)	1	(2.8)
Hot Flush	9	(12.9)	2	(5.6)
Facial Hot Flush	1	(1.4)		
Pruritus	2	(2.9)		
Alopecia	1	(1.4)		
Gingival Papilloma	1	(1.4)		

From the initial experience reported at the University of Pittsburgh in 41 renal transplantation patients,[93] 4 patients required dialysis after transplantation. New-onset hypertension was reported in 27% of the patients at 3 months and 33% at 6 months. Reported serum creatinine over months 1-6 is shown in Table 88.

Table 88: Serum Creatinine (mg/dL) Post Transplant (N = 41)

Month	1	2	3	4	6
Value	1.54	1.70	1.71	1.61	1.75

This degree of nephrotoxicity was reported to be less than that in CBIR-treated patients in this study.

Approximately 10% of these patients had new-onset diabetes mellitus.

In a second publication from the University of Pittsburgh in kidney transplantation,[54] 125 patients were randomized to dual or triple therapy with tacrolimus. Adverse events reported in this trial were 13% CMV infection, 11% new-onset diabetes, and a single case of lymphoproliferative disorder. One patient died of colonic perforation and Pseudomonas sepsis. Serum creatinine at follow-up was 1.9 ± 0.7 mg/mL and BUN was 30 ± 13 mg/mL; these values are lower than those seen in tacrolimus patients in the sponsored trial.

In a third publication,[100] safety results were reported in 54 patients rescued with tacrolimus. Adverse events reported in this trial were new-onset diabetes in two patients and single cases of epistaxis, cecal perforation, sepsis, recurring disease, proteinuria, and bacterial pneumonia. Deaths were due to sepsis and lymphoma in two patients and sepsis, a cerebrovascular accident, and an unknown cause in single cases.

The results of these studies support the relative safety of tacrolimus in kidney transplantation and support the findings in sponsored trials.

8.H.9.3. Safety Data From Heart Transplantation Trials Reported in the Literature

At the University of Pittsburgh, 72 adult patients undergoing orthotopic heart transplantation were treated with tacrolimus and 10 patients were rescued with tacrolimus.[62] Adverse events reported included infections, increased serum creatinine, continued hypertension, new-onset diabetes mellitus, increased serum uric acid and potassium, a cerebrovascular accident, paresthesia, temperature malsensations, akinetic mutism, muscle aches, insomnia, and tremor. In short, these are the same adverse events reported in the ISS database.

8.H.9.4. Safety Data From Other Clinical Trials Reported in the Literature

Other uses of tacrolimus in organ transplantation and autoimmune disorders were summarized in Section 8.F. No unexpected adverse events were seen in any of these publications.

8.H.9.5. Safety Data in Pediatric Patients Reported in the Literature

The University of Pittsburgh recently published the two-year safety results in pediatric patients treated with tacrolimus for various organ transplants, rescue therapy, or autoimmune diseases.[87] Selected adverse events in the overall patient population were reported, including nephrotoxicity "comparable to that in cyclosporine-treated pediatric patients", new-onset diabetes mellitus in 5 patients, seizures in 5 patients, and lymphoproliferative disorder in 16 patients. These reported adverse events are expected, based on the ISS database. These results cannot be compared with the results in pediatric patients enrolled in sponsored studies, because of the mixed nature of the population in this publication. The safety of tacrolimus in pediatric patients can only be substantiated from the sponsored studies.

8.H.10. Safety Data From Sources Other Than Clinical Trials

Safety data are available from patients enrolled in Named Patient studies in Europe and from the literature.

8.H.10.1. Named Patients Treated in Europe

A "Named Patient" is allowed to receive investigational treatment in various European countries when his/her physician has determined that the patient cannot survive without the investigational drug. The physician is responsible for the experimental treatment and no IRB approval equivalent is required. The decision to use the drug is considered within the scope of medical treatment.

A number of patients were enrolled as "Named Patients" in Europe. Considering the scope of this experience, Fujisawa GmbH collected data on these patients. This is essentially equivalent to "Compassionate Use" or rescue treatment in the United States, but is not considered a clinical trial in Europe.

Data on the first 165 patients were reported recently.[191] These patients, other than those discontinued, were followed for a mean of 217 days.

Infections were frequently reported in the named patients. The types and frequency of infections are shown in Table 89.

Table 89: Infectious Complications in the European Named Patients

Infection	Number N = 165	%
Bacterial	35	21.2
Viral	32	19.4
Fungal	2	1.2
Bacterial & Viral	4	2.4
Bacterial & Fungal	5	3.0
Bacterial, Fungal, & Viral	8	4.8
Unspecified	1	0.6
TOTAL	87	52.7

Just over half of the patients had an infectious complication. Bacterial and viral infections were the most common, each appearing in about one-fifth of the patients. Infectious complications in these patients may have been related, in part, to prior immunosuppressive medications that most of the patients received.

Adverse events generally occurred in the first three months after conversion to tacrolimus. The major adverse events reported are summarized in Table 90. The COSTART categorization of these events differs slightly from that used by FUSA. The incidences of death (N = 9) and no drug effect (N = 6) are excluded from the following table.

Table 90: Incidence of Adverse Events by Body System Reported in the European Named Patients

Body System	Adverse Event	Incidence
Body as a Whole	Infection	6
	Sepsis	13
	Ascites	1
	Anomaly Congenital Multi	1
	Carcinoma	1
Cardiovascular	Arterial Thrombosis	1
	Cerebral Infarct	1
	Cerebral Hemorrhage	1
	Encephalic Hypertension	1
	Heart Failure	1
	Hypertension	3
Digestive	Coma Hepatic	1
	Diarrhea	2
	GI Hemorrhage	1
	Hepatitis	1
	Intestinal Perforation	1
	Melena	1
	Pancreatitis	1
Hemic/Lymphatic	Aplastic Anemia	1
	Bleeding Time Increased	1
	Coagulation Disorder	2
	Hemolysis	1
	Lymphoma-like Reaction	6
	Marrow Depression	1
	Pancytopenia	2
	Purpura	1

Table 80 (Continued)		
Body System	**Adverse Event**	**Incidence**
Metabolic/Nutritional	Acidosis	2
	BUN Increased	1
	Creatinine Increased	4
	Hyperglycemia	2
	Ketosis	1
	Uremia	3
Musculoskeletal	Myositis	1
Nervous	Anxiety	1
	Convulsion	1
	Encephalopathy	4
	Grand Mal Convulsion	1
	Neuritis Optic	1
	Personality Disorder	1
	Tremor	2
Respiratory	Pneumonia	3
	Respiratory Disorder	1
Skin/Appendages	Skin Disorder	1
Urogenital	Acute Kidney Failure	3
	Kidney Failure	1
	Kidney Function Abnormal	4
	Toxic Nephropathy	1

Among the adverse events reported in this table, most were also reported in the ISS database, using a similar term. Terms which might require clarification are discussed below.

The congenital anomaly was reported after spontaneous abortion at 19 weeks of pregnancy and consisted of meningocele and genitourinary anomalies. The patient was transplanted for chronic active hepatitis in 1986 and retransplanted in April 1991. Prior to conversion to tacrolimus, this patient

was treated during the pregnancy with cyclosporine, prednisolone (throughout), and sulfamethoxazole-trimethoprim (first trimester).

The optic neuritis consisted of a papillitis of the optic nerve.

Other reported GI adverse events were nausea, vomiting, cholestasis, cholangitis, gastritis, elevated LFT's and anorexia. Other musculoskeletal adverse events were myalgia, arthralgia, and a femur fracture. Diabetes mellitus was also reported along with hyperkalemia.

Malignancies reported in these patients consisted of five cases of lymphoproliferative disorder, and single cases of lymphoblastic lymphoma and cholangiocarcinoma. The former six cases are contained in the table as lymphoma-like reaction. Five of these occurred at a single center, all in children. Three of these children died and the other two were retransplanted and were alive as of the end of 1992, maintained on tacrolimus as primary immunosuppression.

A total of 35 of these patients died after conversion to tacrolimus, following survival ranging from 16 to 775 days. The majority of the deaths (25 of 35) occurred within 3 months of conversion. The primary causes of death were sepsis and failure of one or more organ systems. Three deaths were due to lymphoproliferative disease.

Thus, the incidence of adverse events in these named patients differs little from that seen in the ISS database.

8.H.10.2. Case Reports Published in the Literature

Case reports of adverse events not included in the clinical database are discussed below; these patients were initially treated at an FPC or non-FPC center, then were lost to follow-up and treated locally.

10.2.1. Lymphoproliferative Disorder in a Liver Transplant Patient on FK506

INVESTIGATOR(S): Frayha HH, Nazer H, Kalloghlian A, *et al.*[102]

SOURCE: Lancet 1991;337:296-7

STUDY CENTER:	Transplant was performed at an undisclosed location in the U.S. Patient follow-up was at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
TRANSPLANT HISTORY:	A 6-month-old male with extrahepatic biliary atresia was referred for orthotopic liver transplantation. The patient was treated with FK506 at 1 mg PO twice daily, adjusted according to serum levels. After 1 month of hospitalization, the child was discharged and allowed to return to Saudi Arabia for further recovery on a drug regimen of FK506, nystatin, hydrochlorothiazide, cotrimoxazole, and fludrocortisone.
POST-TRANSPLANT HISTORY:	Six months after discharge, the child presented with fever, lymphadenopathy, and hepatosplenomegaly, with a white cell count of 1900/μL, hemoglobin of 9.2 g/dL, and a platelet count of 32,000/μL. Cytomegalovirus was detected and treated with ganciclovir. Needle biopsy of the submandibular lymph node suggested immunoblastic sarcoma, but plasma cell differentiation indicated a benign accelerated immune response. Pathology of extracted right axillary and left cervical nodes suggested malignant lymphoma. Immunoblastic proliferation was extreme; however, the cell pattern was less monomorphic than would be expected in malignant lymphoma. Further evaluation revealed a substantial B-cell population, but the node background was rich in T-cells.
DIAGNOSIS/ TREATMENT:	Diagnosis was benign polyclonal lymphoproliferation associated with FK506 treatment. Two weeks after dose reduction followed by drug discontinuation, lymph nodes and spleen were reduced in size and an improvement in the patient's blood chemistry was seen.

10.2.2. Lymphoproliferative Disorders after FK506

INVESTIGATOR(S): Kitahara S, Makuuchi M, Kawasaki S, *et al.*[103]

SOURCE: Lancet 1991;337:1234

STUDY CENTER: Shinshu University School of Medicine, Matsumoto, Japan; National Children's Hospital, Tokyo; University of Tokyo

TRANSPLANT HISTORY: A 6-year-old boy underwent a partial liver transplant from a living related-donor because of biliary atresia that could not be fully corrected with Kasai's operation. On postoperative day 50, after an unsatisfactory response to steroid bolus therapy for acute rejection, immunosuppressive therapy was changed from cyclosporine, azathioprine, and prednisone to FK506 plus prednisone. Dosage was adjusted to maintain an FK506 plasma trough level between 0.4 and 1.0 ng/mL.

POST-TRANSPLANT HISTORY: Three months after transplantation, submucosal tumors were detected in the sigmoid colon and rectum; two of those were large and associated with a necrotic center. Tests for Epstein-Barr virus were positive. Lymphadenopathy was not detected.

DIAGNOSIS/ TREATMENT: Malignant lymphoma was diagnosed and characterized by the proliferation of monoclonal B cells. The patient was placed on acyclovir for 6 weeks. FK506 dosage was reduced to maintain a plasma trough level of 0.1 to 0.25 ng/mL. Steroid bolus injections were used to treat two episodes of graft rejection. Two months after dose reduction, the patient had palpable abdominal tumors. Intraoperative endoscopy revealed large ulcero-nodular lesions, a condition consistent with malignant lymphoma. A gradual healing of the ulcers and regression of the tumors was seen over the postoperative recovery period. The FK506 dose

reduction eventually led to complete remission of rectosigmoidal lesions.

10.2.3. QT Prolongation and Torsades de Pointes After Administration of FK506

INVESTIGATOR(S): Johnson MC, So S, Marsh JW, Murphy AM[104]

SOURCE: Transplantation 1992;53:929-30

STUDY CENTER: Washington University School of Medicine, Department of Pediatrics

TRANSPLANT HISTORY: A 10-year-old female underwent orthotopic liver transplantation after developing portal vein thrombosis with secondary portal hypertension, refractory ascites, and gastrointestinal bleeding. The patient had undergone a Kasai procedure at 7 weeks to correct biliary atresia. A pre-surgery electrocardiogram showed nonspecific ST-T changes; otherwise the patient had no history of cardiac dysfunction, nor was there any family history of cardiac dysfunction.

POST-TRANSPLANT HISTORY: FK506 was administered at 2.5 mg IV twice daily beginning 5 hours after transplant. Other postoperative medications included fentanyl, midazolam, metronidazole, morphine, vancomycin, ceftazidime, trimethoprim-sulfamethoxazole, ranitidine, insulin, and antacids.

The first FK506 dose was followed by a brief episode of tachycardia and a prolonged QT interval. The second dose was followed by frequent episodes of ventricular tachycardia (180 beats per minute), which were resolved by bolus lidocaine followed by continuous infusion of lidocaine. The third FK506 dose was followed by frequent bursts of ventricular tachycardia that did not respond to additional boluses of lidocaine, administration of procainamide and phenylephrine, or infusion of isoproterenol.

Electrical cardioversion resulted in a non-sustainable normal sinus rhythm. Esmolol bolus (100 µg/kg) followed by continuous infusion of 100 µg/kg/min produced a sustained normal sinus rhythm. After conversion to oral metoprolol, IV esmolol and lidocaine were discontinued. The patient was discharged on a regimen that included cyclosporine and metoprolol.

DIAGNOSIS/ TREATMENT: Fluctuations in electrolytes may have contributed to the initial tachycardia episode in the patient, but the prolonged cardiac dysfunction was thought to be due to the use of FK506. After discontinuing FK506 and implementing an aggressive regimen of anti-arrhythmic medication, ventricular tachycardia and prolonged QT interval resolved.

8.H.11. Considerations From Animal Safety Data

The preclinical safety profile of tacrolimus, determined from pharmacology and toxicology studies, was generally predictive of the toxicity seen in clinical studies.

Tacrolimus showed a species-dependent toxicity profile in both animal toxicity studies and in animal transplantation models. There were early reports of arteritis in animal transplant models, although these effects also appeared in control animals. Overall, the most sensitive species was the dog; baboons were least sensitive to tacrolimus. The overall profile from acute, subchronic, and chronic toxicity studies revealed few adverse events that would distinguish tacrolimus from cyclosporine. Special toxicity studies showed similar effects of tacrolimus and cyclosporine on endocrine and exocrine pancreatic function of rats.

Carcinogenicity studies are ongoing. Mutagenicity studies showed that tacrolimus was not a mutagen. Reproductive studies showed that tacrolimus had adverse effects on pregnancy, but most appeared to be related to maternal distress, rather than to direct effects on the fetus. Direct toxic effects on the female reproductive organs of rats and skeletal and cardiovascular abnormalities at the highest dose in rabbits were ascribed to tacrolimus, but at doses higher than those used in clinical trials.

8.H.11.1. Gastrointestinal Toxicity/Diabetogenicity

Agents of the macrolide class have generally had an appreciable incidence of GI side effects. Among animal species, dogs are particularly sensitive to such side effects: weight loss and vomiting were common and, in higher dose groups, GI bleeding and intussusception were noted.

It is clear that tacrolimus and cyclosporine/CBIR result in reported incidences of hyperglycemia and diabetes mellitus in humans. Tacrolimus had no effects on exocrine function in rats, but vacuolation and degeneration of the islets of Langerhans have been reported. These changes were reversible following discontinuation of tacrolimus administration. Successful islet transplants have been made under tacrolimus immunosuppression in animal models. It is unclear if tacrolimus is toxic to the islets, although changes in glucose metabolism occurred in rats and baboons during subchronic and chronic administration.

8.H.11.2. Cardiovascular Effects

Tacrolimus was associated with cardiovascular adverse events in humans (e.g., bradycardia and tachycardia) not seen in animal studies. The relationship and relevance of these events to tacrolimus treatment is unclear. The animal studies did not predict cardiovascular toxicity for tacrolimus.

8.H.11.3. Ocular Effects

Ocular changes during tacrolimus treatment occur with a low incidence in humans, but may be drug related, based on studies in rats. Lenticular opacities were noted in studies in rats. However, steroids, which are known to cause cataracts, were used in most patients.

8.H.11.4. Neurotoxicity

Neurotoxicity was seen in animal studies and is reported in detail in the Nonclinical Sections of this submission. In view of the nature of the nervous system abnormalities seen in animal studies with tacrolimus, there may be a connection between these and the occurrences of nervous system disorders such as tremor, paresthesias, neuropathy, insomnia, etc., as seen in the clinical trial experience.

8.H.11.5. Nephrotoxicity

Animals administered tacrolimus were noted to experience decreased renal function (i.e, increased serum creatinine and BUN). Following high doses in toxicity studies, histopathological lesions consisting of tubular atrophy and mineralization were observed. In a few observations made in humans, foamy vacuolization of the proximal tubule cells and crystalloid calcification of the distal and/or proximal tubules have been reported.[104a]

The mechanism of nephrotoxicity of cyclosporine is unknown, although several hypotheses have been proposed. Like cyclosporine, tacrolimus appears to reduce the glomerular filtration rate (GFR), possibly through a decrease in renal blood flow. An initial transient decrease in GFR was evident in an early pharmacokinetics study of tacrolimus in healthy volunteers (FPC-FK506-PK1).[35] As the GFR returned to normal in these subjects, the initial decrease may have been related to decreased renal blood flow. In patients with some degree of renal dysfunction, lower tacrolimus doses may be warranted.

8.H.12. Effects on Pregnancy

Tacrolimus was not to be administered to pregnant females in clinical trials or to those of either sex who did not plan to follow an effective program of contraception. Preclinical studies indicate fetal toxicity, mostly as a consequence of maternal toxicity. However, there were effects, such as abortion, reduced fetal viability and skeletal and cardiovascular abnormalities at the highest doses in rabbits, that appeared to be related to tacrolimus dosing in developmental studies. Therefore, females receiving tacrolimus should not consider pregnancy. The effects on male fertility are less clear, but effects on male organs in preclinical toxicity studies in rats indicate a need for caution. Results from animal studies indicate fetal runting and wasting, as reported previously with cyclosporine.

The overall potential risks of tacrolimus use during pregnancy have not been evaluated in clinical trials. In solid organ transplant patients treated with other immunosuppressants, there are certain risks to the patient (abortion, decreased intrauterine growth, premature delivery, and developmental abnormalities).[105] Successful pregnancies have occurred in transplant patients, and increased fertility appears to result following renal transplantation. In the transplant population, numerous other drugs with potential adverse effects on pregnancy are also used (anti-infectives, antihypertensives). The potential long-term risks to the offspring and potential abnormalities in the second

generation offspring have not been evaluated for any immunosuppressant, largely due to the recent expansion of transplant surgery.[105]

In experience reported by the University of Pittsburgh, eleven female transplant patients maintained on tacrolimus therapy throughout pregnancy delivered twelve babies, with one patient conceiving twice.[106] 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 liver transplantation, developed a CMV infection, which was treated with gancyclovir. The baby was born at 22 weeks and died immediately after birth. Ten pregnancies were successful, four with C-sections. The neonates showed no growth retardation or congenital anomalies. Hyperkalemia was observed in the majority of the babies, but resolved within 24-48 hours without adverse effects.

The limited experience with tacrolimus use during pregnancy, to date, indicates risks to the mother and offspring similar to those seen in patients treated with other immunosuppressants. Spontaneous abortion and postpartum complications have been noted in clinical trials and have been previously reported to appropriate regulatory agencies.

Pregnancy during immunosuppression with tacrolimus, like that during treatment with other immunosuppressants, cannot be recommended. Pregnancy occurring during tacrolimus immunosuppression should be monitored closely with respect to maternal and fetal condition. Factors predisposing to poor outcome with other immunosuppressants include hypertension (pre-existing or *de novo*), infections, decreased renal function, and graft rejection.[105]

Tacrolimus was seen in human breast milk at concentrations comparable to those seen in maternal plasma.[105] Therefore, nursing should be avoided when taking tacrolimus.

The effects of tacrolimus on male transplant patient reproductive capability and offspring viability have not been studied. Limited experience with other immunosuppressants is not conclusive; two infants out of 60 offspring from 45 fathers had abnormalities.[105] Animal studies with tacrolimus, however, showed toxic effects on male rat reproductive organs.

Males undergoing tacrolimus immunosuppression should be warned about possible adverse effects on the offspring. As with offspring of female transplant patients, the potential long-term risks and potential abnormalities in second generation offspring have not been evaluated for tacrolimus or other immunosuppressants.

8.H.13. Drug Interactions

Because of the clinical settings in which they are used (i.e., transplantation) and the effects they may produce (e.g., hypertension, lowered resistance to infection), immunosuppressants are frequently administered with other pharmacologic agents such as steroids, antihypertensives, antifungals, and antibiotics. A summary of the incidence of concomitant medication use in sponsored trials in the United States and Europe is provided in Table 4A, Appendix C. Concomitant medications selected for further safety analysis are listed in Tables 4B and 4C, Appendix C.

There have been no formal *in vivo* studies that assessed the effect of tacrolimus on the pharmacologic effect or pharmacokinetics of a concurrently administered drug. At this point, therefore, information regarding the potential of tacrolimus to interact with other drugs can only be deduced from other sources, such as *in vitro* assessments, studies using animal models, metabolism studies, and case reports of observed reactions in transplant patients undergoing tacrolimus treatment. Analyses of adverse events by concomitant medication use summarized above did not reveal any tendency toward a decreased pharmacological activity or increased adverse events.

Most researchers agree that tacrolimus is metabolized in the liver.[22,23] While the specifics of the hepatic metabolism of tacrolimus remain to be elucidated,[25] the results of a number of *in vitro* studies strongly suggest that tacrolimus is metabolized by the cytochrome P450 system of enzymes,[25,26] and, like cyclosporine,[25,26,107] primarily by cytochrome P450IIIA.

The evidence showing that tacrolimus is metabolized by the cytochrome P450IIIA family suggests the potential for drug-drug interactions with other IIIA substrates -- including macrolide antibiotics, calcium-channel blockers, steroids, and cyclosporine -- tacrolimus can be expected to reduce the rate of metabolism of these agents, thus enhancing their effects.[26]

In this context, the effects of various drugs on the *in vitro* metabolism of tacrolimus by human liver microsomes was determined.[108] The results are shown in Table 91.

Table 91: Inhibition (% ± SD) by Other Drugs of the Metabolism of Tacrolimus by Human Liver Microsomes

Drug	Effect at 10 µM	Effect at 100 µM
Nifedipine	30.0 ± 22.4%	63.6 ± 5.8%
Cyclosporine	30.8 ± 7.4%	62.4 ± 13.4%
Nivaldepine	16.0 ± 9.8%	47.0 ± 8.9%
Diltiazem	34.8 ± 9.9%	44.9 ± 9.5%
Prednisolone	19.8 ± 15.2%	33.8 ± 17.4%
Erythromycin	16.8 ± 11.7%	32.5 ± 12.3%
Fluconazole	8.3 ± 11.0%	27.0 ± 11.6%
Rifampicin	19.9 ± 17.5%	26.3 ± 14.0%
Amphotericin B	7.6 ± 3.3%	19.6 ± 4.1%

Based on these *in vitro* findings, there is a probability that certain drugs will inhibit the metabolism of tacrolimus *in vivo*. Previous clinical data already show excess toxicity when tacrolimus and cyclosporine are coadministered.[109] Drugs metabolized by the same hepatic P450IIIA system as tacrolimus may inhibit the metabolism of tacrolimus and produce high blood levels and related toxicity.

The drug-drug interactions associated with cyclosporine have been well documented. Tacrolimus has been shown to inhibit cyclosporine metabolism.[110] Since it is believed that tacrolimus and cyclosporine are both substrates of cytochrome P450IIIA, it is possible to project drug-drug interactions for tacrolimus that parallel those associated with cyclosporine. Drugs known to induce cyclosporine metabolism include rifampin, sulfadimidine, phenobarbital, phenytoin, phenylbutazone, dexamethasone, sulfinpyrazone, and carbamazepine.[111] Concomitant administration of any of these drugs with cyclosporine is associated with graft rejection.

Drugs known to inhibit cyclosporine metabolism include troleandomycin, erythromycin, josamycin, midecamycin, ketoconazole, miconazole, midazolam,

nifedipine, diltiazem, verapamil, nicardipine, ergotamine, dihydroergotamine, glibenclamide, bromocriptine, ethynyl estradiol, progesterone, cortisol, prednisone, prednisolone, and methylprednisolone. Administration of these drugs with cyclosporine can lead to enhanced effects, notably nephrotoxicity.[111]

The relative extent of tacrolimus-mediated inhibition of cyclosporine metabolism and inhibition mediated by other drugs, including erythromycin, nifedipine, nicardipine, and ketoconazole, was assessed *in vitro*.[112] Tacrolimus was more potent than erythromycin, equipotent with the calcium channel blockers, and less potent than ketoconazole. These results may indicate the potency of interactions between tacrolimus and these agents.

Researchers at the University of Pittsburgh[12] reported that a 55-year-old male who received a liver transplant and whose immunosuppressive regimen included tacrolimus and prednisone experienced an interaction with clotrimazole, an imidazole antifungal agent, administered on the 88th postoperative day. While taking clotrimazole, the patient experienced elevated tacrolimus plasma levels, which continued to rise even after the tacrolimus dose was reduced. Determination of tacrolimus plasma concentrations revealed a 2-fold increase in the area under the plasma concentration-versus-time curve (AUC_{0-24}) of tacrolimus in the presence of clotrimazole, compared to the AUC in the absence of clotrimazole, with no change in the half-life (10.5 and 11.8 hours in the presence and absence of clotrimazole, respectively). The suspected drug interaction was confirmed by discontinuing clotrimazole, then re-initiating the therapy.

The apparent interaction between tacrolimus and clotrimazole appeared to be at the level of the cytochrome P450 system, either in the liver or in the intestine. These investigators cited evidence to indicate that cytochrome P450 enzymes abound in the enterocytes of the human jejunal mucosa, that metabolism of tacrolimus and cyclosporine occurs in the intestines, and that drug interactions in the intestine can also lead to altered drug pharmacokinetics. They suggested that tacrolimus and clotrimazole may compete for the P450 intestinal binding sites, thus decreasing the amount of tacrolimus metabolized in the intestine and increasing the amount available to be absorbed.

Because transplant patients routinely receive antacids prophylactically, a group of researchers examined the effect of these agents on tacrolimus in simulated gastric juice.[113] The study results showed the following:

Table 92: Effects of Antacids on Tacrolimus in Simulated Gastric Juice

Antacid	Tacrolimus Loss	Time
Mylanta	14%	24 h
Tums	30%	24 h
Mag-Ox	98%	12 h
Alum hydroxide	35%	2 min[a]

a: No further changes occurred after 2 minutes.

The results with Mylanta, Tums, and magnesium oxide showed an apparent pH-mediated degradation of tacrolimus over time. The results with aluminum hydroxide showed adsorption of tacrolimus, with no further change after 2 minutes in the amount adsorbed or degraded. These investigators suggested that tacrolimus should not be dosed concomitantly with antacids. However, the pH required in this study to show those effects is unlikely to be obtained *in vivo*.

Concomitant administration of tacrolimus with the following types of drug may produce negative interactions:

- Potentially nephrotoxic agents. Aminoglycoside antibiotics (e.g., amikacin, gentamicin, tobramycin, and netilmicin sulfates), amphotericin B, cisplatin, and other agents known to produce toxic effects in the kidneys may increase the chance or severity of tacrolimus-associated renal insufficiency.

- Drugs that may increase serum potassium levels. Spironolactone, triamterene, amiloride, ACE inhibitors, and any other drugs or nutrients that lead to increased serum potassium may precipitate hyperkalemia if administered with tacrolimus, which also increases serum potassium.

- Potentially neurotoxic drugs. Drugs such as acyclovir, ganciclovir, and ciprofloxacin, as well as other quinolone antibiotics, may potentiate neurotoxic effects if administered concomitantly with tacrolimus.

While no trials have been conducted specifically to determine drug-drug interactions with tacrolimus, many medications believed to have the potential

to indicate such interactions have been administered to a substantial number of patients in clinical trials largely without documented interactions.

8.H.14. Pharmacologic Properties Other than the Property of Principal Interest

Tacrolimus appears to have effects on numerous body systems, including the renal, cardiovascular, digestive tract, endocrine, and central nervous systems. These effects have been fully addressed above in the Adverse Events and Clinical Laboratory sections of this ISS, to the extent that they represented Adverse Events.

The proposed use of tacrolimus is in the prophylaxis or treatment of liver rejection. The immunosuppressive nature of tacrolimus makes it a possible treatment for a number of other immune system-mediated disorders. Published reports and preliminary results from sponsored clinical trials indicate that tacrolimus may prove effective in a number of other indications involving solid organ and bone marrow transplantation or autoimmune disorders. The clinical reports derive mostly from trials at the University of Pittsburgh and often are case reports in solid organ transplant patients who had other immune-mediated disease(s). The published clinical reports are summarized in this ISS; nonclinical reports are summarized in the nonclinical section of this application. Current and future scheduled FPC studies are summarized above; none involve other than transplantation or autoimmune disorders.

8.H.15. Long-Term Adverse Events

Apart from other clinical consequences of solid organ transplantation and the use of immunosuppressive regimens, there are a number of safety concerns relative to long-term use of immunosuppressive agents. The data presented in the various calculations and tabulations within this report generally reflect the one year or 360-day time point as a key endpoint assessment milestone.

The major long-term safety problems expected from chronic immunosuppressant therapies are primarily in two categories. First are lymphoproliferative disorders, lymphomas, and malignancies. The other category is infections.

The incidence of lymphoproliferative disorders, lymphomas, and malignancies seen with tacrolimus treatment was summarized in Section 8.H.4.9 and Table

76 (liver transplantation). In the overall database of 807 patients who have received tacrolimus, there were few reports of malignancy or lymphoproliferative disorders. Although the number of patients receiving tacrolimus for >1 year in duration is limited at this time point, additional long-term patient exposure data will be presented as required by regulations. Nevertheless, the numbers and types of lymphoproliferative and neoplastic disorders seen with tacrolimus patients are not unexpected and certainly not excessive. In comparison with CBIR patients, a lower incidence of neoplasms was seen in the tacrolimus patients.

Under the category of infection, there were a variety of infections seen in these patients. These were profiled in Section 8.H.4.8. The review of these occurrences does not suggest an unexpected or excessive number of infections associated with tacrolimus therapy. The incidence of infection tended to be higher in CBIR patients than tacrolimus patients in comparative studies.

8.H.16. Withdrawal Effects

A review of the entire database of patients reveals no trends of unexpected adverse events or consequences of withdrawal of tacrolimus therapy. Clearly, withdrawal of immunosuppressive agents in this patient population is generally associated with loss of immunosuppression and may lead to organ rejection. In some instances, patients were withdrawn from their immunosuppressive regimen when unacceptable side effects were noted and/or the patients were in a preterminal condition whereby further therapy was deemed to be inappropriate in the best clinical judgment by the investigators. Based on these data, there appear to be no indications of unusual or unexpected withdrawal effects as a consequence of withdrawal of tacrolimus therapy in these patients.

8.H.17. Unexpected Adverse Events

Unexpected adverse events are difficult to discern in a patient population as seriously ill as liver transplant or liver rescue patients, or in patients undergoing kidney transplantation. Based on the previous human experience with cyclosporine, the experience with tacrolimus in non-clinical studies and reported studies in transplantation and other diseases conducted at the University of Pittsburgh, the primary areas of concern regarding adverse events were determined.

The anticipated adverse event categories were addressed above: nephrotoxicity, neurotoxicity, impaired glucose metabolism, gastrointestinal disturbances, infections, and neoplasms. None of these were considered an unexpected complication.

Some cardiovascular disturbances were also anticipated, based on the patient population and previous experience with cyclosporine-based therapy. In liver transplant patients, most of these were probably related to the serious nature of the operation and/or the critical status of the patients. Hypertension was an expected event, based on prior reported experience with cyclosporine.

Anaphylactoid reactions were seen in three patients receiving tacrolimus and two patients receiving CBIR in the controlled liver transplant trials. Although rare, such reactions are not unexpected, as they have been reported in patients receiving intravenous formulations containing castor oil derivatives as surfactants.

The incidence of photosensitivity reactions reported in 6.6% of tacrolimus patients was higher than expected.

Although in part predicted by toxicity studies in rats, the occurrence of lenticular opacities, cataracts, in 10 tacrolimus patients and 12 CBIR patients in sponsored trials was unexpected. These events occurred in patients who were receiving chronic therapy with corticosteroids, sometimes in large amounts. This extenuating circumstance obscures the final determination of relatedness of lenticular opacities to tacrolimus therapy.

8.H.18. Discussion

Patients treated with immunosuppressive medications for primary liver transplantation or for rescue therapy present a complex clinical and laboratory picture. As a result, the determination of the relationship of adverse experiences to the study drug is difficult. However, by evaluating the safety results from large comparative trials of tacrolimus versus cyclosporine regimens, from nonrandomized studies in liver transplantation, and the pattern of adverse events in the kidney transplantation studies, a reasonably complete picture of the safety profile of tacrolimus can be seen.

This safety profile of tacrolimus was reasonably predicted by animal toxicology studies and the reported side effects of cyclosporine.

Nephrotoxicity

Increased BUN and serum creatinine were noted in pre-clinical toxicology studies, as were histopathological lesions of tubular atrophy and mineralization. These effects were similar to those noted in animals receiving cyclosporine. In the studies reported herein, renal abnormalities were reported as adverse events and measurable increases in serum creatinine and decreases in GFR were noted. Reports of nephrotoxicity early in the course of FUSA-sponsored liver transplant trials resulted in recommendations for a decrease in the initial intravenous tacrolimus daily dose and for administration by continuous intravenous infusion rather than by four-hour infusion. Some patients undergoing liver transplantation may be more susceptible to the renal effects of tacrolimus, particularly those with renal compromise at the initiation of therapy. Added nephrotoxicity has been noted in patients receiving tacrolimus concurrently with cyclosporine. Therefore, for rescue use in refractory rejection, it is recommended that tacrolimus not be administered until 24 hours after the last dose of cyclosporine.

The incidence of nephrotoxicity associated with tacrolimus is comparable to that reported for cyclosporine. While somewhat more kidney-related adverse events were reported for tacrolimus patients than for CBIR patients in the comparative trials, this may be part of a more general pattern of increased reporting for the novel agent, tacrolimus, as opposed to the established standard agent cyclosporine. Using more objective measures, such as group mean increases in serum creatinine and mean decreases in GFR, the tacrolimus and CBIR patients are found to have similar degrees of renal compromise in liver transplant trials.

In a study reported from the Mayo Clinic,[114] changes in renal vascular dynamics were studied in liver transplant patients receiving CBIR or tacrolimus immunosuppression. Both drug regimens led to a similar increased renal vascular resistance, decreased renal blood flow, decreased GFR, and increased serum creatinine.

In the kidney transplant trials, tacrolimus and cyclosporine were withheld post-transplant until renal function was well established. In this circumstance, renal function continued to improve to the same degree in both study groups, approaching, but not quite reaching, the normal range. In the FPC-FK506-10 study there was no trend linking nephrotoxicities to increased target blood levels.

Neurotoxicity

Tremor, headache, paresthesia, and insomnia have been among the most frequent adverse events reported in tacrolimus studies, with a similar pattern of high incidence in CBIR comparative groups. Higher incidences were noted in the primary liver transplant trials than in the nonrandomized liver and the kidney transplant trials, but the pattern seems to persist across all trials. These events have shown a correlation to tacrolimus blood trough levels, and have usually responded to dose reduction.

Serious nervous system adverse events were of low, similar incidence in tacrolimus and CBIR-treated patients. The most frequent were convulsions or grand mal convulsions which were noted in 18 patients (3.5%) in each study drug group.

Glucose Metabolism

Hyperglycemia has been a commonly reported adverse event in tacrolimus studies. The incidence was higher in the tacrolimus groups (38%) than in the CBIR groups (27%) in the primary liver transplant controlled trials, with a somewhat lower incidence (17%) in the nonrandomized liver transplant studies. There was a trend toward an increasing incidence of hyperglycemia in the low (21%), medium (33%), and high (41%) target trough tacrolimus blood level subgroups in the concentration-controlled kidney transplant trial. While diabetes mellitus has been reported somewhat more frequently in the tacrolimus than the CBIR groups, insulin usage was similar in these groups. In the kidney transplant study, diabetes mellitus did not show an increase from low to high tacrolimus target blood level groups.

Hyperkalemia

Hyperkalemia has been a frequently reported adverse event across tacrolimus trials, but the absolute incidence has varied and may relate to underlying renal function. Hyperkalemia was reported in 27% of tacrolimus and 16% of CBIR patients in controlled liver transplant trials, and in 21% of tacrolimus patients in nonrandomized trials. Interestingly, hyperkalemia has been noted in newborns of patients receiving tacrolimus during pregnancy, resolving over 24-48 hours after birth. Hyperkalemia was reported at high incidence in the kidney transplant trial, but, again, without a clear relationship to target blood level, being 54% in the high, 67% in the medium, and 55% in the low target tacrolimus groups. When comparing potassium values from the comparative

liver trials, the mean increases noted were small and quite similar in the tacrolimus and CBIR group, with group mean values falling below the upper normal limit.

Gastrointestinal Toxicity

Gastrointestinal (GI) symptoms are common side effects of macrolides and GI toxicity from tacrolimus was predicted by studies in dogs. Diarrhea has been one of the highest incidence adverse events reported across the tacrolimus studies reported herein, generally exceeding the fairly high incidence of diarrhea also reported for comparative groups receiving CBIR immunosuppression. Nausea, anorexia, and vomiting were also reported at a relative high incidence in both groups, but generally were higher for tacrolimus, while constipation was frequent and similar for tacrolimus and CBIR patients. The same pattern emerged, but with a somewhat lessened incidence, for each of the gastrointestinal events in tacrolimus patients in nonrandomized liver transplant studies and the kidney transplant population.

While the overall incidence of those adverse events is high, the percentage of these events classified as serious by the investigators is generally low and quite similar in the tacrolimus and CBIR patient groups. An exception is the reported incidence of study drug discontinuations for GI hemorrhage in the controlled liver transplant trials. This occurred in seven CBIR-group patients, but in no tacrolimus group patients.

Infection and Malignancy

These events are expected sequelae of the profound immunosuppression produced by these potent treatment regimens. These, often serious, events are more frequent in the CBIR-treated population. Factors that contribute to this difference may include increased corticosteroid and anti-lymphocyte antibody therapy associated with the cyclosporine regimens, both as primary therapy and as additionally necessary to treat the increased number of rejection episodes.

Skin/Appendages

Within this category, some of the more prominent differences between tacrolimus and cyclosporine based therapy were detected. Hirsutism, which can be particularly disturbing to women and children, was reported in 19% of CBIR- versus 3% of tacrolimus-treated patients in the liver transplant studies.

Alopecia (12% tacrolimus, 4% CBIR) and pruritus (23% tacrolimus, 12% CBIR) had the opposite comparative incidence pattern.

Hypertension

Hypertension has been a frequently described consequence of cyclosporine therapy, can be difficult to control, and has been the basis of requests for conversion to tacrolimus therapy.

In the comparative studies in liver transplantation, hypertension was prominent in both study drug groups, but of consistently higher incidence in patients receiving CBIR. Serious hypertension was more frequent in the CBIR than the tacrolimus treatment groups. Frequent and even prophylactic use of anti-hypertensive agents characterized both study populations, but the overall use of anti-hypertensive therapy was higher in the CBIR group. One-year follow-up in comparative trials has shown a continued lower incidence of hypertension in the tacrolimus patient group.

A differential effect of CBIR and tacrolimus therapy on post-transplantation vascular dynamics has recently been described.[114] Systemic vascular dynamics during the four weeks post-transplant were compared in 32 CBIR and 14 tacrolimus liver transplant patients studied at the Mayo Clinic.[114] The groups were similar before liver transplantation, with low mean arterial pressure, increased cardiac output, and low systemic vascular resistance. In the first weeks post-transplant, the mean arterial pressure and systemic vascular resistance increased to similar degrees in the two treatment groups. After 2 weeks, these values continued to rise in cyclosporine patients, in many cases to clinically hypertensive levels. Within the first four months post-transplant, 78% of the cyclosporine patients in that study reached sustained pressures of 140/90 or greater and were treated with anti-hypertensive agents, as compared to 28% of the tacrolimus patients.

Lipid Metabolism

A known effect of cyclosporine is an increase in serum cholesterol and plasma lipids. In the controlled liver transplant studies, cholesterol increased in both tacrolimus and CBIR patients. However, the increase was greater in the CBIR-treated patients. The means in the tacrolimus group were 185 mg/dL at 6 months and 162 mg/dL at 12 months, whereas, in the CBIR group, the means were 221 mg/dL at 6 months and 222 mg/dL at 12 months. As cholesterol levels >200 mg/dL are associated with an increased risk of