AC mins
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DRAFT
12-9-93

Food and Drug Administration
Center for Drug Evaluation and Research
SUMMARY MINUTES
ANTIVIRAL DRUGS ADVISORY COMMITTEE
SUBCOMMITTEE ON IMMUNOSUPPRESSANT DRUGS
November 22, 1993
Parklawn Building, Conference Rooms D and E
5600 Fishers Lane, Rockville, Maryland

Antiviral Drugs Advisory Committee Members Present

Deborah J. Cotton, M.D., Chair
John F. Modlin, M.D.

Temporary Voting Members from Other Advisory Committees

Darrell Abernethy, M.D., Ph.D.
Terrence F. Blaschke, M.D.

Consultants Serving as Temporary Voting Members

Gary Burke, M.D.
Paul M. Columbiani, M.D.
Donald E. Hricik, M.D.
Lawrence G. Hunsicker, M.D.
Barry D. Kahan, Ph.D., M.D.
Richard A. Mann, M.D.
Paul Meier, Ph.D.

Guest

Terry B. Strom, M.D.

FDA Presenters

Marc Cavaillé-Coll, Ph.D., M.D.
Angelica Dorantes, Ph.D.
David W. Feigal, M.D., M.P.H.
Lisa Kammerman, Ph.D.

Fujisawa USA, Inc. Presenters

Ronald W. Busuttil, M.D., Ph.D.
William Fitzsimmons, Pharm.D.
Sue McDairmid, M.D.
James Shook, Ph.D.
Russell Wiesner, M.D.

These summary minutes for the November 22, 1993 meeting of the Antiviral Drugs Advisory Committee's Subcommittee on Immunosuppressant Drugs were approved on _____.

I certify that I attended the November 22, 1993 meeting of the Antiviral Drugs Advisory Committee's Subcommittee on Immunosuppressant Drugs and that these minutes accurately reflect what transpired.

Lee L. Zwanziger, Ph.D.
Executive Secretary

Deborah J. Cotton, M.D.
Chair

as an active control the cyclosporine-based regimen preferred by the particular center. In general, there were three active control regimens: double therapy (cyclosporine + steroids), triple therap, (cyclosporine + steroids + azathioprine), or induction therapy (ALG, i.e., antilymphocyte treatment, followed by triple therapy). Triple therapy was most often used, followed by induction therapy. The design was open- label after treatment began, but investigators were blinded to the regimen until the time medication was first administered. Patients suffering rejection could switch treatments, but only those receiving tacrolimus could switch due to adverse events other than rejection. The primary endpoints were survival of patients and of grafts at 12 months. All those enrolled were included in the intent-to-treat analysis. Patient and graft survival rates were very similar for the treatment groups in both trials: 88% for patients and 79 to 82 % for grafts in the US trial, and in Europe, 75 to 81 % for patients and 70 to 76 % for grafts. In each case, any differences favored tacrolimus.

There are many toxicities associated with tacrolimus, as with cyclosporine, compounded by the facts that the patients may be taking some two dozen different drugs plus suffering liver disease. The major toxicities of concern for tacrolimus include nephrotoxicity, neurotoxicity and metabolic disturbances. Clinicians must individualize the dose to avoid rejection and minimize toxicity, but very little is known at present about the pharmacokinetics of the drug and it is difficult to assay blood levels reliably for therapeutic monitoring.

5. QUESTIONS FROM ADVISORY COMMITTEE TO SPONSOR

Dr. Hunsicker questioned the company about the importance of the monitoring device. They responded that it is very important, and the Dr. Feigal confirmed that it is under review. Dr. Modlin asked about the difference in rejection rates in the two studies, since rates were higher in the European study where less steroid was used. Dr. Strom pointed out that both tacrolimus and cyclosporine seem to act by inhibiting calcineurin, a phosphatase that acts in T-cell activation but is also present in nervous tissue, so the drugs have similar efficacy and toxicity profiles. Dr. Kahan questioned the statistical analysis provided by the company, suggesting that multivariate analysis might be helpful to correct for the multiple confounding variables present in the study population, though Dr. Meier commented that if the trial was well-designed, the randomization should take care of that problem. Dr. Cotton asked why there had been no presentation of Phase I-II trials.

6. FDA PRESENTATIONS

FDA staffers presented highlights of the review, noting that while there were some possible problems with the study, such as the different active controls, the Agency substantially agreed

This question stimulated some discussion on the reliability of the blood levels available at the time of the study. Members suggested that there was so much variability that if monitoring was truly necessary, then the drug could not be approved with current assays. Some added that the drug was being "monitored" by clinical results rather than by blood levels, which is what was done with cyclosporine. Members agreed that reliable assays would indeed be helpful, and not only in the clinic but also for establishing basic pharmacokinetic properties of the drug.

3. If the committee concludes that the answer to question 1 is "yes", what phase 4 post-marketing studies does the committee recommend for this indication?

Regarding Phase IV studies, the topic of question 3, members pointed to the lack of PK data, drug interactions, better dose optimization, assessment of the role of the drug and also of steroids in lipid metabolism, and more information on dosing in children. Dr. Abernathy suggested that further study include the development of a range of tablet sizes with bioequivalence and investigation of drug interactions, and Dr. Modlin later suggested fluconozole and dialatin as specific candidates. Dr. Hricik suggested that since the active control groups received higher doses of steroids as concomitant immunosuppressive therapy, there are some differences between the groups that cannot be interpreted, such as rates of infections, hypertension and hyperlipidemia, and that a Phase IV study should control for concomitant immunosuppression. Dr. Kahan and Dr. Cotton concurred.

4. Does the committee have any comment about the safety and effectiveness of tacrolimus for the prophylaxis of organ rejection in pediatric patients (≤ 12 years old) receiving allogeneic liver transplants?

Question 4 specifically addressed use in children, and members repeated the urgent call for more data. Some members felt that the drug was very useful in children. Dr. Columbiani described a body of pediatric experience with tacrolimus, where reducing the use of steroids and switching to tacrolimus benefitted patients Dr. Modlin noted that, while the anecdotal experience is very encouraging, those data have not been submitted for review. Dr. Blaschke encouraged the Agency and the company to pursue the question of whether the drugs differ in their effect on lipid metabolism, as that could be an important factor in managing pediatric cases.

8. ADJOURN

The meeting was adjourned shortly before 4:0 p.m.

to ensure that the policies and practices of programs serving Head Start families support an effective, collaborative, and integrated approach to confronting the myriad of problems that threaten self-sufficiency.

Annual Number of Respondents: 1,900
Frequency: 1
Average Burden Hours Per Responses: .833
Total Burden Hours: 1,583

Dated: October 7, 1993.

Larry Guerrero,

Deputy Director, Office of Information Systems Management.

[FR Doc. 93-25819 Filed 10-20-93; 8:45 am]

BILLING CODE 4184-01-M

Food and Drug Administration

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meeting and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

MEETING: The following advisory committee meeting is announced:

Subcommittee Meeting of the Antiviral Drugs Advisory Committee

Date, time, and place. November 22, 1993, 8 a.m., Parklawn Bldg., Conference rms. D and E, 5600 Fishers Lane, Rockville, MD.

Type of meeting and contact person. Open public hearing, 8 a.m. to 9 a.m., unless public participation does not last that long; open committee discussion, 9 a.m. to 4 p.m.; Lee L. Zwanziger or Valerie Mealy, Center for Drug Evaluation and Research (HFD-9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4695.

General function of the committee. The committee reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of acquired immune deficiency syndrome (AIDS), AIDS-related complex (ARC), and other viral, fungal, and mycobacterial infections

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify a contact person before November 15, 1993, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. The subcommittee will discuss data on safety and efficacy regarding new drug applications (NDA's) 50-708 and 50-709, tacrolimus (Prograf®), Fujisawa USA, Inc., for use in prophylaxis of rejection of primary liver allografts.

FDA public advisory committee meetings may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting involved. There are no closed portions for the meetings announced in this notice. The dates and times reserved for the open portions of each committee meeting are listed above.

The open public hearing portion of each meeting shall be at least 1 hour long unless public participation does not last that long. It is emphasized, however, that the 1 hour time limit for an open public hearing represents a minimum rather than a maximum time for public participation, and an open public hearing may last for whatever longer period the committee chairperson determines will facilitate the committee's work.

Public hearings are subject to FDA's guideline (subpart C of 21 CFR part 10) concerning the policy and procedures for electronic media coverage of FDA's public administrative proceedings, including hearings before public advisory committees under 21 CFR part 14. Under 21 CFR 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants.

Meetings of advisory committees shall be conducted, insofar as is practical, in accordance with the agenda published in this Federal Register notice. Changes in the agenda will be announced at the beginning of the open portion of a meeting.

Any interested person who wishes to be assured of the right to make an oral presentation at the open public hearing portion of a meeting shall inform the contact person listed above, either orally or in writing, prior to the meeting. Any person attending the hearing who does not in advance of the meeting request an opportunity to speak will be allowed to make an oral presentation at the hearing's conclusion, if time permits, at the chairperson's discretion.

The agenda, the questions to be addressed by the committee, and a current list of committee members will be available at the meeting location on the day of the meeting.

Transcripts of the open portion of the meeting may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857, approximately 15 working days after the meeting, at a cost of 10 cents per page. The transcript may be viewed at the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, approximately 15 working days after the meeting, between the hours of 9 a.m. and 4 p.m., Monday through Friday. Summary minutes of the open portion of the meeting may be requested in writing from the Freedom of Information Office (address above) beginning approximately 90 days after the meeting. This notice is issued under section 10(a)(1) and (2) of the Federal Advisory Committee Act (5 U.S.C. app. 2), and FDA's regulations (21 CFR part 14) on advisory committees.

Dated: October 14, 1993.

Jane E. Henney,

Deputy Commissioner for Operations.

[FR Doc. 93-25807 Filed 10-20-93; 8:45 am]

BILLING CODE 4160-01-F

National Institutes of Health

[Billing Code 4140-01]

National Institute of Environmental Health Sciences: Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Identification of a Hormone Interacting With a Novel Hepatic Orphan Nuclear Receptor

AGENCY: National Institute of Environmental Health Sciences, National Institutes of Health, PHS, DHHS.

ACTION: Notice.

SUMMARY: National Institute of Environmental Health Sciences (NIEHS) seek a pharmaceutical company that can effectively pursue the isolation and

B-00[illegible]

MINUTES OF INDUSTRY MEETING
PRE-NDA

DATE: October 16, 1992

IND#:

DRUG: FK 506 (Prograf)

SPONSOR: Fujisawa Pharmaceutical Company

ATTENDEES:

Division of Antiviral Drug Products
James Bilstad, M.D.
Lauren Black, Ph.D.
Carole Broadnax, R.Ph.
Marc Cavaillé-Coll, M.D., Ph.D.
Chi-Wan Chen, Ph.D.
Anthony DeCicco, R.Ph.
Donna Freeman, M.D.
Lawrence Hauptman, Ph.D.
Lisa Kammerman, Ph.D.
Ralph Lillie, R.Ph.
Frank Felsor, Pharm.D.
Larry Rosenstein, Ph.D.
Emil Samara, Ph.D.
Mark Seggel, Ph.D.

Fujisawa Pharmaceutical
Ihor Bekersky, Ph.D.
Steve Carrier, Ph.D.
B. Fitzsimmons, Pharm.D.
Ken King, Ph.D.
Ramona Krailler, Ph.D.
Ira Lawrence, M.D.
Nelson Levy, M.D., Ph.D.
Qais Mekki, M.D., Ph.D.
P. Schechter, M.D., Ph.D.
Jim Shook, Ph.D.
Don Steinmuller, M.D.
Vince Uthoff, Ph.D.
Daniel Zabrowski, Ph.D.

Introductions were made by both the Division and Fujisawa Pharmaceutical Company (FPC).

Dr. Shook gave an overview of the proposed indications for FK 506. FK 506 will be indicated for the prophylaxis of organ rejection in liver, kidney and heart allogenic transplants. It may also be used in the treatment of

FPC studies currently have approximately 2000 patients enrolled and approximately 800 of these patients have reached the 12 month mark. FPC believes that the proposed indications are supported by the database.

Dr. Fitzsimmons provided the background history of FK 506. He indicated that FPC would file a heart transplant protocol shortly.

Dr. Steinmuller provided an overview of the clinical studies for liver, kidney and heart. The primary efficacy variables would be patient and graft survival. Regarding protocol FK506-7 (randomized, controlled U.S. Liver Trial), Dr. Cavaillé-Coll asked how many patients were evaluable at one year. FPC responded that 29 subjects have been followed out to more than 360 days. Dr. Steinmuller commented that historical controls show that in the past one-year graft survival was approximately 50% with corticosteriods alone. Dr. Cavaillé-Coll commented that there were other interventions besides immunosuppressive therapy that have contributed to improved graft and patient survival over the years.

Dr. Steinmuller provided the following benefits of FK 506:

* Superior efficacy over cyclosporine.
  +A decrease in the incidence of rejection.
  +A decrease in the use of corticosteroids, azathioprine, OKT3 and ALG.
  +Improved patient and graft survival.
* Effective rescue therapy for refractory rejection in liver, kidney and heart.
* Similar or decreased infectious complications and rare malignancies.

Dr. Carrier gave the statistical presentation. He presented a slide on Hazard Functions (Actuarial Risks of Graft Loss in Controlled Trials) for liver transplantation. He argued that most of the clinical events occured early and that the relative hazard remained unchanged after more than 3 months post-transplantation.

Dr. Zabrowski stated that FPC planned to submit the NDA the week of October 26, 1992. He suggested that correspondence with the FDA could be by the following means: CSO telephone contact, facsimile, electronic mail and other informal means. He stated that FPC wanted to avoid regulatory letters. As an alternative, FPC would submit to the NDA on a monthly basis a compilation of all FDA correspondence (i.e., memorandums of telephone conversations, facsimiles, etc.)

DISCUSSION

Dr. Freeman provided the following observations, expectations and concerns:

1. Data set problem. It is difficult to tell what is going on with data follow-up. Where is the rest of the data? When will it become available?

2. She asked if FPC was arguing that FK 506 was equivalent to cyclosporine or superior to cyclosporine. FPC said that they claimed that FK 506 was equivalent to cyclosporine in patient and graft survival and superior to cyclosporine in reducing the incidence of rejection and other secondary parameters.

3. Would FPC extrapolate kidney and heart data from liver studies? FPC responded that there was limited controlled data on kidney and heart. They feel that they could extrapolate from the large liver studies and from the large uncontrolled studies for kidney and heart. In particular, if they could show that FK 506 was superior to a cyclosporine based regimen in liver transplantation, they intend to extrapolate that this relationship would be the same in kidney and heart transplantation. Dr. Freeman commented that this was not the strategy that was proposed prior to this meeting. On the face, it would be very difficult to support such a reasoning.

4. How confident are you in the quality of the data from the Pittsburgh studies? How much of this information would be retrievable and reviewable?

In response to question #1, FPC commented that their feeling was that the FDA would not learn anything more from one year data. They have 6 month follow-up on 100% of the patients in the proposed NDA.

Regarding dosing, Dr. Cavaillé-Coll asked what proportion of the subjects had been treated with the proposed recommended dose in the NDA package. Since the protocols were amended to change the doses this might affect the proportion of subjects with 6 month or 12 month follow-up that were treated with the proposed recommended dose. This proportion might be very small. Dr.

Cavaillé-Coll stated that he would need to know what proportion of the patients were treated at the dose FPC is recommending among patients with 3, 6 and 12 month followup. FPC commented that the dosing amendments concerned only the I.V. dose and that patients were taken off of I.V. FK 506 at 2 weeks. They stated that there was not much difference between the oral dose administered to those with 180 day and 360 day follow-up. Dr. Freeman requested that FPC submit this data.

Dr. Freeman emphasized that the 45 day review decision would be based on the data that was in the application at the time of submission to the FDA. FPC responded that they were cognizant of this. They plan to submit data on all patients up to 90 days. FPC stressed the fact that nothing significant occurred after 90 days. They commented that they would like and will have longer term follow-up data which they will submit to the NDA in a data update.

Dr. Bilstad presented FDA's views on filing. He stated that the FDA had become more hard-nosed because of incomplete submissions that lengthen the review process. With the advent of user's fees, the FDA would be expected to adhere to timelines for NDA review. This would not be possible if incomplete data was submitted. The standard that was applied to the cyclosporine NDA was 12 month graft survival and 12 month patient survival. FPC should have one year follow-up data as previously recommended. He asked why FPC did not have more recent data. He commented that the data lock point was one year ago and added that FPC needed to address this fact.

FPC responded that their case report forms were 2 volumes thick and that it was a challenge to pursue and verify the data. However, they were still actively collecting data. In addition, for the 2 primary endpoints of patient and graft survival, they have a tracking system. Dr. Hauptman asked whether they could update the data for 12 month patient and 12 month graft survival. This data should be able to be retrieved in a short period of time without requiring complete verification of the data in the CFRs. FPC replied that this would be possible to do.

Dr. Hauptman had the following additional comments:

* Regarding 6 month data on however many number of patients, have that many patients completed 6 months or

is this just the number of patients FPC has available data on? FPC responded that the database was complete for all subjects having reached a 6 month follow-up point.

* Intent to treat analysis should be the primary analysis and should include any patient who should have been randomized (i.e., patients who violated major inclusion criteria could be excluded). FPC responded that they present 4 analyses including an intend to treat analysis in the data package.

* In the intend to treat analysis, patients are not censored if they go off drug. If a patient was off drug and died, this should be reported as a death. Dr. Cavaillé-Coll commented that FPC should include retransplanted patients in this analysis.

* Each patient should have data on survival and graft status at 12 months.

* Confidence intervals for the treatment effect should be submitted. FPC responded that this would be included in the data package.

* Analyses should take into consideration the effect of center. FPC responded that they had done this.

* Cyclosporine based immunosuppressive regimens were not the same at all study sites. FPC should make sure that this is addressed in a subset analysis. FPC responded that they have included this analysis.

Dr. Cavaillé-Coll asked how many pediatric subjects were included in the pivotal studies for the NDA. FPC responded that at the age of 12 or less there were 50 patients total. 30 were randomized on FK 506 and 20 were randomized on cyclosporine. In the U.S. study, 22% (28/125) of the patients were less than 12 years old.

Regarding dosing in the pediatric group, FPC commented that higher I.V. and oral doses were required to achieve similar plasma levels. Also, all primary and rescue liver trials at the University of Pittsburgh included pediatric patients.

A discussion of historical controls followed. Regarding the [redacted] study, Dr. Kammerman asked FPC to identify the source of the patients and the data which were used for comparisons with FK 506 in the pre-NDA meeting package (page 87). FPC did not address Dr. Kammerman's request. FPC responded that they had the following difficulties with historical controls: 1) data from studies conducted previously are not comparable because of changes in case management; 2) patient selection criteria were difficult to control (i.e., impairment of liver function, biopsy results and demographics); 3) lack of suitable reports in the literature; and 4) lack of databases. Dr. Bilstad commented that the FDA could not consider efficacy data without any controls at all. They must at least submit their best attempt at a historical control comparison. Dr. Cavaillé-Coll commented that at the May 23, 1991 meeting, FPC was asked by the Division of Oncology (HFD-150) to submit a proposal for historical controls analysis for review with supporting rationale. FPC responded that they have looked into this and that they would provide the requested information.

Dr. Cavaillé-Coll stated that FPC needed to have comparative data for rescue kidney and heart. FPC has presented only uncontrolled open labeled information. FPC responded that they would make attempts to identify this historical control data for comparison. Dr. Freeman requested that FPC include a description of the attempts they have made to identify historical controls, whether they were successful or not.

Dr. Chen asked if they planned to submit both dosage forms (oral and I.V.) at the same time. FPC stated that they planned to submit both dosage forms under the same NDA. Dr. Chen stated that it was preferred to have the different dosage forms under separate NDA numbers. The second NDA, which contains the chemistry, manufacturing and controls (CMC) of either the oral or the I.V. dosage form, could cross-reference the first NDA for pharmacology/toxicology, clinical, as well as the CMC of the drug substance.

Dr. Bilstad asked if FPC had a timetable for submission of the NDA. FPC said that they could not answer at this time. They do not want to submit a NDA if they suspect that the FDA is not comfortable with filing it.

The meeting was cordial throughout.

IND ORIG.

Concur:
HFD-530/SMO/DFreeman/10-31-92
HFD-530/MO/Cavaillé-Coll/10-27-92
HFD-530/SChem/CWChen/10-21-92
HFD-715/SStat/LHauptman/10-29-92
HFD-715/Stat/LKammerman/10-21-92
HFD-530/CSO/CBroadnax/RD 10-21-92/Edit 10-30-92/11-2-92

cc:
HFD-500/OD/JBilstad
HFD-530/DD/DFeigal
HFD-530/Preclin/LRosenstein
HFD-530/SMO/DFreeman
HFD-530/MO/MCavaillé-Coll
HFD-530/Pharm/LBlack
HFD-530/SChem/CWChen
HFD-530/Chem/MSeggel
HFD-530/SBiopharm/FPelsor
HFD-530/Biopharm/ESamara
HFD-715/SStat/LHauptman
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax
HFD-530/AADPM/RLillie
HFD-530/SCSO/TDeCicco

MINUTES OF MEETING

May 23, 1991
IND

Sponsor: Fujisawa

Participants:

FDA- Dr. Burke, Dr. Justice, Dr. Lieberman, Dr. Hoberman, Ellen Cutler

Fujisawa- Dr. Gubish, Regulatory Affairs
Dr. Whisnant, V.P., Medical
Dr. Leavitt, Senior Medical Director
Dr. D. Steinmuller, Clinical Immunology
Dr. A. Piergies, Clinical Pharmacology
Dr. J. Shook, Data Management & Biostatistics
Dr. W. Fitzsimmons, Clinical Immunology
Dr. M. Nishiyama, Project Manager

Dr. Lieberman opened the meeting. He said that in the future Fujisawa should submit data and slides in advance if they want comments and feedback from the Agency at the meeting. The purpose of the meeting was to discuss the clinical development and data management for FK-506 in liver transplantation. Fujisawa plans to file a NDA for the prophylaxis of organ rejection in liver allogeneic transplants (primary therapy) in combination with adrenal corticosteroids and the treatment of rejection in patients previously treated with other immunosuppressive agents

A copy of the publication containing Demetris' data on conversion from cyclosporine to FK-506 will be submitted to the IND.

Dr. Leavitt presented data on the therapy study. (See pp. 8-13 of meeting package.) Ninety one of 114 patients who received FK-506 for rejection following liver transplantation are evaluable for response. These patients have been treated according to protocol -03 under compassionate use except for modification of the I.V. dose as described in the primary transplantation protocol (-07). (Protocol -03 is on hold for concerns pertaining to design and the historical control.) Dr. Lieberman asked how many patients in the study at Pittsburgh would have qualified for Fujisawa's protocol. These could be matched and the outcomes compared. However, this would not be a satisfactory control group for NDA purposes. Patients evaluable for response received a minimum of 28 days of therapy and information was available on initial histology [i.e., acute (cellular infiltrate) rejection, chronic (duct loss) rejection, or acute and chronic rejection]. Patients were considered not evaluable (treated less than 28 days) due to death, retransplantation, toxicity, progression or lack of response. Dr. Burke said that the primary analysis should include all 114 patients treated with FK-506. Data should include information on patients with worsening renal function while receiving FK-506. Dr. Lieberman indicated that this was an

observational database which could be analyzed by estimation methods and not necessarily by standard hypothesis testing. They are estimating a survival or response rate.

Dr. Steinmuller presented data on the randomized primary liver transplant studies. (See pp. 14-20 of meeting package.) A total of 12 centers are participating in Fujisawa's U.S. protocol. These centers plus Pittsburgh account for ~75% of liver transplants in the U.S. Ten of the centers are using a standardized cyclosporine-based control regimen. An 8 center European study is being conducted. A uniform cyclosporine-based control arm has not been used in the European study. Access to the CRFs will be available. Present analysis shows no excess deaths or graft loss. Dr. Lieberman asked if this analysis constituted an interim analysis. The anticipated completion of enrollment is 4th quarter 1991. Dr. Lieberman asked about the role and organization of the endpoint evaluation committee. Fujisawa said all cases would be reviewed at the end to validate the treatment failure endpoint.

Dr. Shook presented the data management activities. (See pp. 20-27 of meeting package.) The U.S. study is monitored by Parexel and the European study is monitored by Besselaar. Q.A. activities are performed by Fujisawa and Klinge. The goals are to assure compliance with the protocol and to collect accurate data from each site for inclusion into the data system. Dr. Hoberman said he is pleased with the plan for data collection undertaken by Fujisawa which standardizes codes for ADEs, response criteria and other important parameters. There is some concern by Fujisawa that CRFs at Pittsburgh may not reflect all the information available. Data will be useful for toxicities but information regarding individualized dosing may not be available. The data is being collected by Pittsburgh and contract people. Data analysis is being done by Fujisawa. Dr. Whisnant said that if the data base from Pittsburgh can be validated, the information will be used towards approval, however, the summary on p. 27 of the meeting material does not include Pittsburgh patients.

Dr. Steinmuller presented information on renal dysfunction 0-14 days post liver transplantation (p. 28 of meeting package). He said that patients may be susceptible or predisposed to renal dysfunction and that a decrease in dose does not necessarily decrease the incidence. Fujisawa plans to submit a protocol amendment to change the initial management of FK-506 dosing to allow for more flexibility (delay onset beyond six hours for earlier assessment of renal function). The change will also base dosing on ideal body weight. Dr. Piergies said that further PK studies may lead to more information as to whether there are predisposing factors so that treatment can be individualized. Dr. Lieberman said that Fujisawa should look to correlate patient specific factors to outcome using scatter plots, distribution, frequency plots and multiple logistic regression.

Dr. Piergies said that there is a high volume of distribution (~1300 L) and that the drug is extensively distributed into tissues. There is a narrow range to correlate plasma level to toxicity. PK may not explain PD variations among patients. Dr. Steinmuller said that more data is needed for an appropriate analysis. The analysis will include plasma and whole blood determinations, renal and hepatic function prior to surgery, hemodynamic parameters (ascites, obesity, etc.) and dose vs. blood level at steady state correlations to AUC. Dr. Lieberman encouraged collection of this information as soon as possible.

Dr. Leavitt stated the need for an appropriate control comparison for the rescue protocol. He suggested an investigator/consultant meeting to determine the criteria as determined by experts. Possibilities for the source of the control include using the patient as his/her own control by looking at what the outcome would have been if the patient had not received the drug (i.e, retransplantation, death). Use of an historical control may include matching case controls, literature experience, an historical control data base of ~100 patients separated into acute or chronic rejection, or looking at patients who met the eligibility criteria but did not go on study (outcome of retransplantation). Fujisawa must determine which control comparison would be the most achievable and reliable and submit a proposal to the Division for review. A discussion of the rationale behind the decision should be included. Dr. Lieberman suggested a concurrent or historically matched control in patients with refractory rejection who are retransplanted. Pittsburgh may be a source. Dr. Lieberman asked Fujisawa to identity sources of control patients.

Dr. Whisnant requested guidance from the Agency regarding a reference of a biostatistical epidemiologist for analysis of the historical control. Dr. Hoberman said he will try to provide the name of a specialist.

Dr. Gubish said that Fujisawa would like to meet with the Division before the August conference at Pittsburgh to discuss the information to be presented at the meeting.

Dr. Gubish said that Fujisawa should be ready for a pre-NDA meeting with the Division by December 1991. They were told to put together a meeting package describing the proposed content and format of the NDA.

cc:
IND
HFD-150/div file
FDA meeting attendees
ECutler/CSO/6-3-91
R/D init by: RLiebermanMD/6-4-91
RJusticeMD/6-6-91
FUJMIN.1

END

J.H.M. RESEARCH &DEVELOPMENT, INC. 5776 SECOND STREET,N.E. WASH. DC 20011