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E.A. Memo

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DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls Section

NDA #: 50-708
CHEMISTRY REVIEW #: 1 DATE REVIEWED: January 21, 1994

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	July 23, 1993	July 26, 1993	July 28, 1993
NC	Sept. 9, 1993	Sept. 10, 1993	Sept. 13, 1993
BC	Oct. 1, 1993	Oct. 4, 1993	Oct. 6, 1993
AC	Oct. 1, 1993	Oct. 4, 1993	Oct. 8, 1993
BC	Oct. 19, 1993	Oct. 20, 1993	Oct. 25, 1993
BC	Oct. 20, 1993	Oct. 20, 1993	Oct. 25, 1993
BC	Oct. 21, 1993	Oct. 22, 1993	Oct. 28, 1993
BC	Oct. 28, 1993	Oct. 29, 1993	Nov. 1, 1993
BC	Nov. 4, 1993	Nov. 5, 1993	Nov. 10, 1993
BC	Nov. 17, 1993	Nov. 18, 1993	Dec. 3, 1993
BC	Dec. 10, 1993	Dec. 13, 1993	Dec. 13, 1993
BC	Jan. 26, 1994		
BC	Jan. 27, 1994		

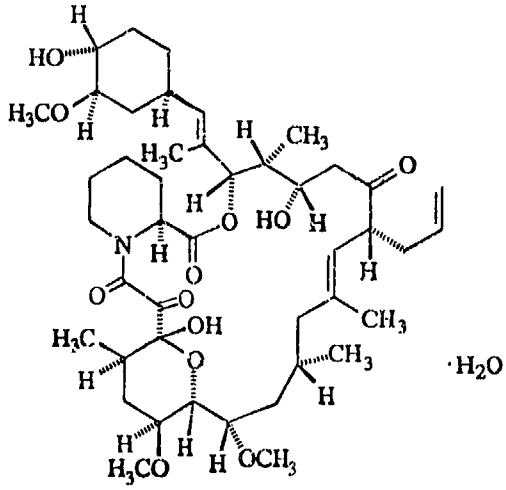
NAME/ADDRESS OF APPLICANT: Fujisawa USA, Inc.
Parkway North Center
Deerfield, IL 60015

DRUG PRODUCT NAME
- Proprietary: Prograf
- Nonproprietary: Tacrolimus
- Code Name/#: FR-900506, FR900506, FK506, FK 506, FK-506
- Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY: Immunosuppressant
INDICATION: Prophylaxis of organ rejection in patients receiving allogenic liver transplants

DOSAGE FORM/STRENGTH: Capsule, 1 mg and 5 mg
ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:
[3S-[3R*[E(1S*,3S*,4S*)],4S*,5S*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate
Molecular formula: $C_{44}H_{69}NO_{12}\cdot H_2O$ Formula weight: 822.05



Tacrolimus (FK506)

SUPPORTING DOCUMENTS:

IND
IND
DMF
DMF
DMF
DMF

RELATED DOCUMENTS:

NDA 50-709	Tacrolimus injection
Facsimiles sent to FUSA	8/31/93, 9/23/93, 10/26/93, 11/12/93 (see Appendix 5), 1/25/94
Facsimiles from FUSA	10/4/93, 10/11/93, 10/21/93, 10/25/93,12/17/93, 12/27/93, 1/21/94, 1/25/94, 1/26/94
Telephone Conversations with FUSA	9/20/93, 9/24/93, 9/28/93, 10/1/93, 10/5/93, 10/14/93, 10/19/93, 10/20/93, 10/27/93, 10/28/93, 11/4/93, 11/8/93, 11/10/93, 11/16/93, 12/9/93, 12/14/93, 12/16/93, 12/27/93, 1/11/94, 1/21/94, 1/24/94, 1/25/94, 1/26/94, 1/27/94

CONSULT REVIEWS:

TRADE NAME (Reviewed by the CDER Labeling and Nomenclature Committee)
Environmental Assessment (Reviewed by Dr. Su Tso, HFD-520, for Dr. Phillip Vincent, HFD-102)

REMARKS/COMMENTS:

Tacrolimus (FK506) is a macrolide (macrolactam) antibiotic produced by the fungus *Streptomyces tsukubaensis*. This fungus was first isolated from a soil sample from Tsukuba City, Ibaraki Prefecture, Japan in 19[illegible]. The structure of tacrolimus has been elucidated by spectroscopic methods and chemical degradation and is well documented in the literature. Recently, tacrolimus has been prepared by total synthesis, which further supports the previously established structure. The absolute stereochemistry of tacrolimus has been established. In the solid state only one isomer is observed. In solution cis and trans conformational isomers are observed (related to the amide bond). Epimerization also occurs in solution.

DRUG SUBSTANCE

A description of tacrolimus is adequately provided in the NDA. The structural elucidation is accomplished by spectroscopic methods. A wide range of physico-chemical properties are presented. It is virtually insoluble in water (< 1 µg/mL) independent of pH, but is very soluble in methanol and chloroform. The stability of tacrolimus under a variety of storage conditions has been demonstrated. Tacrolimus, which is isolated as the monohydrate, is not hygroscopic, nor is it air-sensitive. Degradation is observed at elevated temperatures. Tacrolimus is also somewhat light-sensitive. However, in general, tacrolimus has excellent long term stability.

Commercially, tacrolimus will be obtained by process at Fujisawa Pharmaceutical Company's Iwaki, Japan facility. The resulting is filtered and extracted. Purification is achieved by Tacrolimus obtained from the original extraction/purification process is equivalent (batch analyses, impurity profiles, IR, X-ray diffraction, stability) to material obtained via the commercial process. Fujisawa has revised the raw material controls and the description of the manufacturing procedure as recommended by us.

The identity, quality, strength and purity of the drug substance will be controlled through appropriate tests, including identification by IR, color reaction test and reverse phase HPLC, assay and 'tautomeric' compounds by reverse phase HPLC, specific rotation, related substances by normal phase HPLC, organic volatiles by GC, water content by titrimetric method, heavy metals, bacterial endotoxins, and microbial contents. The HPLC method has been added to the identification tests at our request to supplement the IR and color reaction test. Following discussions with the Division, Fujisawa has agreed to narrow the limits for impurities in the bulk drug substance. A limit on an impurity referred to as peak "A" has been added. The revised limits are supported by batch analyses and stability test results. The analytical methods are adequately documented in the NDA. Fujisawa has made a commitment to continue efforts to improve the regulatory method for impurities, especially as it applies to the resolution and identification of the components of peak "A".

Stability testing of tacrolimus drug substance has been performed on samples stored under both accelerated and long-term conditions. The proposed retest interval of two years is acceptable based on the available data.

DRUG PRODUCT

Tacrolimus will be available as 1- and 5-mg capsules, and as a 5-mg/mL injection. NDA 50-708 covers the manufacture of the drug substance and the capsules, while the injection is covered by NDA 50-709.

Because of the low aqueous solubility of tacrolimus µg/mL), an intermediate granule containing mixture of tacrolimus, hydroxypropyl methylcellulose (HMPC 2910), croscarmellose and lactose is prepared, yielding a material with "higher thermodynamic activity" and an increased aqueous solubility of µg/mL. The SDF will be manufactured in Japan and shipped to Ireland, where it will and filled into capsules. The components/composition of the SDF and the finished capsules in both strengths is clearly delineated in the submission.

The manufacturing process is adequately described. The identity, purity, and strength of the SDF are controlled by chromatographic methods. Particle size is controlled by in-process testing. Upon receipt by Fujisawa Ireland, the same control measures are taken, including particle size distribution at our request.

The identity, quality, strength and purity of tacrolimus capsules will be properly controlled for the following attributes: appearance, identification by HPLC, TLC and color reaction, assay and 'tautomeric' compounds by HPLC, related substances by HPLC, content uniformity, dissolution, water, and microbial limits. As proposed, the release/shelf-life limits are, with the exception of related

substances and dissolution, generally reasonable and are supported by batch analyses and stability testing results. After numerous discussions with the Division, Fujisawa has agreed to tighten the limits on both identified and unidentified impurities. Limits for individual peaks, including two identified degradation products typically observed in aged samples, and peak "A" have been added. The revised limits on impurities more closely reflect actual experience with the drug product and stability under normal storage conditions than those originally proposed. In addition, Fujisawa has revised the dissolution method (paddle speed) and limit. The analytical methods are adequately described in the NDA. Fujisawa has made a commitment to continue efforts to improve the regulatory method for impurities, especially as it applies to the resolution and identification of the components of peak "A".

Tacrolimus capsules will be packaged in amber glass bottles with a clic-loc closure. The multiple dose bottle will contain a desiccant. Fujisawa has recently decided to withdraw its proposal to market capsules in While Fujisawa has considerable experience with the drug product in a , only limited (ca. 1 month) stability data for the capsules in the proposed 'commercial' blister (German vendor) are available. Fujisawa has been made aware that, contrary to their understanding of 21 CFR 314.70 regarding post-approval changes in container/closure systems, certain proposed changes described in the NDA would require supplemental approval by FDA instead of reporting through annual report.

The stability of tacrolimus capsules has been demonstrated under a variety of conditions. After a recent update on stability data, satisfactory results are now available on pilot-scale batches packaged in clear glass bottles for up to 30 months and in blister packs (supplied by Japanese vendors) for up to 18 months, and on production-scale batches packaged in amber glass bottles for 9 months. The proposed 2-year expiry for drug product stored under controlled room temperature is acceptable. The marketed product stability protocol has been revised, at our request, to include storage at 40°C for 6 months. The protocol for extension of the expiry has also been revised at our request It will now be based on full shelf-life data obtained on marketed product, rather than on continuation of studies initiated on pilot batches.

ENVIRONMENTAL ASSESSMENT

A review of the abbreviated Environmental Assessment was completed and deficiencies noted. The applicant has submitted Certificates of Compliance in response to a deficiency letter issued by Dr. Vincent. These documents have been reviewed and a FONSI has been drafted.

METHODS VALIDATION

The validation of the analytical methods has not been completed by FDA laboratories at this time. Samples were collected in December during the GMP inspections. The available data in the NDA indicates that the methods are adequate. However, additional system suitability tests have been added to the HPLC method at our request. Data on several individual related substances has also been submitted in support of the HPLC method. Fujisawa has agreed to provide additional data and assistance, if necessary, for the completion of the methods validation by the FDA, and to make any modifications to those methods deemed necessary.

LABELING

At our request, the package insert has been revised to conform with 21 CFR 210.57 as it relates to chemistry. In addition, the established name of the drug product now contains the dosage form descriptive, while the trademark, Prograf, does not, thus properly reflecting the drug product as intended.

ESTABLISHMENT EVALUATION

EER's for the Toyama, Japan facility and the Killorglin, Ireland facility were submitted on 8/19/93. The GMP inspections of these two sites were completed in December, 1993. Although the official recommendation from the Office of Compliance has not been received, there has been no report of any major GMP deficiencies which would prevent the approval of this NDA.

CONCLUSIONS & RECOMMENDATIONS:

The deficiencies in the original submission, including controls of raw materials, description of the manufacturing process and controls, analytical test methods and specifications, limited stability data, and protocols for packaging changes, have been adequately addressed by the applicant. The NDA, as amended, for tacrolimus capsules is thus approvable from the chemistry, manufacturing and controls perspective.

Mark R. Seggel, Review Chemist

Concurrence:
HFD-530/CChen CRC 1/28/94
cc:
Orig. NDA
HFD-530/Div. File
HFD-530/CChen
HFD-530/MSeggel
HFD-530/MCavaille-Coll
HFD-530/LBlack
HFD-530/CBroadnax
HFD-102/CKumkumian

File: 50-708.CR1

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DIVISION OF ANTIVIRAL DRUG PRODUCTS
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BC	Oct. 28, 1993	Oct. 29, 1993	Nov. 1, 1993
BC	Nov. 4, 1993	Nov. 5, 1993	Nov. 9, 1993
BC	Nov. 16, 1993	Nov. 17, 1993	Nov. 23, 1993
BC	Dec. 10, 1993	Dec. 13, 1993	Dec. 13, 1993
BC	Dec. 27, 1993	Dec. 28, 1993	Jan. 4, 1994
BC	Jan. 26, 1994		
BC	Jan. 27, 1994		

NAME/ADDRESS OF APPLICANT: Fujisawa USA, Inc.
Parkway North Center
Deerfield, IL 60015

DRUG PRODUCT NAME
- Proprietary: Prograf
- Nonproprietary: Tacrolimus
- Code Name/#: FR-900506, FR900506, FK506, FK 506, FK-506
- Chem. Type/Ther. Class: 1P

PHARMACOLOGICAL CATEGORY: Immunosuppressant
INDICATION: Prophylaxis of organ rejection in patients receiving allogenic liver transplants.

DOSAGE FORM/STRENGTH: Sterile solution, 5 mg/mL, 1-mL ampule
ROUTE OF ADMINISTRATION: "For Intravenous Infusion Only"

CHEMICAL NAME/STRUCTURAL FORMULA:
[3S-[3R*[E(1S*,3S*,4S*)],4S*,5S*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate
Molecular formula: $C_{44}H_{69}NO_{12}\cdot H_2O$ Formula weight: 822.05

bibliography of publications on tacrolimus (FK506) with a cut-off date of the end of the first quarter 1993, with additional entries to June 1993 is enclosed in Section 8.O.

8.F.7. Overall Summary of Other Studies and Information

Tacrolimus is a powerful immunosuppressant which has shown efficacy in controlled clinical trials involving kidney and bone marrow transplantation, diabetes mellitus, and uveitis. In uncontrolled trials, tacrolimus was effective in kidney, heart, small bowel, bone marrow, and islets of Langerhans transplantation and diseases such as uveitis, nephrotic syndrome, psoriasis, and pyoderma gangrenosum. In most cases, these diseases were refractory to conventional immunosuppressants.

Patients treated with tacrolimus for indications other than liver transplantation generally reported the same types of adverse events as were reported by liver transplant patients. These include nephrotoxicity, neurotoxicity, gastrointestinal disturbances, impaired glucose metabolism, and infections. These adverse events will be discussed further in the Integrated Summary of Safety (Section 8.H.).

8.G. INTEGRATED SUMMARY OF EFFICACY

8.G.1. Summary

Tacrolimus (FK506) is a novel macrolide immunosuppressant which is 50-100 times more potent than cyclosporine in inhibiting T-cell activation *in vitro*. The efficacy of tacrolimus in preventing and treating allograft rejection after liver transplantation has been evaluated in four Fujisawa-sponsored clinical studies:

Table 7: Fujisawa Liver Transplant Studies

Protocol	Indication	Control	Tacrolimus (N)	CBIR (N)
FPC-FK506-7	Primary Prevention	Active Cyclosporine-Based Therapy	263	266
GHBA-157	Primary Prevention	Active Cyclosporine-Based Therapy	270	275
FPC-FK506-9	Rescue Therapy	Historical Cyclosporine-Based Therapy	125	-
FPC, Japan	Primary Prevention and Rescue Treatment	Uncontrolled	24	-

Two adequate and well-controlled trials, one performed in the U.S. (FPC-FK506-7) and one performed in Europe (GHBA-157), compared the safety and efficacy of tacrolimus in combination with small doses of corticosteroids to cyclosporine-based immunosuppressive regimens (CBIR) as primary rejection prophylaxis after liver transplantation. All patients were followed for one year post-transplantation.

The third adequate and well-controlled trial, FPC-FK506-9, studied the efficacy and safety of tacrolimus in treating liver allograft rejection refractory to all conventional immunosuppressive therapies. Results were compared to three historical control groups, one group consisting of patients who continued on a cyclosporine-based therapy and two groups receiving the only other alternative to further pharmacologic therapy for refractory rejection, i.e., retransplantation of the liver.

The fourth study evaluated tacrolimus therapy in recipients of living-related donor liver transplants. This was an uncontrolled trial performed in Japan, where brain death is not widely recognized; therefore, cadaveric organ transplantation is not typically performed.

Kaplan-Meier estimates of one-year patient and graft survival from these four studies are summarized in Table 8.

Table 8: Kaplan-Meier Estimates of One-Year Patient and Graft Survival in the Four Liver Transplant Studies

Protocol	One -Year Patient Survival		One-Year Graft Survival	
	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	88%	88%	82%	79%
GHBA-157	81%	75%	76%	70%
FPC-FK506-9	71%	78% 57%** 38%**	56%	48%* 53%* 33%**
FPC, Japan	66%	-	66%	-

* P<0.05 ** P<0.001

Based on results from the two randomized, controlled studies of tacrolimus in primary liver transplantation (FPC-FK506-7 and GHBA-157), one-year patient and graft survival rates with tacrolimus are equivalent to rates with cyclosporine-based immunosuppressive regimens with trends toward superiority in patient and graft survival with tacrolimus therapy in the GHBA-157 study. Patient and graft survival rates in the historically controlled rescue study of tacrolimus in refractory liver transplantation demonstrate significant improvement over historical control regimens.

A summary of the cumulative incidence of acute rejection and discontinuation of therapy for lack of efficacy in these four studies is presented in Table 9.

Table 9: Acute Rejection and Discontinuation for Lack of Efficacy at Six Months in the Four Liver Transplant Studies

Protocol	Six-Month Acute Rejection Rate		Six-Month Rate of Discontinuation for Lack of Efficacy	
	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	66%*	73%	3%*	13%
GHBA-157	41%*	54%	3%*	10%
FPC-FK506-9	41%	-	27%	-
FPC, Japan	17%	-	0%	-

* Tacrolimus rates are lower than CBIR rates: $P \leq 0.001$.

Both the rates of acute rejection and refractory rejection resulting in discontinuation of therapy for lack of efficacy were significantly lower with tacrolimus therapy compared to cyclosporine-based regimens in the comparative trials. These superior results with tacrolimus were achieved with significant reductions in the amount of concomitant corticosteroids administered compared to CBIR and with the avoidance of concomitant azathioprine or anti-lymphocyte therapy for the prevention of rejection.

The combined overall results of these studies demonstrate that tacrolimus is effective for prophylaxis of organ rejection in patients receiving allogeneic liver transplants and for the treatment of refractory rejection in patients previously treated with cyclosporine-based immunosuppressive therapy. This efficacy profile is consistent in the following subsets of the overall population:

1. Patients receiving the proposed recommended starting dose in the labeling, i.e., intravenous: 0.05-0.10 mg/kg/day as a continuous infusion; oral: 0.15-0.30 mg/kg/day in two divided doses.
2. Pediatric and adult patients.
3. Male and female patients.
4. Patients of different races.
5. Patients administered various cyclosporine regimens, including combinations of steroids, azathioprine, and anti-lymphocyte preparations.

In conclusion, tacrolimus has been shown to be effective in liver transplantation patients with the advantages over CBIR of:

1. significantly decreased incidence and severity of allograft rejection,
2. more rapid improvement in liver function assessed by total serum bilirubin concentration, and
3. a reduced requirement for additional immunosuppressants, including higher doses of steroids, OKT3, or azathioprine.

Additionally, tacrolimus therapy results in significant improvement in patient and graft survival in patients with refractory hepatic allograft rejection where the only alternatives for further treatment include intensification of existing immunosuppressant therapy with its resultant risks, or retransplantation of the liver. Finally, tacrolimus is also effective in patients who receive partial liver allograft from a living-related donor.

8.G.2. Introduction

Orthotopic liver transplantation has emerged over the last decade as a life-saving therapeutic modality for patients with chronic end-stage liver disease, fulminant hepatic failure, inborn errors of metabolism, or primary hepatic malignancies.[15,16,77,78] Cyclosporine-based immunosuppressive regimens (CBIR) improved patient and graft survival rates in solid organ transplantation compared to the best previous therapy: anti-lymphocyte globulins, azathioprine, and corticosteroids. One-year patient and graft survival rates in recipients of first transplants have approached 80% and 70%, respectively, under CBIR. Although technical and immunological advances have improved patient and graft survival rates, rejection remains one of the most common complications after transplantation and is one of the most frequent causes of graft dysfunction.[16,77] Following liver transplantation, approximately 60% of recipients experience at least one episode of acute rejection.[15,16,79] Additionally, CBIR are associated with complications related to over-immunosuppression (e.g., infection and lymphoproliferative disease) and toxicity (e.g., hypertension, nephrotoxicity, neurotoxicity, and hyperlipidemia). Because of these limitations in CBIR, especially the rate of rejection and toxicity associated with cyclosporine, Fujisawa Pharmaceutical Company, Ltd. initiated an active screening program to search for new immunosuppressants leading to the discovery of a novel macrolide immunosuppressant FK506 (tacrolimus). Initial clinical investigations were performed under Investigator INDs at the University of Pittsburgh. Patients experiencing refractory liver allograft rejection under CBIR were converted to tacrolimus therapy. Based on encouraging results in reversing ongoing rejection processes,[16,79] clinical studies were expanded to include tacrolimus as primary immunosuppression after solid organ transplantation (liver,[43,46,47] kidney,[53,59] and heart[61,63]). The efficacy in single-center pilot studies formed the clinical basis for initiation of Fujisawa-sponsored multicenter US, European, and Japanese studies of tacrolimus in liver transplantation.

Table 10: Fujisawa Studies of Tacrolimus in Liver Transplantation

Study	Indication	Control	N
FPC-FK506-7	Primary liver, randomized	CBIR	529
GHBA-157	Primary liver, randomized	CBIR	545
FPC-FK506-9	Liver rescue, non-randomized	Historical CBIR	125
FPC, Japan	Primary and rescue liver, non-randomized, living-related donor	Uncontrolled	24

Results from three adequate and well-controlled and one uncontrolled study (Table 10) have demonstrated that tacrolimus significantly reduces the incidence and severity of rejection, as compared to CBIR after liver transplantation. Additionally, tacrolimus was effective in reversing acute and chronic refractory hepatic allograft rejection that had failed all conventional immunosuppressive therapies, including CBIR. Patient and graft survival are similar between treatment groups with trends toward improvement with tacrolimus as compared to CBIR for prophylactic therapy after liver transplantation. Survival rates with tacrolimus treatment are significantly better than historical controls in patients experiencing refractory hepatic allograft rejection. The efficacy of tacrolimus is demonstrated despite significant reductions in the amounts of concomitant immunosuppressive therapies including corticosteroids, azathioprine, and anti-lymphocyte preparations. These results form the basis of evidence that demonstrate the effectiveness of tacrolimus for the indication of prophylaxis of organ rejection in patients receiving allogeneic liver transplants and for the treatment of refractory rejection in patients previously treated with CBIR.

The results of these clinical trials will be presented, compared, and discussed. Additionally, publications from clinical investigations performed under investigator INDs will be discussed.

8.G.3. Analysis and Comparison of Clinical Studies in Orthotopic Liver Transplantation

8.G.3.1. Randomized CBIR-Controlled Studies in Primary Liver Transplantation

3.1.1. Study Objectives

The randomized, controlled, primary liver transplant studies compared the efficacy and safety of tacrolimus plus small doses of corticosteroids to those of CBIR in the prevention of hepatic allograft rejection following first-time liver transplantation. The primary objectives were to evaluate patient and graft survival at one year post-transplant. Secondary objectives included the comparative analysis of incidence of acute, steroid-resistant, and refractory rejection, as well as a comparative analysis of allograft function.

3.1.2. Study Design/Methods

Two open-labeled, multicenter, randomized, comparative, primary liver transplant studies were conducted under the auspices of Fujisawa: a Phase III study conducted in the United States (FPC-FK506-7) and a phase II/III study conducted in Europe (GHBA-157). Details of the randomized, controlled, primary liver transplant studies are presented in Table 11.

Table 11: Details of the FPC-FK506-7 and GHBA-157 Studies

Protocol Parameter	FPC-FK506-7	GHBA-157
Study Design	Open-labeled, multicenter, randomized, comparative	Open-labeled, multicenter, randomized, comparative
Patient Enrollment	8/90 to 10/91	9/90 to 1/92
Informed Consent	Required	Required
Time of Randomization	Prior to surgery	Prior to surgery
Study Endpoint	One-year patient and graft survival	One-year patient and graft survival
Number of Investigative Sites	12	8

3.1.2.1. Tacrolimus Therapy

Tacrolimus was supplied by a single source (Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan) for both the IV formulation and 1 mg and 5 mg hard gelatin capsules. Intravenous dosing was administered within a specific time following surgery, at a defined dosage and infusion rate. Oral dosing was administered within a few days after surgery (or when oral dosing was tolerated), sometimes overlapping IV dosing for up to 12 hours. Generally, IV methylprednisolone as a bolus injection was given on the day of surgery in both studies. Thereafter, oral prednisone was given at a specified initial dose and tapered as clinically indicated.

3.1.2.2. Patient Populations

The two randomized, controlled, primary liver transplant studies had differing inclusion/exclusion criteria related to prognostic factors for patient and graft survival. Both studies excluded multiple-organ transplants, retransplants of the liver, and ABO-incompatible donor grafts.

The FPC-FK506-7 study did not have an age restriction on enrollment, but excluded patients with renal dysfunction (defined as serum creatinine >2.0 mg/dL, glomerular filtration rate <30 mL/min, or dialysis-dependency), patients with an hepatic tumor having a high risk

of recurrence, patients experiencing stage IV hepatic encephalopathy, and cancer patients, except those who had been treated for and cured of carcinoma *in situ* of the cervix or basal cell carcinoma of the skin.

The GHBA-157 study excluded pediatric patients (≤16 years), cancer patients with active neoplastic disease, and patients with primary liver cancer with evidence of metastasis. Patients in stage IV encephalopathy were enrolled into this study and stratified by the presence or absence of fulminant hepatic failure prior to treatment randomization. Table 12 summarizes these different entry criteria.

Table 12: Differing Entry Criteria in the FPC-FK506-7 and GHBA-157 Studies

	Renal Dysfunction	Fulminant Hepatic Failure (FHF)	Malignancies	Pediatrics
FPC-FK506-7	Excluded[1]	Excluded FHF patients in stage IV hepatic encephalopathy	Excluded most cancer patients[2]	Included
GHBA-157	Eligible	Eligible	Excluded primary liver cancer and active neoplasms	Excluded

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

2 Except those treated for and cured of carcinoma *in situ* of the cervix or basal cell carcinoma of skin; no hepatic tumors with a likelihood of recurrence

3.1.2.3. CBIR Therapy

In CBIR therapy, cyclosporine (CyA), the primary immunosuppressant, was given with steroids alone or combined with azathioprine; some centers used an induction course of an anti-lymphocyte agent prior to initiating CyA dosing. These drug combinations have been developed to allow a decrease in CyA dosage in an attempt to reduce the risk of toxicity without compromising the desired immunosuppressive effect. CBIR treatment varied from center to center in the use of steroids, azathioprine, and anti-lymphocyte agents and the dose and timing of administration. Double therapy is defined as CyA *plus* steroids; triple therapy is defined as CyA *plus* steroids *plus* azathioprine; induction therapy is defined as the administration of an anti-lymphocyte agent, such as ALG, for several days post-transplant prior to the administration of

CyA. This latter regimen allows for stabilization of renal function prior to CyA initiation; anti-lymphocyte induction therapy is followed by triple therapy once CyA dosing is started. One center in the FPC-FK506-7 study used a double-drug regimen, one center used induction therapy, and 10 centers used triple therapy for CBIR. Three of eight centers in the European GHBA-157 study used an induction CBIR; the remaining five centers used triple therapy. Table 13 presents the number of patients in the CBIR treatment group at each of the centers using a specific CBIR regimen.

Table 13: Summary of CBIR Treatment by Study. Percentages Indicate the Number of Patients Enrolled at Centers that Used a Specific CBIR Treatment

Study	Double Therapy	Triple Therapy	Induction Therapy
FPC-FK506-7	11.6% (31/266)	78.2% (208/266)	10.2% (27/266)
GHBA-157	0%	59.6% (164/275)	40.4% (111/275)

Double Therapy: CyA plus steroids
Triple Therapy: CyA plus steroids plus azathioprine
Induction Therapy: Anti-lymphocyte treatment followed by triple therapy

3.1.2.4. Definition and Treatment of Rejection

Three rejection types were classified:

- the first acute rejection episode, typically treated with increased steroid dosages;
- steroid-resistant rejection, a rejection episode unresponsive to a steroid bolus and recycle; and
- refractory or intractable rejection, a rejection episode unremittant to all conventional immunosuppressive therapies.

Historically, approximately 60%[16] of liver allograft patients experience at least one episode of acute allograft rejection under CBIR, usually within the first few months after transplantation. The first episode of acute rejection is typically treated with increased doses of corticosteroids; continued acute rejection, referred to as steroid-resistant

rejection, is treated with augmented steroids and/or monoclonal (OKT3) or polyclonal (ALG) anti-lymphocyte agents.

Refractory rejection (acute or chronic rejection unresponsive to remedial immunosuppressive therapies) results in discontinuance from the study for lack of efficacy and may result in the need for retransplantation. Chronic rejection usually occurs between the third and sixth post-operative month and is characterized by a condition described pathologically as vanishing bile duct syndrome (the destruction of small- and medium-sized intrahepatic bile ducts) and vasculopathy of large- and medium-sized arteries. Biopsies of grafts suspected of undergoing chronic rejection will generally show progressive lesions. Chronic rejection is not as common as acute rejection, occurring in approximately 5-20% of liver allograft recipients, and is associated with a high rate of graft loss. It is estimated that 80% of chronic rejection cases develop from previous acute rejection episodes unresponsive to conventional therapy.[80]

Table 14 presents a summary of the various rejection treatments used in the controlled, randomized, primary liver transplant studies.

Table 14: Summary of Standard Treatment for First-Time Acute, Steroid-Resistant (Second-Time), and Refractory Rejection Episodes

Study	Treatment Course for Allograft Rejection			
	1st	2nd	3rd	4th
FPC-FK506-7	Steroids	OKT3	Steroids	Failure*
GHBA-157	Steroids	Steroids or OKT3/ALG	Failure*	-

* Patients failing treatment were discontinued from study for lack of efficacy and treated as clinically indicated.

Both studies required biopsy confirmation of a rejection diagnosis. The first episode of rejection was treated similarly in both studies: a bolus corticosteroid injection followed by a six-day recycle of corticosteroids. The FPC-FK506-7 study called for a second bolus/recycle steroid treatment if a patient experienced a second biopsy-confirmed rejection episode more than 30 days after the first bolus/recycle steroid treatment.

If the first bolus/recycle treatment did not produce a complete response, or if rejection occurred within 30 days of the first bolus/recycle steroid treatment, OKT3 was used for 10 to 14 days. If rejection continued unabated, another bolus/recycle steroid treatment was used; subsequent refractory rejection meant the patient met study endpoint. Refractory rejection required failure of three courses of treatment for allograft rejection in the FPC-FK506-7 study.

The GHBA-157 study allowed each investigational site to use its standard anti-rejection therapy. In general, most first-time rejection episodes were treated with a bolus injection of corticosteroids followed by a six-day recycle of corticosteroids. One site (Cambridge) allowed the use of ALG in the case of severe first-time rejection episodes. Most rejection episodes unresponsive to a bolus and recycle of corticosteroids were treated with a second bolus and recycle. However, some patients experiencing rejection despite a bolus and recycle of corticosteroids were treated with ALG or OKT3 as a second-line therapy for steroid-resistant rejection. Refractory rejection in the GHBA-157 study was defined as failure of two courses of anti-rejection treatment.

3.1.2.5. Efficacy Parameters

One-year patient and graft survival were the primary efficacy variables in both studies. Secondary efficacy parameters included frequency of acute rejection episodes, the use of OKT3 for treatment of rejection, the incidence of refractory rejection/treatment failure (discontinuation for lack of efficacy), and allograft function. Liver function was monitored by laboratory values of total serum bilirubin, SGOT, and SGPT.

Patient and graft survival were followed for one year post-transplant for all patients in both studies. Data on secondary efficacy parameters are available to one year for the FPC-FK506-7 study and to six months for the GHBA-157 study. Rejection data will be presented to six months post-transplant for both studies.

3.1.3. Results

In total, 1074 patients were enrolled in these two studies: 533 patients were randomized to tacrolimus treatment and 541 were randomized to CBIR treatment. In the FPC-FK506-7 study, 529 patients were enrolled: 263 randomized to tacrolimus treatment and 266 to CBIR

treatment. In the GHBA-157 study, a total of 545 patients were enrolled: 270 randomized to tacrolimus treatment and 275 to CBIR treatment. (Appendix B; Table B.1)

3.1.3.1. Patient and Graft Survival

Table 15 presents the Kaplan-Meier estimates for the 6- and 12-month patient and graft survival rates for the randomized, controlled, primary liver transplant studies, FPC-FK506-7 and GHBA-157. (See also Appendix B, Tables B.1 and B.2; Figures 1.1, 1.2, 2.1, and 2.2)

Table 15: Patient and Graft Survival Rates for the Controlled, Randomized, Primary Liver Transplant Studies (FPC-FK506-7, GHBA-157)

Controlled, Randomized Liver Transplant Study	Patient Survival		Graft Survival	
	6 Months	12 Months	6 Months	12 Months
FPC-FK506-7:				
tacrolimus	90%	88%	85%	82%
CBIR	90%	88%	83%	79%
GHBA-157:				
tacrolimus	84%	81%	80%	76%
CBIR	79%	75%	75%	70%

One-year patient survival rates in the FPC-FK506-7 study were comparable for the tacrolimus and CBIR groups; the one-year graft survival rate was higher in the tacrolimus group; however, the difference was not statistically significant (P = 0.55). In the GHBA-157 study, patient and graft survival rates for tacrolimus were higher at one year than those for CBIR with the difference approaching statistical significance (P = 0.078, patient survival; P = 0.073, graft survival).

Additionally, patient and graft survival rates for both the tacrolimus and CBIR treatment groups of the GHBA-157 study tended to be lower than in the FPC-FK506-7 trial, with a greater difference seen between CBIR treatment groups than tacrolimus treatment groups.

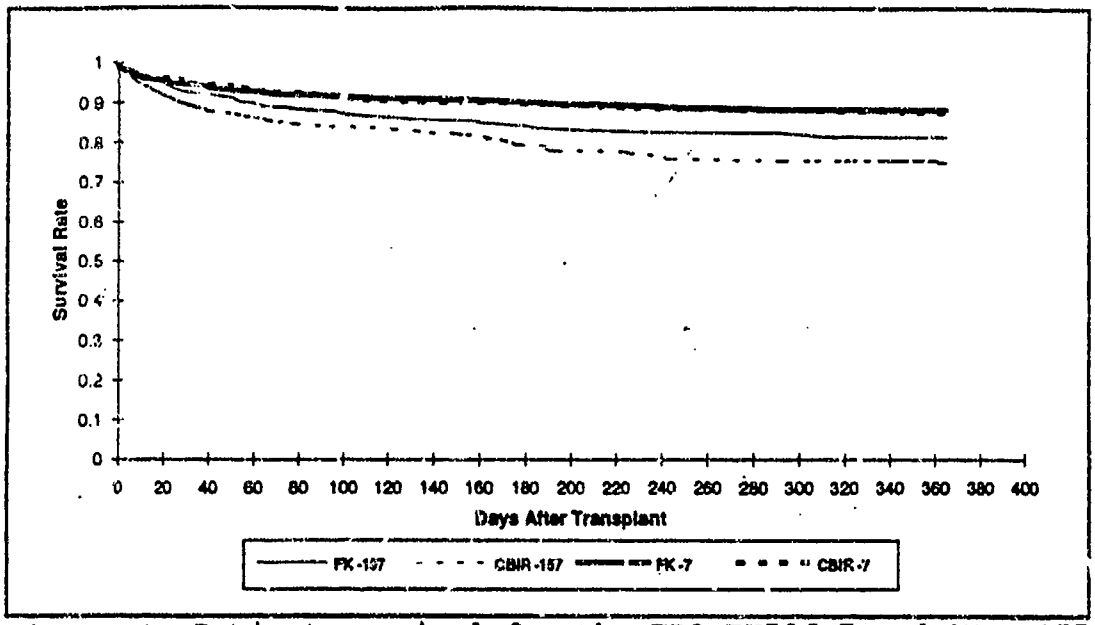

Figure 1. Patient survival for the FPC-FK506-7 and GHBA-157 study populations, tacrolimus (FK) versus CBIR.

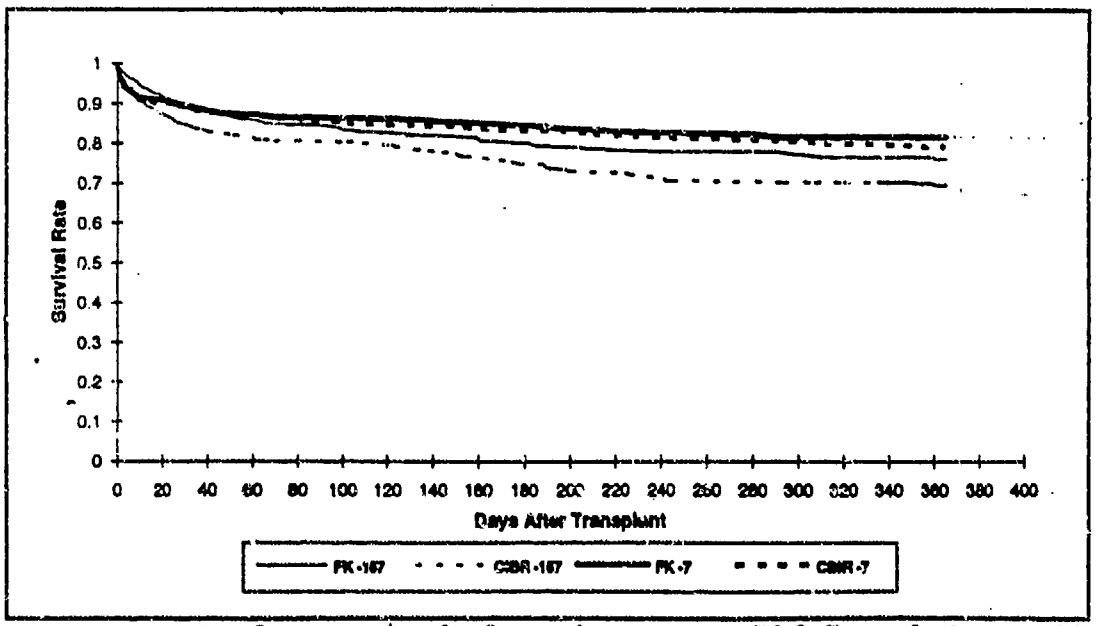

Figure 2. Graft survival for the FPC-FK506-7 and GHBA-157 study populations, tacrolimus (FK) versus CBIR.

Figures 1 and 2 show the comparative Kaplan-Meier patient and graft survival

curves for the FPC-FK506-7 and GHBA-157 studies.

One of the possible reasons for the difference in survival rates between the FPC-FK506-7 and GHBA-157 studies is the differential inclusion of patients at greater risk for graft loss. Patients ≤3 years old and those ≥60 years old have lower one-year survival rates than patients in any other age category.[82] Fulminant hepatic failure (FHF) patients, often with severe hepatic encephalopathy, have low short-term survival rates, approximately 62% at one year,[78,81] mostly due to their medically fragile condition at the time of transplantation. Malignancies are associated with a one-year patient survival rate of 60%, but, due to tumor recurrence in at least 70% of patients, long-term survival is poor (28% at three years).[82] Adult patients transplanted for cholestatic cirrhosis have higher one-year survival rates than patients with malignancies (84% vs 60%, respectively).[81]

Since the patient population in the GHBA-157 study included patients at higher risk for graft loss than the FPC-FK506-7 study, subset analyses were performed to compare similar patient populations. The subset analyses excluded patients in the GHBA-157 study who did not meet eligibility criteria for the FPC-FK506-7 protocol, i.e., patients with pre-existing renal dysfunction (serum creatinine >2.0 mg/dL), stage IV encephalopathy, and patients with active neoplastic disease. This subset of the GHBA-157 study was compared to the adult subset of the FPC-FK506-7 study, since the GHBA-157 study excluded pediatric patients. Results of these analyses are shown in Table 16. (See also Appendix B, Table B. 9, and B.10; Figures 6.1, 6.2, 7.1, and 7.2.)

Table 16: Patient and Graft Survival Rates in Comparable Study Group Subsets and Overall Study Groups of the FPC-FK506-7 and GHBA-157 Studies

Parameter & Population		FPC-FK506-7		GHBA-157	
		Tacrolimus (N)	CBIR (N)	Tacrolimus (N)	CBIR (N)
Patient Survival One-Year	Overall	88% (262)	88% (266)	81% (270)	75% (275)
	Subset	89% (233)	88% (235)	86% (222)	79% (206)
Graft Survival One-Year	Overall	82% (263)	79% (266)	76% (270)	70% (275)
	Subset	83% (233)	80% (235)	80% (222)	72% (206)

An analysis of similar-risk populations demonstrates that one-year patient survival is similar in the tacrolimus group of both studies. The difference in one-year patient survival between studies for the tacrolimus-treated patients is three percentage points (89% versus 86%) compared to seven percentage points in the overall study populations. Similarly, there is a three percentage point difference in graft survival in the similar-risk tacrolimus groups as compared to a six percentage point difference in the overall population at one year. Although the differences in CBIR survival rates between studies are less in these similar-risk populations (nine percentage points difference in patient survival and eight percentage points in graft survival), compared to the overall population (13 percentage points difference in patient survival and 9 percentage points difference in graft survival), survival in the CBIR arm of the FPC-FK506-7 study remains higher than that in the GHBA-157 study.

Thus, the difference in tacrolimus survival rates between the two studies may have been due to the inclusion of higher risk patients in the GHBA-157 study. However, the difference in CBIR rates may also relate to local practice and experience with CBIR, which varied by center; whereas tacrolimus was used in double therapy with corticosteroids in both studies and with the same recommended starting dose between centers within each study. There were no obvious differences in other demographic variables that would predict a lower survival rate in the GHBA-157 population compared to the FPC-FK506-7 population.

3.1.3.2. Rejection

Acute rejection rates were statistically significantly higher among CBIR-treated patients than among tacrolimus-treated patients in both the FPC-FK506-7 and GHBA-157 studies (P = 0.001 and P <0.001, respectively). OKT3 use was statistically significantly higher among CBIR-treated patients than among tacrolimus-treated patients in the FPC-FK506-7 study (P <0.001). Statistically significantly fewer tacrolimus-treated patients experienced refractory rejection (i.e., discontinued treatment for lack of efficacy) than did CBIR-treated patients in the FPC-FK506-7 and GHBA-157 studies (P <0.001). Table 17 presents the rates of acute rejection, OKT3 use, and refractory rejection for the FPC-FK506-7 and GHBA-157 studies. (See also Appendix B, Tables B.3, B.4, and B.5; Figures 3.1, 3.2, 4.1, 4.2, 5.1, and 5.2.)

Table 17: Rate of Acute Rejection, OKT3 Use, and Refractory Rejection (Discontinuation for Lack of Efficacy) in the Randomized, Controlled Liver Transplant Studies

Randomized Liver Transplant Studies	Acute Rejection Rate		OKT3 Use		Refractory Rejection Rate	
	183 days		183 days		183 days	
	Tacrolimus	CBIR	Tacrolimus	CBIR	Tacrolimus	CBIR
FPC-FK506-7	66%**	73%	19%**	36%	3%**	13%
GHBA-157	41%**	54%	8%	10%	3%**	10%

** P ≤ 0.001 compared to CBIR

Differing rejection rates, as shown in Figure 3, observed in these two studies may be related to the number and timing of protocol-mandated biopsies. The GHBA-157 study stipulated liver biopsy on post-operative day 7 and at one year (or study withdrawal, whichever occurred first). Rejection was diagnosed on the basis of clinical and biochemical parameters and confirmed by histologic evaluation. If a biopsy showed histological evidence of rejection that was not indicated clinically or biochemically, initiation of rejection therapy was not required. The FPC-FK506-7 study stipulated liver biopsy on post-operative day 7, post-operative day 28, and one year after transplant (or at study end,

whichever came first). The FPC-FK506-7 study also required all suspected cases of rejection to undergo histologic evaluation; histologic evidence of rejection alone was sufficient to initiate anti-rejection treatment. Additionally, the FPC-FK506-7 study stipulated a repeat biopsy seven days after completion of rejection treatment to assess rejection state. No post-rejection-treatment graft assessment was specified in the GHBA-157 protocol.

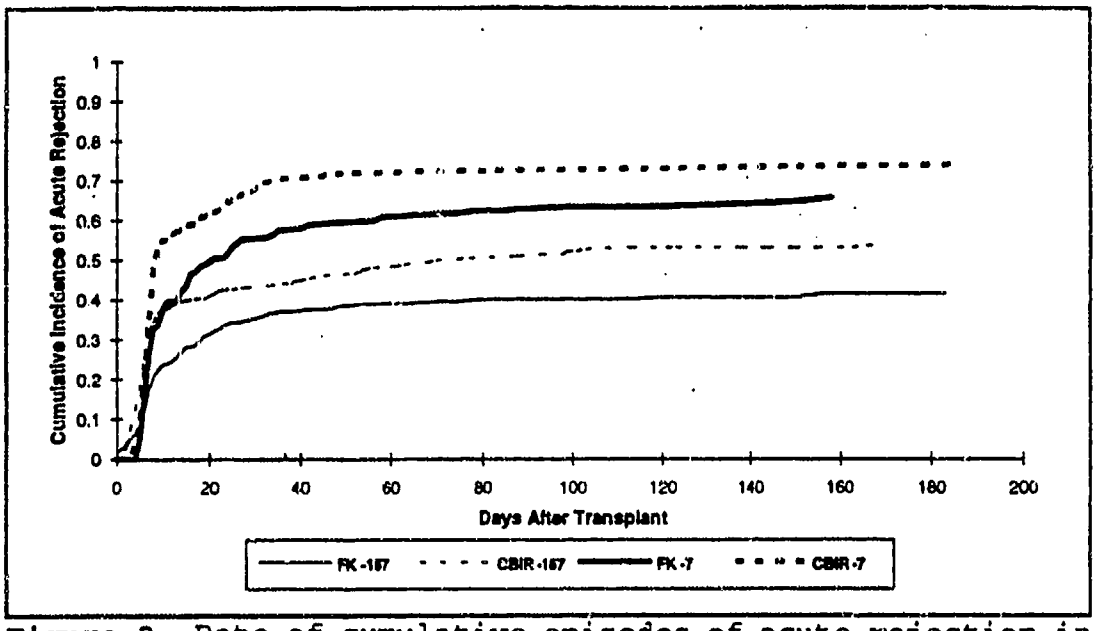

Figure 3. Rate of cumulative episodes of acute rejection in the FPC-FK506-7 and GHBA-157 study, tacrolimus (FK) versus CBIR.

In addition to the effect of more frequently performed biopsies, the high rejection rates observed in the CBIR treatment group of the FPC-FK506-7 study compared to the CBIR treatment group of the GHBA-157 study may also relate to differential use of CBIR treatment between studies. Among FPC-FK506-7 CBIR-treated patients, 11.6% received double therapy, 78.2% received triple therapy, and only 10.2% received induction therapy. This is in contrast to 40.4% of patients transplanted at centers in the GHBA-157 study using induction therapy and 59.6% of patients transplanted at centers using triple therapy. (See Table 13 and discussion of subset analysis by CBIR 8.G.5.2.) The use of non-specific anti-lymphocyte induction therapy early post-transplant results in a broad, potent immunosuppression. This potent immunosuppression is intended to reduce the early incidence of acute rejection

and to reduce the risks associated with CyA; however, it is balanced against the risks of over-immunosuppression, including the risks of viral infections and lymphoproliferative diseases.

The FPC-FK506-7 protocol specified the use of OKT3 earlier in the rejection treatment regimen than did the GHBA-157 protocol. This factor, along with the European investigators' reluctance to use OKT3, gave rise to a greater use of OKT3 among FPC-FK506-7 patients than among GHBA-157 patients. In the FPC-FK506-7 study, OKT3 was used in the case of steroid-resistant rejection, whereas, in the GHBA-157 study, OKT3 was used infrequently and usually after two discrete treatments of bolus injection and six-day recycle with steroids.

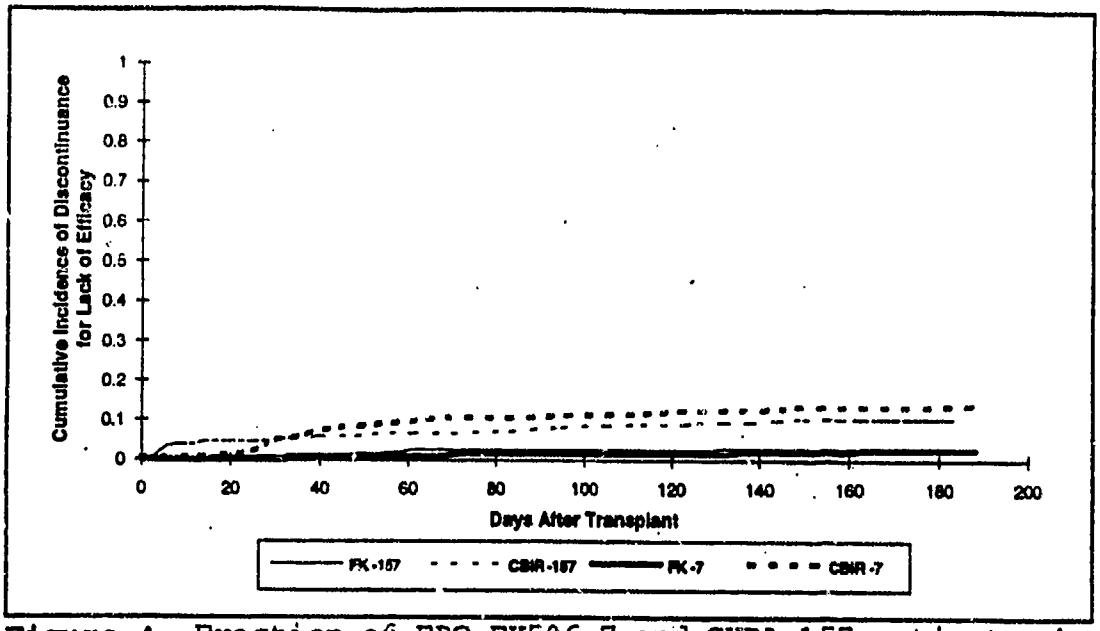

Figure 4. Fraction of FPC-FK506-7 and GHBA-157 patients who discontinued for lack of efficacy, tacrolimus (FK) versus CBIR.

Despite differences in the treatment algorithms for acute rejection, similar rates of refractory rejection were seen within treatment groups between studies and a significant decrease ($P < 0.001$) in refractory rejection rates with tacrolimus compared to CBIR was demonstrated in both studies. The cumulative rate of discontinuance for lack of efficacy in the controlled, randomized liver transplant studies is shown in Figure 4.

3.1.3.3. Liver Function

Liver function, as assessed by total serum bilirubin, improved post-transplant with a more rapid trend towards normalization in the tacrolimus group compared to the CBIR group in both the FPC-FK506-7 and GHBA-157 studies (Table 18 and Appendix B, Table B.6). Serum transaminases (GOT, GPT) demonstrated improvement post-transplant with similar values in the tacrolimus and CBIR groups (see Appendix B, Tables B.7 and B.8).

clinical significance. The incidences of most of these adverse events were lower in the nonrandomized study than in tacrolimus-treated patients in the controlled trials. It is difficult to ascribe many of these adverse events to a drug effect, because of the serious nature of the operation and underlying conditions due to liver dysfunction. The lower incidence in the nonrandomized trials may reflect the relative absence of transplant operation-related effects.

The comparative incidence of the more frequently reported physical adverse events possibly related to neurotoxicity in tacrolimus- and CBIR-treated kidney transplant patients is shown in Table 66

Table 66: Incidence of Adverse Events Possibly Related to Neurotoxicity in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Incidence (%)	
	Tacrolimus N = 106	CBIR N = 34
Headache	12 (11.3)	3 (8.8)
Neuropathy	4 (3.8)	0 (0.0)
Paresthesia	15 (14.2)	1 (2.9)
Tremor	25 (23.6)	5 (14.7)

The incidences of headache, neuropathy, paresthesia, and tremor were lower in these kidney transplant patients than those reported in the controlled liver transplant trials in tacrolimus patients.

Other adverse events possibly related to neurotoxicity in kidney transplant patients are shown in Table 67.

Table 67: Incidence of Other Adverse Events Possibly Related to Neurotoxicity in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Kidney Incidence (%)	
	Tacrolimus N = 106	CBIR N = 84
Anxiety	5 (4.7)	2 (5.9)
Depression	3 (2.8)	1 (2.9)
Dizziness	7 (6.6)	0 (0.0)
Emotional Lability	3 (2.8)	2 (5.9)
Hallucinations	1 (0.9)	0 (0.0)
Hypertonia	5 (4.7)	5 (14.7)
Insomnia	15 (14.2)	2 (5.9)
Nervousness	5 (4.7)	1 (2.9)
Somnolence	1 (0.9)	1 (2.9)

Insomnia was the most common of the nervous system cognitive adverse events in tacrolimus patients, followed by dizziness, anxiety, hypertonia, and nervousness. In CBIR patients, hypertonia was most common. Other adverse events involved only a few patients. These adverse events were less frequent in the kidney patients than in liver patients in controlled trials.

8.H.4.6. *Comparison of Adverse Events Possibly Related to Impaired Glucose Metabolism*

The comparative incidence of adverse events associated with impaired glucose metabolism in liver transplant patients treated with tacrolimus and with CBIR in controlled trials and tacrolimus in non-randomized trials is shown in Table 68, as extracted from Tables 5A and 6A, Appendix C.

Table 68: Incidence of Adverse Events Possibly Related to Impaired Glucose Metabolism: Comparison between Tacrolimus and CBIR in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Adverse Event	Incidence (%)		
	Controlled		Nonrandomized Tacrolimus N = 141
	Tacrolimus N = 512	CBIR N = 511	
Diabetes mellitus	52 (10.2)	24 (4.7)	3 (2.1)
Glycosuria	5 (1.0)	8 (1.6)	1 (0.7)
Hyperglycemia	194 (37.9)	137 (26.8)	24 (17.0)

The incidence of glycosuria was low in both treatment groups. Hyperglycemia was higher in incidence in tacrolimus patients and diabetes mellitus was reported in 52 tacrolimus and 24 CBIR patients. However, insulin use was only slightly higher in tacrolimus patients (47.5%) than that in CBIR patients (43.4%), as was overall antidiabetic use (48.0% and 43.4%, respectively; Table 4A Appendix C). This small difference in the use of insulin in the two treatment groups is not in-line with the higher reported incidences of diabetes and hyperglycemia in the tacrolimus patients. In the nonrandomized studies, these adverse events were less commonly reported than in controlled patients, although insulin use was comparable (44.4%). These effects on glucose metabolism will be addressed further in Section 8.H.8.2 of this ISS.

The comparative incidence of adverse events associated with impaired glucose metabolism in patients treated with tacrolimus and with CBIR in kidney transplant trials is shown in Table 69, as extracted from Table 6A, Appendix C.

Table 69: Incidence of Adverse Events Possibly Related to Impaired Glucose Metabolism in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Incidence (%)	
	Tacrolimus N = 106	CBIR N = 34
Diabetes mellitus	7 (6.6)	1 (2.9)
Glycosuria	4 (3.8)	0 (0.0)
Hyperglycemia	33 (31.1)	8 (23.5)

Hyperglycemia and diabetes mellitus again were apparent in the tacrolimus group. The incidences of these adverse events were generally slightly lower in the kidney transplant patients than in liver transplant patients treated with tacrolimus. Insulin usage was 50.9% in the tacrolimus-treated kidney patients and 38.2% in the CBIR-treated patients. These results suggest that tacrolimus (like CBIR) can cause glucose metabolism abnormalities. These effects on glucose metabolism will be addressed further in the laboratory section of this ISS (8.H.8.2).

8.H.4.7. Comparison of Adverse Events Possibly Related to Drug-Induced GI Disturbances

The comparative incidence of gastrointestinal adverse events that may be related to therapy in liver transplant patients treated with tacrolimus and with CBIR in controlled studies and with tacrolimus in nonrandomized studies is shown in Table 70.

Table 70: Incidence of Adverse Events Possibly Indicating Drug-Induced GI Disturbances: Comparison Between Tacrolimus and CBIR Treatment Regimens in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Adverse Event	Incidence (%)		
	Controlled		Nonrandomized Tacrolimus N = 141
	Tacrolimus N = 512	CBIR N = 511	
Anorexia	101 (19.7)	70 (13.7)	22 (15.6)
Constipation	111 (21.7)	120 (23.5)	6 (4.3)
Diarrhea	264 (51.6)	177 (34.6)	46 (32.6)
Dyspepsia	74 (14.5)	50 (9.8)	2 (1.4)
Flatulence	47 (9.2)	46 (9.0)	0 (0.0)
GI Disorder	39 (7.6)	53 (10.4)	3 (2.1)
GI Hemorrhage	36 (7.0)	33 (6.5)	16 (11.3)
GI Perforation	40 (7.8)	27 (5.3)	0 (0.0)
Ileus	19 (3.7)	19 (3.7)	0 (0.0)
Increased Appetite	34 (6.6)	40 (7.8)	1 (0.7)
Nausea	194 (37.9)	150 (29.4)	31 (22.0)
Nausea & Vomiting	52 (10.2)	34 (6.7)	12 (8.5)
Vomiting	97 (18.9)	60 (11.7)	28 (19.9)

In the controlled trials, the most frequently reported events (diarrhea, nausea, and/or vomiting) occurred more frequently in patients treated with tacrolimus than with CBIR. The incidences of anorexia, dyspepsia, and gastrointestinal perforation were higher in tacrolimus patients, but the incidences of constipation, GI hemorrhage, and ileus, were comparable in the two treatment groups. GI disorder was more commonly reported in CBIR patients. The COSTART category GI perforation includes T-tube leakage.

Adverse events related to liver dysfunction, which may be reflective of the status of the transplanted organ as well as rejection episodes in liver transplant patients, are shown in Table 71.

Table 71: Incidence of Adverse Events Possibly Indicating Hepatic Dysfunction: Comparison Between Tacrolimus and CBIR Treatment Regimens in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Adverse Event	Incidence (%)		
	Controlled		Nonrandomized Tacrolimus N = 141
	Tacrolimus N = 512	CBIR N = 511	
Alkaline Phosphatase Increased	33 (6.4)	39 (7.6)	1 (0.7)
Ascites	82 (16.0)	70 (13.7)	7 (5.0)
Bilirubinemia	41 (8.0)	57 (11.2)	5 (3.5)
Cholangitis	59 (11.5)	71 (13.9)	3 (2.1)
Cholestatic Jaundice	37 (7.2)	36 (7.0)	1 (0.7)
Hepatitis	48 (9.4)	40 (7.8)	5 (3.5)
Jaundice	69 (13.5)	53 (10.4)	8 (5.7)
LFTs Abnormal	103 (20.1)	81 (15.9)	6 (4.3)
SGOT Increased	32 (6.3)	31 (6.1)	1 (0.7)
SGPT Increased	38 (7.4)	25 (4.9)	1 (0.7)

Adverse events related to liver dysfunction (e.g., jaundice, hepatitis, abnormal liver function tests) were reported more often in tacrolimus patients. Since rejection episodes occurred significantly less often in tacrolimus patients compared to CBIR patients (see Section 8.G. Integrated Summary of Efficacy), the higher reported incidence in tacrolimus patients may reflect a difference in reporting of adverse events for the novel agent, tacrolimus, and the standard CBIR.

Compared to the findings in the controlled liver transplant trials, few adverse events related to decreased hepatic or biliary function were reported for patients in the nonrandomized trials. Since the nonrandomized study population received tacrolimus later post transplantation than the controlled population, many of the liver disorders noted in the former population are more likely to reflect early pathophysiologic events specific to liver transplantation rather than drug-related adverse reactions. Examination of

the relative laboratory data (e.g., SGOT, SGPT, and alkaline phosphatase) in controlled and nonrandomized patients reveals higher mean levels at baseline and during much of the study in the nonrandomized patients. Therefore, the lower reporting of increased levels of these parameters as adverse events in the nonrandomized trials is likely to reflect a reporting bias based on baseline or expected levels.

The incidence of gastrointestinal adverse events that may be related to therapy in kidney transplant patients treated with tacrolimus and with CBIR is shown in Table 72.

Table 72: Incidence of Adverse Events Possibly Indicating Drug-induced GI Disturbances in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Incidence (%)	
	Tacrolimus N = 106	CBIR N = 34
Constipation	11 (10.4)	6 (17.6)
Diarrhea	23 (21.7)	6 (17.6)
Dyspepsia	14 (13.2)	1 (2.9)
Nausea	18 (17.0)	2 (5.9)
Stomatitis	6 (5.7)	2 (5.9)
Nausea & Vomiting	6 (5.7)	1 (2.9)
Vomiting	10 (9.4)	1 (2.9)

Diarrhea, nausea and/or vomiting, and dyspepsia were again noted in patients treated with tacrolimus, but the incidences were lower than those reported in tacrolimus patients in controlled liver transplant trials. This seems to indicate that tacrolimus may have a direct irritant effect on the GI tract, which is consistent with its macrolide nature. The incidence of stomatitis in both treatment groups was higher than that noted in liver transplant patients (2% and 1.8%, for tacrolimus and CBIR, respectively).

Adverse events possibly related to liver dysfunction in kidney transplant patients are shown in Table 73.

Table 73: Incidence of Adverse Events Possibly Indicating Hepatic Dysfunction in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Incidence (%)	
	Tacrolimus N = 108	CBIR N = 34
Alkaline Phosphatase Increased	4 (3.8)	0 (0.0)
LFTs Abnormal	4 (3.8)	1 (2.9)
SGOT Increased	5 (4.7)	0 (0.0)
SGPT Increased	7 (6.6)	0 (0.0)

Adverse events related to hepatotoxicity were notably less frequent in the kidney transplant patients than liver transplant patients. The incidence of elevated liver function tests is low to moderate, and compatible with mild liver dysfunction often seen in kidney failure patients.[92]

8.H.4.8. Comparison of Adverse Events Possibly Related to Infection

Infections are not directly related to immunosuppressive agents, but result from a suppression of the immune system and subsequent invasive activity by endogenous pathogens. The immunosuppressed patient also is more subject to infections from acquired pathogens, including those contained in the donor graft in transplanted patients.[75,90,93,94] Infectious complications are a direct or contributing cause of death in many transplant patients. Thus, aggressive prophylaxis and treatment are commo[illegible].

The comparative incidence of adverse events possibly related to infections in liver transplant patients treated with tacrolimus or CBIR and the incidence in nonrandomized studies is shown in Table 74.

Table 74: Incidence of Adverse Events Related to Infection: Comparison Between Tacrolimus and CBIR Treatment Regimens in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Adverse Event	Incidence (%)		
	Controlled		Nonrandomized Tacrolimus N = 141
	Tacrolimus N = 512	CBIR N = 511	
Abscess	45 (8.8)	39 (7.6)	5 (3.5)
Cryptococcosis	2 (0.4)	1 (0.2)	0 (0.0)
Fever	160 (31.3)	188 (36.8)	19 (13.5)
Flu Syndrome	6 (1.2)	14 (2.7)	2 (1.4)
Infection	172 (33.6)	200 (39.1)	21 (14.9)
Peritonitis	18 (3.5)	19 (3.7)	3 (2.1)
Sepsis	66 (12.9)	89 (17.4)	11 (7.8)
Endocarditis	0 (0.0)	1 (0.2)	0 (0.0)
Moniliasis	13 (2.5)	23 (4.5)	2 (1.4)
Cutaneous moniliasis	3 (0.6)	0 (0.0)	0 (0.0)
GI moniliasis	5 (1.0)	7 (1.4)	0 (0.0)
Oral moniliasis	36 (7.0)	41 (8.0)	5 (3.5)
Respiratory moniliasis	4 (0.8)	6 (1.2)	1 (0.7)
Vaginal moniliasis	11 (2.1)	7 (1.4)	1 (0.7)
Encephalitis	0 (0.0)	1 (0.2)	0 (0.0)
Meningitis	2 (0.4)	3 (0.6)	0 (0.0)
Pharyngitis	64 (12.5)	57 (11.2)	6 (4.3)
Pneumonia	59 (11.5)	63 (12.3)	12 (8.5)
Fungal dermatitis	5 (1.0)	0 (0.0)	0 (0.0)
Herpes simplex	50 (9.8)	47 (9.2)	5 (3.5)
Herpes zoster	4 (0.8)	14 (2.7)	2 (1.4)
Urinary tract infection	91 (17.8)	91 (17.8)	9 (6.4)

The results of this tabulation reflect a tendency toward more infectious complications in CBIR patients. For instance, fever, infection, and sepsis were reported more frequently in CBIR patients than tacrolimus patients. Since immunosuppressive therapy is associated with an impaired host response to infections, infectious complications were not unexpected in this patient population. This lower incidence in tacrolimus patients may reflect, in part, the use of lower doses of adrenocorticosteroids and avoidance of other immunosuppressant agents in these patients compared to the CBIR patients. Comparison of anti-infective use in the tacrolimus and CBIR patients revealed approximately equal use of antibacterials (70.7% and 70.1%, respectively) and antivirals (50.6% and 51.1%, respectively) in the treatment groups, and a slightly higher use of antifungals in the CBIR (27.4%) compared to the tacrolimus (24.6%) patients (Table 4B, Appendix C).

In addition to infections reported as COSTART adverse events, the incidences of clinically treated and microbiologically confirmed infections were treated as formal study endpoints in the GHBA-157 comparative trial. Both clinically treated (77% tacrolimus, 81% CBIR) and proven (58% tacrolimus, 63% CBIR) infections were significantly increased in CBIR patients.

The lower incidence of reported infectious complications in the tacrolimus patients in the nonrandomized studies was not expected, as the rescue patients in this compilation had been treated with numerous immunosuppressive agents prior to conversion to tacrolimus. Concomitant usage of anti-infectives was higher in these patients compared to patients in controlled trials, with 77.8% receiving antibacterials and 37.6% antifungals. The exception was a comparable incidence of antiviral usage (51.3%) in the nonrandomized studies (Table 4B, Appendix C).

Aggravation of tuberculosis was reported in one tacrolimus patient and reactivation in one tacrolimus and one CBIR patient in controlled trials.

The incidence of infections and adverse events possibly related to infections in kidney transplant patients treated with tacrolimus and with CBIR is shown in Table 75.

Table 75: Incidence of Adverse Events Related to Infection in Tacrolimus and CBIR Patients in a Controlled Kidney Transplant Trial

Adverse Event	Incidence (%)	
	Tacrolimus N = 106	CBIR N = 34
Fever	13 (12.3)	6 (17.6)
Infection	10 (9.4)	7 (20.6)
Sepsis	3 (2.8)	0 (0.0)
Herpes simplex	6 (5.7)	1 (2.9)
Moniliasis	2 (1.9)	0 (0.0)
Oral moniliasis	6 (5.7)	1 (2.9)
Vaginal moniliasis	1 (0.9)	0 (0.0)
Pharyngitis	3 (2.8)	1 (2.9)
Urinary tract infection	10 (9.4)	4 (11.8)

Infectious complications were less frequent in these kidney transplant patients than in the liver transplant patients in controlled trials; several events seen in liver transplant patients were absent in these patients. For those events which occurred in more than one CBIR patient (i.e., fever, infection, and urinary tract infection), the reported incidence in CBIR patients was higher than that in tacrolimus patients. This finding supports the lower incidence of infectious complications in tacrolimus compared to CBIR liver transplant patients.

8.H.4.9. Neoplasms and Lymphoproliferative Disorder

Neoplasms, especially those involving the skin and lymphomas, and lymphoproliferative disorder are reported more frequently in transplant patients than in the general population.[78,90,94] As with infections, these appear to be related not to the agent per se, but to immunosuppression. It was reported that these complications were more related to the extent of immunosuppression early post transplant than to any single agent, although use of monoclonal antibodies might increase the risk.[78]

Tacrolimus is not a mutagen or genotoxic agent, based on non-clinical testing (see Section 5.G. Mutagenicity Studies). Carcinogenicity tests in rodents are ongoing.

The incidence of all neoplasms reported in liver transplant patients is shown in Table 76 (Tables 5A and 6A, Appendix C).

Table 76: Incidence of Neoplasms: Comparison Between Tacrolimus and CBIR Treatment Regimens in Controlled Liver Transplant Trials and Incidence in Nonrandomized Trials

Adverse Event	Incidence (%)		
	Controlled		Nonrandomized Tacrolimus N = 141
	Tacrolimus N = 512	CBIR N = 511	
Carcinoma	3 (0.6)	4 (0.8)	0 (0.0)
Neoplasm	0 (0.0)	3 (0.6)	0 (0.0)
Sarcoma	0 (0.0)	1 (0.2)	0 (0.0)
GI Carcinoma	0 (0.0)	2 (0.4)	0 (0.0)
Hepatic Neoplasia	0 (0.0)	1 (0.2)	0 (0.0)
Hepatoma	1 (0.2)	0 (0.0)	0 (0.0)
Lymphoma-Like Reaction	2 (0.4)	2 (0.4)	4 (2.8)
Bone Neoplasm	0 (0.0)	1 (0.2)	0 (0.0)
Carcinoma of Larynx	0 (0.0)	1 (0.2)	0 (0.0)
Carcinoma of Lung	0 (0.0)	1 (0.2)	0 (0.0)
Skin Benign Neoplasm	3 (0.6)	7 (1.4)	0 (0.0)
Skin Carcinoma	1 (0.2)	2 (0.4)	0 (0.0)
Skin Melanoma	1 (0.2)	0 (0.0)	0 (0.0)
Cervix Carcinoma	1 (0.2)	0 (0.0)	0 (0.0)
Prostatic Carcinoma	0 (0.0)	1 (0.2)	0 (0.0)

Neoplasms were reported with a low incidence in the treatment groups in the controlled liver transplant trials. However, 12 neoplasms were reported in tacrolimus patients compared to 26 in CBIR patients. In the nonrandomized trial, only 4 cases of lymphoma-like reaction were reported. The lower incidence of neoplasms in the tacrolimus-treated patients compared to CBIR patients also may reflect the lower doses of concomitant immunosuppressants, especially corticosteroids, used in the tacrolimus patients (see Section 8.G. Integrated Summary of Efficacy). In addition, the decreased usage of OKT3, ALG, or azathioprine in the tacrolimus patients (Table 4B, Appendix C), may have contributed to the decreased incidence of neoplasms.

In kidney transplant patients, single cases of neoplasm and benign skin neoplasm were reported in tacrolimus patients and single cases of adenoma and lymphoproliferative disorder in CBIR patients. However, the size of the study and the short-term follow-up of these patients (42 days) precludes definitive statements about the expected incidence of neoplasms.

8.H.5. Incidence of Adverse Events by Standard Stratifications

Standard stratifications were made on the ISS database for tacrolimus patients starting with overall tabulations of all adverse events (Tables 5A and 6A, Appendix C), followed by tabulations of common (≥3% incidence; Tables 5B and 6B, Appendix C) and frequent (≥2% incidence; Tables 5C and 6C, Appendix C) adverse events. For subsequent stratifications (i.e., age, gender, and race), overall adverse events and those adverse events which had a ≥3% incidence in any of the strata columns (e.g., male or female in a gender stratification) were tabulated. Only those events with an incidence ≥3% were subjected to further stratification (e.g., dosing, concomitant medication usage). This level was chosen because incidences of a smaller magnitude were not expected to reveal any differences among groups. Therefore, only adverse events with a ≥3% incidence will be discussed. In the stratifications by duration of oral and IV dosing, data for tacrolimus and CBIR are presented in parallel. The 0-12 month adverse events in the FPC-FK506-7 study were integrated with the 0-6 month adverse events from the GHBA-157 trial in these stratifications.

Because of the small numbers of patients entered into kidney trials, those stratifications generally will not be discussed here, although summary tabulations are presented in Appendix C.

8.H.5.1. Incidence of Common (≥3%) Adverse Events by Gender

The overall incidence of adverse events in male (N = 325) and female (N = 328) patients enrolled in liver transplant studies was comparable at 98.5%. However, within the COSTART body systems, some differences (≥2% relative incidence) were notable (Table 7A, Appendix C). For instance, in the Body as a Whole, the incidences of abdominal pain (39.1% vs. 35.4%) and pain (35.4% vs. 32.9%) were higher in males, but back pain (13.5% vs. 22.9%) was higher in females. The incidences of abscess (8.6% vs. 6.7%), infection (32.0% vs. 27.1%), and sepsis (14.2% vs. 9.5%), as well as asthenia (28.3% vs. 23.8%), hernia (4.9% vs. 0.9%), and shock (3.1% vs. 0.0%), were higher in males.

In the Cardiovascular System, arrhythmia (4.6% vs. 2.1%), hypertension (35.1% vs. 31.7%), hypotension (12.6% vs. 8.2%), and tachycardia (12.0% vs. 7.9%) were more common in males, while chest pain (6.8% vs. 8.8%), and vasodilatation (2.8% vs. 5.8%) were more common in females.

In the Digestive System, the incidences of anorexia (16.3% vs. 21.3%), cholestatic jaundice (4.3% vs. 7.3%), constipation (16.9% vs. 18.9%), GI hemorrhage (6.6% vs. 9.1%), nausea (27.4% vs. 41.5%), and nausea and vomiting (7.4% vs. 12.2%) were higher in females, while GI disorder (8.3% vs. 4.6%), GI perforation (7.4% vs. 4.9%), hepatitis (10.8% vs. 5.5%), and liver function tests abnormal (17.8% vs. 15.5%) were more common in males.

Diabetes mellitus was more common in males than females (9.8% vs. 7.0%), although hyperglycemia was more common in females (32.0% vs. 34.8%).

Prothrombin decreased (4.9% vs. 2.7%) and splenomegaly (3.7% vs. 0.9%) were more common in males. Bilirubinemia (5.8% vs. 8.2%), edema (8.9% vs. 11.9%), generalized edema (2.2% vs. 4.6%), and hypokalemia (14.8% vs. 18.3%) were more common in females. In contrast, acidosis (8.0% vs. 5.8%), alkalosis (4.3% vs. 1.2%), hyperlipemia (6.5% vs. 2.1%), hypomagnesemia (27.7% vs. 22.3%) were more common in males. Weight loss (3.7% vs. 1.5%), myalgia (9.5% vs. 5.8%), and myasthenia (6.2% vs. 4.0%) were more common in males.

While headache (40.9% vs. 47.9%) and paresthesia (22.2% vs. 24.1%) were more commonly reported in females, the incidence of tremor (48.3% vs. 43.3%) was higher in males. Males also had a higher incidence of confusion (14.5% vs. 7.0%), hypertonia (8.0% vs. 5.2%), insomnia (41.2% vs. 37.5%), somnolence (10.5% vs. 7.0%), and abnormal thinking (5.5% vs. 3.4%).

Apnea (3.4% vs. 1.2%) and pneumonia (12.0% vs. 9.8%) were more common in males, whereas pharyngitis (9.2% vs. 12.2%), pleural effusion (22.8% vs. 27.1%), and rhinitis (5.2% vs. 8.5%) were more common in females. Voice alterations were reported more frequently in males (5.5% vs. 3.0%). Alopecia (7.4% vs. 13.1%), *Herpes simplex* infection (6.2% vs. 10.7%), pruritus (20.0% vs. 29.0%), rash (12.3% vs. 14.9%), and sweating (8.3% vs. 11.0%) were all reported more often in females.

Several indices of kidney dysfunction [e.g., increased BUN (20.0% vs. 14.9%), hematuria (4.0% vs. 1.8%), kidney failure (8.3% vs. 4.9%), and abnormal kidney function (32.0% vs. 29.0%)] were reported more often in males. The incidence of increased serum creatinine was comparable (28.3% vs. 27.4%). Finally, urinary tract infections (UTI) were reported in 7.1% of males and 23.5% of females; this disparity parallels that for reported UTI in the general population. Vaginal adverse events included vaginal hemorrhage (2.1%), vaginal moniliasis (3.7%), and vaginitis (4.3%).

It is unclear why many of these differences exist between males and females in the reported incidence of adverse events. The relative differences between some of these may be due to chance alone, especially those which occurred with a high incidence and differed little between the sexes (e.g., paresthesia at 22.2% vs. 24.1%). Others may be due to differences in reporting (e.g, pain or back pain). Potential underlying differences between male and female patients requiring liver transplantation cannot be ruled out. However, the overall incidence of adverse events was comparable in males and females, despite higher incidences of some in males and others in females. Therefore, no differences in dosing based on gender can be recommended.

8.H.5.2. Incidence of Common (≥3%) Adverse Events by Age

5.2.1. Incidence of Common Adverse Events in Pediatric versus Adult Patients

The overall incidence of adverse events in pediatric (≤12 years; N = 74) and adult (>12 years; N = 579) patients in liver trials was tabulated (Table 6F, Appendix C). In the Body as a Whole category, pediatric patients had a higher incidence of abdomen enlarged (10.8% vs. 5.9%) and fever (31.1% vs. 26.9%). In contrast, infection (27.0% vs. 29.9%) and sepsis (8.1% vs. 12.3%) were reported more frequently in adult patients. Other adverse events reported more frequently in adults were abdominal pain (17.6% vs. 39.7%),

ascites (8.1% vs. 14.3%), asthenia (4.1% vs. 28.8%), back pain (2.7% vs. 20.2%), pain (14.9% vs. 36.6%), and photosensitivity reaction (0.0% vs. 6.0%).

The increased reporting of pain in adult patients was also seen for chest pain (1.4% vs. 8.6%). It is unclear if these findings are a real difference between the two subgroups of patients or an artifact of reporting. Since certain adverse events must be volunteered by the subject, these cannot be easily collected in small children. Of the 74 pediatric patients in this tabulation, 45 were aged 0-3 years.

Cardiovascular adverse events reported more frequently in pediatric patients were hemorrhage (12.2% vs. 9.3%) and tachycardia (12.2% vs. 9.7%). Arrhythmia (0.0% vs. 3.8%), hypertension (25.7% vs. 34.4%), and hypotension (6.8% vs. 10.9%) were reported more frequently in adult patients.

Adverse events involving the digestive tract were more frequently reported in adult than in pediatric patients. Only gastrointestinal hemorrhage (21.6% vs 6.2%), oral moniliasis (3.1% vs. 6.0%), pancreatitis (5.4% vs. 1.9%), and stomatitis (4.1% vs. 1.4%) were reported more frequently in pediatric patients. Digestive tract adverse events reported more frequently in adults were anorexia (16.2% vs. 19.2%), cholangitis (1.4% vs. 10.5%), cholestatic jaundice (0.0% vs. 6.6%), constipation (1.4% vs. 20.0%), diarrhea (31.1% vs. 49.6%), dyspepsia (4.1% vs. 12.6%), dysphagia (0.0% vs. 3.3%), flatulence (1.4% vs. 7.9%), GGTP increased (0.0% vs. 3.5%), GI disorder (0.0% vs. 7.3%), GI perforation (0.0% vs. 6.9%), hepatitis (1.4% vs. 9.0%), nausea (8.1% vs. 37.8%), and nausea and vomiting (5.4% vs. 10.4%).

A review of these gastrointestinal adverse events indicates that tacrolimus is better tolerated by pediatric than adult patients. Gastrointestinal hemorrhage, which was reported more frequently in children, is likely to be a result of the more difficult procedure of liver transplantation in such patients.

Diabetes mellitus was only reported in adult patients (9.5%) and hyperglycemia was reported in more adults (18.9% vs. 35.2%).

Anemia (27.0% vs. 22.3%), coagulation disorder (8.1% vs. 5.9%), and leukocytosis (18.9% vs. 15.4%) were reported more frequently in pediatric patients. Thrombocytopenia (10.8% vs. 13.3%) was more frequently reported in adults. Lymphoproliferative disorder (2.7% vs. 0.7%) was reported in 2 children and 4 adults.

Acidosis (14.9% vs. 5.9%), dehydration (6.8% vs. 2.6%), hypophosphatemia (10.8% vs. 7.1%), and hypovolemia (4.1% vs. 1.2%) were reported more frequently in children. Alkaline phosphatase increased (2.7% vs. 5.5%), bilirubinemia (4.1% vs. 7.4%), edema (6.8% vs. 10.9%), hypokalemia (13.5% vs. 16.9%), hypomagnesemia (23.0% vs. 25.2%), peripheral edema (2.7% vs. 18.0%), SGOT increased (1.4% vs. 5.5%), and SGPT increased (1.4% vs. 6.6%) were more frequently reported in adults.

Leg cramps (2.7% vs. 5.2%), myalgia (2.7% vs. 8.3%), and myasthenia (0.0% vs. 5.1%) were more common in adults.

Headache (12.2% vs. 48.5%), paresthesia (2.7% vs. 25.7%), and tremor (16.2% vs. 49.6%) were more common in adults, whereas convulsions (6.8% vs. 4.8%) were more common in children. Agitation (13.5% vs. 7.4%) and nervousness (14.9% vs. 5.9%) were reported more frequently in children. In contrast, anxiety (2.7% vs. 6.6%), confusion (0.0% vs. 12.1%), depression (2.7% vs. 11.9%), dizziness (1.4% vs. 10.7%), emotional lability (2.7% vs. 4.7%), euphoria (0.0% vs. 2.4%), hypertonia (0.0% vs. 7.4%), incoordination (1.4% vs. 10.5%), insomnia (13.5% vs. 42.7%), psychosis (0.0% vs. 2.9%), and abnormal thinking (0.0% vs. 5.0%) were more commonly reported in adults. These findings would seem to indicate less physical and cognitive adverse events from tacrolimus in children compared to adults.

Lung disorder (10.8% vs. 8.8%), lung edema (8.1% vs. 3.5%), and pharyngitis (17.6% vs. 9.8%) were more commonly reported in children. Atelectasis (9.5% vs. 13.6%), dyspnea (8.1% vs. 14.5%), pleural effusion (10.8% vs. 26.8%), pneumonia (8.1% vs. 11.2%), respiratory disorder (2.7% vs. 4.8%), and voice alteration (0.0% vs. 4.8%) were more frequently reported in adults.

Herpes zoster was more common in children (2.7% vs. 0.7%), whereas *Herpes simplex* was more common in adults (2.7% vs. 9.2%). Alopecia (4.1% vs. 11.1%, hirsutism (0.0% vs. 3.3%), pruritus (18.9% vs. 25.2%), rash (8.1% vs. 14.3%), and sweating (4.1% vs. 10.4%) were more frequently reported in adults. Similarly, abnormal vision (0.0% vs. 5.4%), amblyopia (1.4% vs. 12.3%), and tinnitus (0.0% vs. 4.7%) were more common in adults.

Several indices of nephrotoxicity [e.g., serum creatinine increased (16.2% vs. 29.4%), hyperkalemia (23.0% vs. 25.9%), kidney failure (2.7% vs. 7.1%), kidney function abnormal (10.8% vs. 33.0%), and oliguria (9.5% vs. 14.7%)] were more frequently reported in adults. Only hyperuricemia (5.4% vs. 3.3%) was more common in children. Urinary frequency (0.0% vs. 2.1%), urinary tract infection

(8.1% vs. 16.2%), vaginal moniliasis (0.0% vs. 2.1%), and vaginitis (0.0% vs. 2.4%) were more common in adults.

An examination of all of the above adverse events indicates that tacrolimus is better tolerated by children than adults.

5.2.2. Incidence of Common Adverse Events by Age Groups

The incidence of adverse events by age group for all subjects enrolled in FPC liver transplant trials is shown in Tables 8A, Appendix C (overall) and 8B (≥3% incidence). Because of limited subject numbers in some of the groups (e.g., >3-6, >6-12, >12-18, and >65 years), conclusions involving these groups were usually difficult to make. In general, the overall incidence of adverse events by body system in the 0-3 year-old group was lower than that in the >18-35-year-old group, while a higher incidence was reported in the >50-65- and >65-year-old groups. One or more adverse events were reported in 88.9% of patients aged 0-3 years, 100% of those aged >18-35, 99.1% of those aged >35-50, 99.6% of those aged >50-65, and 100% of those aged >65 years.

In the COSTART category Body as a Whole, the overall incidence of adverse events increased with age. The incidence of infection increased with increasing age in adults (26.5% to 38.5%), but was higher in the 0-3 years group (33.3%) than adults, except those >65 years. While the overall incidence of adverse events involving the Cardiovascular System appeared to increase with age, most adverse events were reported with a low incidence. Most of the adverse events seen in only one or a few subjects were reported in the >35-50- and >50-65-years age groups. Arrhythmia, hypertension, hypotension, and tachycardia appeared to increase in incidence with age, although the incidences of hypertension and tachycardia were higher in the 0-3 years group than in young adults.

Adverse events involving the Digestive System generally increased with age; most notable in incidence in this category were anorexia, increased appetite, jaundice, and liver function tests abnormal. Pediatric patients in the 0-3 years group had a moderately high incidence of abnormal LFTs (24.4%). Adverse events involving the Endocrine System were rare in pediatric subjects, with only two reports of Cushing's syndrome and no diabetes mellitus in subjects up to 18 years of age. The incidence of diabetes mellitus increased with age among the >18-35, >35-50, and >50-65 years groups. A similar pattern was seen for hyperglycemia with a lower incidence in the 0-3 years group and increases in the adult population with age.

The overall incidence of adverse events involving the Hemic and Lymphatic Systems also generally increased with age in adults, but only the incidences of anemia, ecchymosis, and leukocytosis appeared to increase with age in adults. Patients in the 0-3 years group had a higher incidence of hemic adverse events overall than adults, except those in the >50-65 and >65 years groups. Adverse events with a moderately high incidence in this pediatric group as compared with adults included anemia, coagulation disorder, leukocytosis, and thrombocytopenia.

In the category of Metabolic and Nutritional Disorders, the overall incidence of adverse events appeared to increase with age, as did the incidence of several individual adverse events. These included acidosis, hypocalcemia, and hypophosphatemia in adults. The overall incidence of adverse events involving the Musculoskeletal System did not change with age and the incidence of most individual adverse events was low. The lowest incidence was in the 0-3 years group.

The overall incidence of adverse events involving the Nervous System was lower in the 0-3 years group than in adults and was comparable in the adult groups >18 years old. Notably, certain adverse events which require reporting by the patient (e.g., amnesia, confusion, dizziness, etc.) were not reported in the 0-3 years group. Incoordination and neuropathy showed apparent increases in incidence with age. The incidences of headache and tremor did not appear to be clearly related to age in adults and were low in incidence in the 0-3 years group compared with adults. Adverse events involving the Respiratory System which appeared to increase with age included atelectasis, dyspnea, lung disorder, and pleural effusion. Adverse events involving the Skin and Appendages and the Special Senses did not appear to increase with age. The incidence of individual adverse events was low, with the exceptions of abnormal vision, amblyopia, and tinnitus, all of which had the highest incidence in the >35-50 years group. Adverse events involving the Urogenital System showed an apparent increase with age, due mostly to the increase in the incidence of abnormal kidney function with age. Hyperkalemia also increased with age in adults, but had a moderately high incidence in the 0-3 years group.

The increase in reported adverse events with increasing age in the adult patients is not unexpected, based on the expected increase in complications in the aging adult population.[95-96] Aged patients are rarely considered for transplantation. The reasons for this include a shortage of organs, an expected lower success rate, and expected complications in such patients.

A higher incidence of certain adverse events in liver transplantation patients ≤3 years of age is expected. These patients generally have a number of congenital abnormalities and are a difficult population with respect to the operation: hepatic artery thrombosis is common[86] and size-reduced transplants or living related-donor grafts are required.[78,94] These very young pediatric patients appeared to do well with tacrolimus therapy.

5.2.3 Comparative Incidence of Common Adverse Events in Pediatric Patients in a CBIR-Controlled Trial

An important aspect of the FPC-FK506-7 trial was the relatively large number of children who were enrolled. Until recently, the number of pediatric liver transplants was exceeded by adults, due to many factors including a shortage of appropriate donors.[64] In this trial, a total of 51 pediatric patients were enrolled: 30 received FK506 and 21 received CBIR.

Since children require higher doses of tacrolimus to maintain comparable blood trough levels, there is concern about the potential risk for increased adverse events.[40] The number of children discontinued for an adverse event was the same between the two treatment groups. Several adverse events which were reported with greater frequency in the overall tacrolimus treatment group, were reported with similar frequency in both treatment groups in children, especially creatinine increased (tacrolimus 17.2%; CBIR 20.0%); diarrhea (58.6% vs 55.0%); and headache (17.2% vs 15.0%). Several events were reported less frequently in children receiving tacrolimus, including infection (41.4% vs 55%); leukocytosis (48.3% vs 65.0%); hypertension (41.0% vs 75.0%); hypomagnesemia (34.5% vs 50.0%); and hyperglycemia (34.5% vs 50.0%). There were a few events reported more frequently in children receiving tacrolimus, most notably agitation (31.0% vs 20.0%); insomnia (24.1% vs 15.0%); and tremor (10.3% vs 5.0%).[40]

While patient and graft survival in children were similar between the two treatment groups, for children treated with tacrolimus, rejection was less, concomitant immunosuppression, especially corticosteroids, was less, and adverse event reporting was similar or, in some cases, less frequent.[40] Thus, tacrolimus would appear to offer a clinical advantage in children. Corticosteroid use, especially in children, has clearly been associated with significant side effects, most notably growth retardation.[60] Similarly, OKT3 use has predisposed children to a significantly increased risk of infection, a frequent cause of death in pediatric liver transplant patients, making the observation of fewer infections in children receiving tacrolimus even more

notable.[64,65] Finally, hypertension was reported less frequently in children receiving tacrolimus. Clearly, long-term hypertension in such a young population raises the specter of accelerated cardiovascular events. A drug which is potentially required for life that might reduce this risk, such as tacrolimus, would offer significant advantages.

8.H.5.3. Incidence of Common (≥3%) Adverse Events by Race

One or more adverse events were reported in approximately equal incidence in caucasians and hispanics (524/528: 99.2% and 45/45: 100%, respectively; Table 9A, Appendix C). The incidence in blacks was lower (30/32: 93.8%) and the incidence in orientals was the lowest (36/40: 90.0%). This same pattern was seen in the overall incidence of adverse events within most body systems. When individual adverse events were examined, large differences were seen between the groups for many of these and the hispanic group often had the highest reported incidence. However, as the number of noncaucasians is low, no analyses of individual adverse events will be attempted here. When only controlled studies were examined for common adverse events, no differences were seen by race overall, although caucasians appeared to have a lower incidence in most body systems.

8.H.5.4. Incidence of Common (≥3%) Adverse Events by Selected Concomitant Medication Usage

The incidence of common (≥3% incidence) adverse events in patients treated with antihypertensive agents, nephrotoxic agents, and hyperglycemic agents was tabulated (Table 11, Appendix C). The incidences of hypertension, hypotension, and hyperkalemia were compared among patients in the tacrolimus and CBIR primary liver transplantation groups overall (Table 6A, Appendix C) and in the subsets treated with antihypertensive agents. The incidences of each of these events was lower in the treated subgroups, although the relationship seen in the overall groups between tacrolimus and CBIR was continued in the subgroups.

Various indices of nephrotoxicity (e.g., increased BUN, increased creatinine, hyperkalemia, kidney failure, kidney function abnormal, and oliguria) were compared between the two treatment groups in the controlled liver transplantation trials and in subsets treated with potentially nephrotoxic agents. Interestingly, the incidence of these adverse events was about 50% (or more) lower in those patients who also received nephrotoxic agents (Table 11, Appendix C). The reasons for this unexpected finding are unknown. An

hypothesis is that potentially nephrotoxic agents were carefully administered in the trials in those patients with renal dysfunction related to primary drugs or other reasons. Both protocols specified careful usage of such agents to avoid additive nephrotoxicity.

A lower incidence of hyperglycemia was also seen in patients treated with potentially hyperglycemic agents compared to the respective overall patient groups. However, the potentially hyperglycemic agents considered were total parenteral nutrition (TPN) and thiazides. As TPN is limited in scope and duration largely to hospitalized patients, this finding was not surprising.

The incidence of common adverse events in patients treated with antifungals, antibacterials, and antivirals was tabulated (Table 12, Appendix C). The incidence of various nondefined infections (e.g., abscess, fever, infection, etc.) was evaluated by the use of antivirals, antibacterials, and antifungals. Overall, infections were lower in treated patients in both drug groups than the overall populations.

8.H.5.5. Incidence of Common (≥3%) Adverse Events by Daily IV Dose at Onset

The incidence of common (≥3% incidence) adverse events in tacrolimus patients in liver allograft trials was tabulated according to the IV dose (<0.05, 0.05-0.10, or >0.10) at onset of the adverse event (Table 13A, Appendix C). Since IV dosing generally occurred over the first few days after transplantation or conversion, this tabulation reflects mostly the early experience with tacrolimus. In addition, categories are not mutually exclusive, as a patient may have received differing IV doses.

Overall, and in some body systems, there was an increase in the incidence of common adverse events with increasing IV dose. Among individual adverse events, abdomen enlarged (1.1%, 1.3%, 3.0%), pain (6.4%, 8.1%, 10.2%), anorexia (0.6%, 2.0%, 3.0%), diarrhea (4.7%, 5.6%, 6.6%), and nausea (2.2%, 5.9%, 6.6%) increased in incidence with the IV dose. Edema (2.0%, 2.7%, 3.0%) showed a small increase with IV dose. In the Nervous System, common adverse events increased with dose, as did the incidences of paresthesia (1.4%, 2.2%, 3.6%) and tremor (3.6%, 5.1%, 8.4%). The incidence of pruritus (2.0%, 2.4%, 7.8%) increased with IV dose.

The incidence of adverse events possibly related to nephrotoxicity, e.g., BUN increased (3.6%, 4.8%, 7.2%) and creatinine increased (3.4%, 5.4%, 6.6%)

increased with increasing IV dose. Headache (4.5%, 4.6%, 7.8%), atelectasis (3.9%, 4.0%, 7.2%) and pleural effusion (5.3%, 6.2%, 10.8%) increased with IV dose.

Overall, these findings seem to indicate that some adverse events involving GI disturbances, neurotoxicity, and nephrotoxicity may be related to the IV dose. Interestingly, the initial IV dose was decreased during the course of these trials because of perceived nephrotoxicity from the higher doses used initially. The currently recommended IV dose (0.05-0.10 mg/kg/day) may decrease the incidence of some of these adverse events.

8.H.5.6. Incidence of Common (≥3%) Adverse Events by 3-Day Average Daily Dose at Onset (Adult versus Pediatric Subjects)

Pediatric patients were not entered into the GHBA-157 trial, but were enrolled in the other liver allograft trials. Because of differences in adult and pediatric dosing and measured tacrolimus blood concentrations, the incidence of adverse events by the 3-day average oral dose (<0.15, 0.15-0.30, or >0.30 mg/kg/day) at onset was tabulated separately by adult and pediatric patients (Tables 14A and 14C, Appendix C). The differences between adult and pediatric patients in dosing and resulting blood concentrations are detailed in the FPC-FK506-7 Report (Section 8.M.1.1).

In adults, there was no evidence of an increase in adverse events incidence with an increase in the oral dose, either overall or in any body system. No individual adverse event, except leukocytosis (6.7%, 6.8%, 7.0%), showed an increase in incidence with dose. Jaundice (7.8%, 5.2%, 0.8%) and liver function tests abnormal (11.0%, 8.0%, 1.6%) showed a negative correlation with oral dose; this may reflect increased rejection episodes at lower tacrolimus doses.

In pediatric patients, a number of body systems and individual adverse events showed an increased incidence with increasing dose. Such adverse events included abdomen enlarged (0.0%, 3.8%, 6.3%), infection (0.0%, 13.5%, 15.9%), sepsis (0.0%, 0.0%. 7.9%), tachycardia (3.7%, 3.8%, 6.3%), diarrhea (7.4%, 21.2%, 25.4%), GI hemorrhage (3.7%, 11.5%, 12.7%), liver function tests abnormal (0.0%, 5.8%, 9.5%), oral moniliasis (0.0%, 3.8%, 6.3%), vomiting (3.7%, 9.6%, 14.3%), leukopenia (0.0%, 1.9%, 6.3%), increased BUN (0.0%, 7.7%, 9.5%), increased creatinine (0.0%, 3.8%, 17.5%), dehydration (0.0%, 1.9%, 6.3%), hyperglycemia (0.0%, 7.7%, 7.9%), hyperkalemia (3.7%, 5.8%, 14.3%), hypomagnesemia (0.0%, 13.5%, 14.3%), arthralgia (0.0%, 5.8%, 6.3%),

nervousness (3.7%, 5.8%, 12.7%), somnolence (3.7%, 3.8%, 6.3%), lung disorder (0.0%, 1.9%, 6.3%), pharyngitis (0.0%, 5.8%, 14.3%), pneumonia (0.0%, 1.9%, 7.9%), kidney function abnormal (3.7%, 3.8%, 6.3%), and urinary tract infection (0.0%, 1.9%, 6.3%). While these relationships with increasing oral dose exist, the total number of patients is relatively small and the relationships are based on numerous observations in this subgroup of patients. A number of other adverse events showed an apparent increase with dose, but involved only 2 or 3 patients in the high-dose group.

8.H.5.7. Incidence of Common (≥3%) Adverse Events by Route of Administration

The incidence of common (≥3% incidence) adverse events was tabulated according to the route of administration at the time of onset of the adverse event (Table 15, Appendix C). Since oral administration of tacrolimus extended for up to a year and IV administration for just a few days, a higher incidence of adverse events was expected in the oral dosing subset. This was the case overall and in each body system. There was no adverse event in this tabulation seen exclusively in the IV subset. Some adverse events occurred only or almost exclusively in the oral subset: chills (PO: 4.5%, IV: 0.0%), chest pain (8.2%, 0.2%), hernia (3.0%, 0.0%), peritonitis (3.0%, 0.4%), cholestatic jaundice (5.8%, 0.5%), dysphagia (3.0%, 0.0%), hepatitis (8.3%, 0.2%), alkaline phosphatase increased (5.1%, 0.4%), dehydration (3.0%, 0.2%), healing abnormal (3.5%, 0.5%), depression (10.9%, 0.5%), hypertonia (6.4%, 0.5%), nervousness (6.9%, 0.5%), leg cramps (5.0%, 0.2%), bronchitis (3.0%, 0.2%), cough increased (5.8%, 0.2%), rhinitis (7.2%, 0.0%), *Herpes simplex* (8.5%, 0.5%), skin disorder (3.2%, 0.2%), and abnormal vision (4.6%, 0.4%).

Adverse events which showed a high incidence in the IV subset, especially as compared to the oral subset (e.g., about 50% of the oral subset incidence), were abdomen enlarged (PO: 4.8%, IV: 2.5%), ascites (10.3%, 4.8%), pain (27.2%, 12.5%), sepsis (9.0%, 3.9%), hemorrhage (6.9%, 4.1%), hypertension (26.1%, 13.4%), hypotension (7.7%, 3.8%), tachycardia (6.7%, 4.7%), coagulation disorder (3.7%, 3.2%), hypochromic anemia (3.5%, 2.0%), thrombocytopenia (8.7%, 5.9%), acidosis (5.1%, 2.5%), BUN increased (12.3%, 7.7%), bilirubinemia (5.1%, 2.5%), edema (7.9%, 3.9%), hyperglycemia (21.6%, 17.2%), hypocalcemia (6.6%, 6.1%), hypokalemia (10.7%, 8.6%), agitation (5.9%, 3.4%), anxiety (5.0%, 2.2%), atelectasis (7.9%, 7.2%), lung disorder (6.4%, 3.8%), pleural effusion (16.8%, 10.9%), respiratory disorder (3.2%, 2.0%), voice alteration (3.2%, 1.4%), kidney failure (4.3%, 2.7%), and kidney function abnormal (22.8%, 13.6%).

Lung edema (1.9%, 2.3%) and oliguria (7.1%, 9.5%) occurred more frequently in the IV subgroup.

L.H.5.8. Incidence of Common (≥3%) Adverse Events by Duration of Oral Treatment

The incidence of common (≥3% incidence) adverse events was tabulated according to the duration of oral therapy in the controlled liver transplant trials (Table 16A, Appendix C). No correction was made for the differing lengths of exposure in the periods used in this tabulation (e.g., ≤7 days vs. 29-90 days). The overall incidence of these common adverse events was highest in the first week in the tacrolimus patients and during days 29-90 in the CBIR patients. After day 180, the incidence of adverse events dropped in both treatment groups.

Hypertension showed an initial (≤7 days) moderately high incidence in the tacrolimus group, then a decrease in both groups through day 28. Between days 29-90 and 91-180, there was an increase in the incidence of hypertension, with a decrease after day 180. The incidence of headache showed a similar apparent increase between days 29-90 and 91-180. The apparent increases between days 29 and 90 may reflect the longer reporting interval.

The incidences of constipation, diarrhea, jaundice, and nausea were highest in the first week and decreased steadily thereafter. A similar but more dramatic decrease was seen in the incidences of leukocytosis, pleural effusion, and oliguria after the first week. Decreases were also seen in increased BUN, increased serum creatinine, hyperglycemia, hypocalcemia, hypomagnesemia, insomnia, atelectasis, and kidney function abnormal after the first week.

In the nonrandomized liver transplant studies, most adverse events occurred in the first week of oral dosing (Table 17, Appendix C). An apparent increase in adverse events between days 29-90 was probably related to the increase in the dosing interval being considered. A high incidence of adverse events in the first week was seen for abdominal pain, asthenia, fever, anorexia, diarrhea, nausea, vomiting, anemia, increased BUN, increased creatinine, hyperkalemia, headache, insomnia, tremor, nervousness, and pruritus.