COUNTY OF SAN MATEO
Departmental Correspondence

DATE: NOV 2 7 2001
HEARING DATE: DEC 4 2001

TO: Honorable Board of Supervisors

FROM: Margaret Taylor, Interim CEO, Hospital and Clinics

SUBJECT: Agreement with Roche Laboratories, Inc.

RECOMMENDATION

Adopt a resolution authorizing the President of the Board to execute an agreement with Roche Laboratories, Inc. to accept funding totaling $628,828 for a clinical research study.

Background

The Clinical Trials and Research Unit of the San Mateo County Health Center was established in 2000 to provide a mechanism and infrastructure for the conduct of clinical treatment trials and medical or psychosocial research projects for the benefit of San Mateo County residents. A preliminary assessment by Unit staff identified Hepatitis C Virus (HCV)-associated-cirrhosis as a problem affecting many of the County's patients with HIV, for which there is no clinically proven method of screening in this population.

Discussion

The Clinical Trials and Research Unit submitted a proposal to Roche Pharmaceuticals for an Evaluation Phase II Open Label Treatment with Pegylated Inteferon alfa-2a plus ribavirin in patients with HCV-associated-cirrhosis and HIV infection in response to a Request for Proposals for research projects involving people with HIV. Roche Pharmaceuticals informed the County that the Health Center has been awarded $628,828 over a two-year period.

The primary purpose of this study is to evaluate the activity and safety of pegylated interferon alpha – 2a with ribavirin in HIV-positive patients with chronic Hepatitis C and advanced fibrosis or compensated cirrhosis, in patients who are interferon naïve, and in patients who have failed interferon or interferon with ribavirin. The proposed study includes two major outcome objectives included in the Evaluation Work Plan:

1. To study if pegylated interferon alfa-2a plus ribavirin is safe and effective at clearing HCV (<50 IU/mL) in patients who are HIV+ and have advanced fibrosis or cirrhosis at 24 weeks.

2. To determine which proportion of patients have sustained virologic response at 72 weeks after treatment and interferon and ribavirin for 48 weeks.

Term and Fiscal Impact

The term of this agreement is from December 14, 2001 through December 30, 2003.

The total grant award included in the agreement is $628,828. An Appropriation Transfer Request accepting and appropriating the additional funding will be brought forward for approval shortly, once the project budget has been finalized. However, Roche is requiring that this agreement be executed in early December to ensure the funding allocation from Roche. Administrative oversight, technical assistance, and project monitoring will be provided by existing Clinical Trials and Research staff. There is no net county cost associated with this project.

RESOLUTION NO. _____

BOARD OF SUPERVISORS, COUNTY OF SAN MATEO, STATE OF CALIFORNIA

* * * * * * * * * *

RESOLUTION AUTHORIZING EXECUTION OF AN AGREEMENT WITH ROCHE LABORATORIES, INC. FOR PHASE II OPEN LABEL TREATMENT WITH PEGYLATED INTERFERON ALFA-2a PLUS RIBAVIRIN IN PATIENTS WITH HCV-ASSOCIATED-CIRRHOSIS AND HIV INFECTION

RESOLVED, by the Board of Supervisors of the County of San Mateo, State of California, that;

WHEREAS, there has been presented to this Board of Supervisors for its consideration and acceptance an Agreement, reference to which is hereby made for further particulars, whereby Roche Laboratories, Inc. will allocate funds for the provision of a research study concerning Phase II open label treatment with Pegylated Interferon alfa-2a plus ribavirin in Patients with HCV associated cirrhosis and HIV infection; and

WHEREAS, this Board has been presented with a form of the Agreement and has examined and approved it as to both form and content and desires to enter into the Agreement:

NOW, THEREFORE, IT IS HEREBY DETERMINED AND ORDERED that the President of this Board of Supervisors be, and is hereby, authorized and directed to execute said Agreement for and on behalf of the County of San Mateo, and the Clerk of this Board shall attest the President's signature thereto.

CLINICAL RESEARCH AGREEMENT

This Agreement is entered into as of this Twentieth day of November, 2001, by and between San Mateo County Health Center ("Institution") located at 2222 West 39th Avenue, San Mateo, CA 94403 and Roche Laboratories Inc., with its office and place of business at 340 Kingsland Street, Nutley, New Jersey 07110 ("Roche").

WHEREAS, the Institution wishes to conduct a clinical research study of Pegasys®, RO 25-8310; and

WHEREAS, subject to the terms and conditions set forth herein, Roche is willing to provide financial support for the conduct of the Study;

NOW THEREFORE, in consideration of the terms and conditions set forth herein, and other good and valuable consideration, the parties hereto agree as follows:

1. Scope of Work/Payment

(A) Roche shall use reasonable efforts to supply Institution with sufficient clinical supplies of the compound known as Pegasys®, RO 25-8310 and the compound known as ribavirin (the "Compounds") to perform the Study. Roche represents and agrees that the Compound supplied to Institution will be appropriately formulated pursuant to FDA standards for Investigational compounds. Roche agrees to provide Principal Investigator with an investigator brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the Compounds. If such information is revised while the Study is in progress, the latest revisions will also be sent to the Principal Investigator at that time.

(B) Institution shall perform those research activities and tests with the Compound as described in the protocol set forth as Exhibit A entitled, "Phase II open label treatment with Pegylated Interferon alfa-2a plus ribavirin in Patients with HCV associated cirrhosis and HIV infection" Protocol Number PEG086 (hereinafter "Study"). A copy of Exhibit A is attached hereto and made a part hereof as if fully set forth herein.

(C) The payment schedule and budget setting forth all the activities described in the Study and the expenses that Institution shall incur in connection with each such

activity is set forth as Exhibit B (the "Budget"). A copy of Exhibit B is attached hereto and made a part hereof as if fully set forth herein. Roche shall make payments in accordance with the payment schedule and budget set forth in Exhibit B. Payment as set forth in this Section and the total amount payable as set forth in the Budget attached as Exhibit B shall constitute full payment for the Study, and Roche shall have no other payment obligations either under this Agreement or in connection with the Study or services of any subcontractor.

(D) Institution shall comply with all the terms and requirements of the Study and Budget, and shall not make any changes thereto, nor deviate therefrom, without the prior written consent of Roche. If any terms of this Agreement are in conflict with any terms of the Study or Budget, the terms of this Agreement shall govern.

2. Principal Investigator

The Principal Investigator for the Study shall be Dennis Israelski, MD ("Principal Investigator"). The Principal Investigator is an employee of the Institution and shall be responsible for performing the Study and the direct supervision of any individual performing any portion of the Study. In the event the Principal Investigator becomes unable to perform any of the activities in the Study, and a mutually acceptable substitute is not available to assume responsibility for the Study within ninety (90) days, either Institution or Roche may immediately terminate the Study and this Agreement by giving written notice of termination to the other.

3. Confidentiality

(A) During the term of this Agreement, Institution may obtain certain Confidential Information, as defined in Section 3(B), either from Roche or through its performance of the Study.

(B) "Confidential Information" shall mean (i) any and all information, data, know-how, whether written or oral, technical or non-technical, as well as tangible materials, including without limitation samples, models, drawings, or diagrams which Institution receives from Roche or on behalf of Roche; (ii) case reports and any other data or information resulting from the Study which is not authorized by Roche for publication as provided in Section 4; and (iii) the terms of this Agreement.

(C) Institution agrees (i) to use the Confidential Information only in connection with its performance of this Agreement; (ii) to treat the Confidential Information as it would its own proprietary and confidential information; (iii) to disclose the Confidential Information only to employees or agents of the Institution that agree to be bound by these confidentiality obligations and who need to know such Confidential

Information because they are assisting with the Study; and (iv) to take all reasonable precautions to prevent the disclosure of the Confidential Information to any third-party without the prior written consent of Roche. Notwithstanding the foregoing, Institution may use and disclose the methods and results of the Study for (a) internal research purposes; (b) clinical care of patients enrolled in the Study; and (c) publication in accordance with Section 4 of this Agreement.

(D) Institution shall be relieved of all obligations under this Section regarding Confidential Information that: (i) was known to Institution prior to receipt hereunder as set forth in written records; or (ii) at the time of disclosure to Institution was generally available to the public, or which after disclosure hereunder, becomes generally available to the public, through no fault of the Institution; or (iii) is hereafter made available to Institution from any third-party having a right to do so; or (iv) is needed for purposes of treating a patient that participated in the Study; or (v) is required by law, regulation, subpoena, governmental order or judicial order to be disclosed, provided Institution shall notify Roche prior to any such disclosure to permit Roche to oppose same by appropriate legal action.

4. Publications

(A) Institution shall have the right, consistent with academic standards, to publish or present the results of work performed pursuant to the study, provided that any proposed publication or presentation (collectively, "Proposed Publication") is first reviewed by Roche. Institution shall forward the Proposed Publication to Roche at least forty-five (45) days prior to the planned submission date. Roche shall complete its review of the Proposed Publication within forty-five (45) days after receipt of the Proposed Publication from Institution. If Roche believes that any Proposed Publication contains any information relating to patentable items, the disclosure of such Proposed Publication to any third party shall be delayed for up to an additional ninety (90) days to permit the filing of a patent application. However, if at the end of such ninety (90) day period, despite the use of diligent efforts on the part of Roche, additional time is necessary to complete the filing of a patent application, Roche may request, and Institution shall grant, an extension of the period of time within which to file the patent application for a period not to exceed an additional ninety (90) days. If Roche believes that any Proposed Publication contains any Confidential Information, Roche shall so notify Institution, and Institution shall remove all references to such Confidential Information.

(B) Notwithstanding the foregoing, Institution shall not issue a press release that references the Study or its results, or that uses Roche's name or trademarks without the prior written consent of Roche.

5. Promotional Activities

(A) Neither party shall use the other party's or its affiliates' names or trademarks for publicity or advertising purposes, except with the prior written consent of the other party.

(B) However, notwithstanding the foregoing, Institution and Principal Investigator hereby give permission to use the name of Institution, Principal Investigator and/or other Institution employees agents in Study newsletters. These Study newsletters are sent out periodically to all Study sites to keep all Principal Investigators and other Study sites informed as to Study developments, the status of enrollment, and other issues of general interest to Study sites.

6. Patent Rights

(A) The Compounds and all other materials supplied by Roche hereunder shall only be used by Institution as specified on Exhibit A.

(B) Institution shall promptly disclose only to Roche any discovery or invention resulting from performance of this Agreement.

(C) The entire right, title and interest in and to any invention or discovery resulting from performance of this Agreement shall be owned by Roche. Roche shall have the sole and exclusive right to obtain, at its option, patent protection in the United States and foreign countries on any such invention. Institution shall assign to Roche all right; title and interest in and to any invention or discovery relating to the Compounds Institution shall also render all reasonable assistance to Roche in the filing and prosecution of U.S. and foreign counterpart patent applications.

(D) Institution shall ensure that all individuals working on the Study, including the Principal Investigator and all subcontractors, have assigned to Institution their rights to any invention resulting from performance of this Agreement.

7. Term

This Agreement shall become effective when it has been executed by duly authorized representatives of both parties and shall continue in force until the Study has been completed and a final study report is submitted to Roche, unless terminated in accordance with Section 8. Institution shall use its best efforts to complete the Study by December 30, 2003.

8. Termination

(A) Either party may terminate this Agreement if the other party breaches any of its obligations or provisions of this Agreement, provided however, that the defaulting party shall be given not less than thirty (30) days prior written notice of such default and the opportunity to cure the default during such period.

(B) Roche may terminate this Agreement immediately for safety reasons relating to the use of the Compounds, or if the FDA requests that the Study be terminated.

(C) Roche may terminate this Agreement for any reason upon thirty (30) days prior written notice. Upon receipt of notice of termination from Roche, Institution shall immediately stop entering patients into the Study and, to the extent medically permissible, cease administering the Compounds and conducting procedures on patients already entered into the Study. Roche shall pay all costs reasonably incurred by Institution, including all non-cancelable costs that are entered into by Institution prior to the effective date of the termination.

(D) Institution shall use all reasonable efforts, upon the request of Roche, to (i) complete reports for all patients that have been entered into the Study as of the termination date of this Agreement and/or (ii) write a final report for that portion of the Study that has been completed as of the termination date.

(E) Upon termination, Roche's sole obligation shall be to pay Institution on a pro rata basis in accord with the Budget (Exhibit B) for actual work performed by Institution pursuant to the Study. Institution shall refund to Roche, within thirty (30) days after termination; any amounts already paid by Roche to Institution that are in excess of what Institution is due under this Section.

(F) Termination of this Agreement shall not affect any rights or remedies of either party at law or in equity.

9. Scientific Communications

All medical and scientific communications directed to the Institution, whether or not containing Confidential Information, shall be addressed to the Principal Investigator. All such information directed to Roche shall be addressed to Peggy Siemon-Hryczyk at 340 Kingsland Street, Nutley, New Jersey 07110.

10. Supply of Compound

(A) Roche shall use reasonable efforts to provide necessary amounts of the Compounds for fifty (50) patients in this Study, for a total of 2400 vials of Pegasys®, and 250 bottles of ribavirin. In no event will Roche provide more than the amount of Compound or placebo specified herein.

(B) Institution shall not charge any patient enrolled in the Study, or any third party payor, for the Compound, nor shall Institution include the cost of such drug in any cost report to third party payors.

11. Indemnification

A) Roche agrees to indemnify, defend, and hold harmless Principal Investigator, directors, officers, agents, and employees, (" Sponsor Indemnified Parties") against any claims, suits, or judgments made or instituted against the Sponsor Indemnified Parties to the extent that they are caused by Roche's failure to formulate the Compound in accordance with FDA standards for investigational compounds, except to the extent that the claim, suit, or judgment is the result of an Sponsor Indemnified Party's negligence, willful misconduct, or failure to follow the Protocol. Sponsor and Principal Investigator must promptly notify Roche within a reasonable period after notice of any claim or action covered by the indemnity in this Section 19(A). Sponsor and Principal Investigator will cooperate with and authorize Roche to carry out the defense of the claim or action. Roche agrees to provide attorneys at its own expense to defend against any actions brought or filed against Indemnified Parties with respect to the indemnity provided for in this Section 18(A), whether or not those claims are rightfully brought or filed. The Sponsor Indemnified Parties shall at all times have the right to fully participate in the defense at their own expense. If Roche, within a reasonable time after notice, fails to defend, the Sponsor Indemnified Parties shall have the right, but not the obligation, to undertake the defense of and to compromise or settle the claim or other matter on behalf, for the account, and at the risk of Roche. If the claim is one that cannot by its nature be defended solely by Roche, then the Sponsor Indemnified Parties shall make available all information and assistance that Roche may reasonably request at the Indemnified Parties' expense.

B) Institution and Principal Investigator agree to indemnify, defend, and hold harmless Roche, its directors, officers, agents, and employees ("Roche Indemnified Parties") against any claims, suits, or judgments made or instituted against the Roche Indemnified Parties to the extent that they are caused by the Institution's failure to follow the Protocol,

except to the extent that the claim, suit, or judgment is the result of Roche Indemnified Party's negligence or willful misconduct. Roche must promptly notify Sponsor and Principal Investigator of any claim or action covered by the indemnity in this Section 18(B). Roche will cooperate with and authorize Sponsor to carry out the defense of the claim or action. Sponsor agrees to provide attorneys at its own expense to defend against any actions brought or filed against Roche Indemnified Parties with respect to the indemnity provided for in this Section 18(B), whether or not those claims are rightfully brought or filed. The Roche Indemnified Parties shall at all times have the right to fully participate in the defense at their own expense. If neither Sponsor nor Principal Investigator, within a reasonable time after notice, fails to defend, the Roche Indemnified Parties shall have the right, but not the obligation, to undertake the defense of and to compromise or settle the claim or other matter on behalf, for the account, and at the risk of Sponsor and Principal Investigator. If the claim is one that cannot by its nature be defended solely by Sponsor and Principal Investigator, then the Roche Indemnified Parties shall make available all information and assistance that Sponsor and Principal Investigator may reasonably request at the Roche Indemnified Parties' expense.

12. Disclaimer of Warranty

INSTITUTION UNDERSTANDS AND AGREES THAT ROCHE MAKES NO WARRANTY, EITHER EXPRESSED OR IMPLIED, REGARDING THE USE OF THE COMPOUNDS IN THE STUDY. WITHOUT LIMITING THE FOREGOING, ROCHE EXPRESSLY DISCLAIMS ANY WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

13. Debarment Certification

(A) Institution hereby certifies that it has not been debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §335a(a) and (b). In the event that during the term of this Agreement, Institution (i) becomes debarred, or (ii) receives notice of an action or threat of an action with respect to its debarment, Institution shall notify Roche immediately.

(B) In the event that Institution becomes debarred, this Agreement shall automatically terminate without any further action or notice by either party. In the event that Roche receives notice from Institution or otherwise becomes aware that a debarment action has been brought against Institution or that Institution is threatened with a debarment action as set forth in clause (ii) above, then Roche shall have the right to terminate this Agreement immediately.

(C) Institution hereby certifies that it has not and will not use in any capacity the services of any individual, corporation, partnership or association which has been debarred under 21 U.S.C. §335a(a) or (b). In the event Institution becomes aware of the debarment or threatened debarment of any individual, corporation, partnership or association providing services to Institution which directly or indirectly relate to activities under this Agreement, Institution shall notify Roche immediately. Upon the receipt of such notice by Roche or if Roche otherwise becomes aware of such debarment or threatened debarment, Roche shall have the right to terminate this Agreement immediately.

14. Compliance with Law/Reports

Institution shall obtain an Investigational New Drug Application ("IND") to perform the Study from the FDA under its own name. Institution shall conduct the Study in accordance with all rules and regulations promulgated by the FDA, including 21 CFR Part 312, and all other applicable federal, state and local laws, rules and regulations. With regard to any adverse experience associated with the use of the Compound at any of the study sites, the Principal Investigator shall notify the FDA in accordance with all such applicable FDA laws and requirements and shall provide Roche with copies of all such reports. Further, Roche shall be notified of and be provided with copies of reports any serious adverse event, as defined in 21 CFR Part 312, within 24 hours.

15. Access

Institution agrees to allow Roche, its employees and agents, and authorized employees of the FDA access to the Institution, its personnel and their records for the purpose of determining compliance with the terms of this Agreement and compliance with FDA and other applicable laws, rules and regulations. Any examination, inspection, auditing, and copying by Roche shall be done in a manner so as not to unreasonably disrupt or interfere with Institution's normal operations or the care of its patients.

16. Ownership of Documents

All documents, protocols, data, know-how, methods, operations, formulas, Confidential Information, and materials of any kind provided to Institution pursuant to this Agreement are and shall remain Roche's property. The Completed Case Reports and other results of the Study, if any, shall also be owned by Roche. Copies of any or all documents referenced herein shall be returned to Roche or its designee upon Roche's request.

17. Assignment

This Agreement may not be assigned by Institution without the prior written consent of Roche.

18. Independent Contractors

For purposes of this Agreement, neither the Institution, the Principal Investigator nor their employees and/or the other individuals assigned by them to perform services under this Agreement ("staff members") are an agent, servant, partner, joint venturer or employee of Roche. Thus, they do not have the authority to take action on Roche's behalf or to bind Roche without Roche's prior written consent. The Institution, Principal Investigator and their staff members are acting in the capacity of independent contractors of Roche. Roche is not responsible for withholding, and shall not withhold, FICA or taxes of any kind from any payments it owes to the Institution or the Principal Investigator. The Institution and/or the Principal Investigator are responsible to provide any and all compensation, benefits and/or insurance to their staff members. It is also understood and expressly acknowledged that neither the Institution, the Principal Investigator nor their staff members are eligible to participate in, nor are they eligible for coverage under, any of the Roche's benefit plans, programs, employment policies, procedures or worker's compensation insurance. In consideration of Roche's performance hereunder, Roche will be released from any liability arising from Roche's failure to provide such plans, programs, policies, procedures and worker's compensation insurance.

19. No Waiver

Either party's failure to require the other party to comply with any provision of this Agreement shall not be deemed a waiver of such provision or any other provision of this Agreement.

20. Force Majeure

Neither party shall be liable for the failure to perform its obligations under this Agreement if such failure is occasioned by a contingency beyond such party's reasonable control, including, but not limited to, strikes or other labor disturbances, lockouts, riots, wars, fires, floods or storms. A party claiming a right to excused performance under this Section shall immediately notify the other party in writing of the extent of its inability to perform, which notice shall specify the occurrence beyond its reasonable control that prevents such performance.

21. Notices

Whenever any notice is to be given hereunder, it shall be in writing and sent by certified return receipt mail to the addresses set forth first above. Notices sent to Roche shall be addressed to Peggy Siemon-Hryczyk, with a copy to the "Corporate Secretary," and notices sent to the Institution shall be addressed to Dennis Israelski, MD San Mateo County Health Center, 2222 West 39th. Avenue, San Mateo, CA 94403. Notices given hereunder shall be deemed effective three (3) days after being mailed.

22. Entire Agreement

This Agreement represents the entire understanding of the parties with respect to the subject matter hereof.

23. Survival of Provisions. Sections 3, 4, 5, 6, 11, 14, 15, 16, 21, and 22 hereof shall survive termination or expiration of this Agreement.

24. Roche complies with offering equal benefits, as defined by Chapter 2.93, to its employees with spouses and its employees with domestic partners subject to the eligibility criteria for the Roche plans.

IN WITNESS WHEREOF, Roche and Institution have caused this Agreement to be executed by their respective duly authorized representatives as of the respective dates written below.

San Mateo County Health Center	ROCHE LABORATORIES INC.
By: _____	By: _____
Name: _____	Name: Russell Ellison, M.D.
Title: _____	Title: VP Medical affairs
Date: _____	Date: _____

Reviewed by:_____
Date:_____

104473

5/98

PRINCIPAL INVESTIGATOR'S CERTIFICATION

I acknowledge that I have read the Clinical Research Agreement between Roche Laboratories Inc. ("Roche") and I agree to and will comply with all its terms both as an individual and as an employee of Institution.

I represent that my entering into this Agreement shall not conflict with or be a breach of any other agreement to which I am a party or am bound.

I certify that I have not been disqualified by the federal Food and Drug Administration or otherwise disqualified from serving as a Principal Investigator.

I certify that I have not been debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §335a(a)
and (b). In the event that I,

(i) become debarred; or
(ii) receive notice of an action or threat of an action with respect to my debarment

during the term of this Agreement, I agree to immediately notify Roche and Institution. I also agree that in the event that I become debarred, I shall immediately cease all activities relating to this Agreement.

I understand that in the event Roche receives notice or otherwise becomes aware that (i) I have been debarred, (ii) a debarment action has been brought against me, or (iii) I have been threatened with a debarment action, Roche shall have the right, at its sole discretion, to (i) terminate this Agreement immediately, or (ii) agree with Institution to a substitute Principal Investigator who will assume full responsibility and perform all the remaining activities under this Agreement.

PRINCIPAL INVESTIGATOR

Dennis Israelski, MD
Print Name

Signature

Date: 11/26/01

104473

1. EXHIBIT A

PROTOCOL NUMBER PEG086

Version Date: July 20, 2001

PROTOCOL

Phase II open label treatment with Pegylated Interferon alfa-2a plus ribavirin in Patients with HCV associated cirrhosis and HIV infection

Principal investigator:

Dennis M. Israelski, MD, Chief, Infectious Diseases and AIDS Medicine and Director Clinical Research Unit, San Mateo County Health Center;
Associate Clinical Professor Stanford.

Co investigators:

Nancy Shulman, MD, Research Associate of Infectious Diseases, Stanford University

Joanne Imperial, MD, Associate Professor of Gastroenterology, Stanford University

PURPOSE AND OVERVIEW

Purpose:

The purpose of this study is 1) to study the activity and safety of pegylated interferon alpha- 2a with ribavirin in HIV+ patients with chronic hepatitis C and advanced fibrosis or compensated cirrhosis in patients who are interferon naïve and in patients who have failed interferon or interferon with ribavirin.

Overview:

A goal of 50 patients with HIV and HCV and advanced fibrosis or cirrhosis who meet the inclusion and exclusion criteria will be treated. They will be treated with a combination of pegylated interferon alfa-2a and ribavirin for a period of 24 weeks. Patients who have no detectable HCV RNA in the serum at week 24 will continue on combination treatment until week 48.

BACKGROUND

Hepatitis C is an emerging cause of morbidity and mortality among HIV-infected patients. In the U. S., an estimated 20-30% of HIV infected individuals are co-infected with HCV. With the widespread use of effective antiretroviral therapy, mortality from AIDS-related illness is declining and recent studies have shown an increase in mortality due to liver disease largely due to hepatitis C. A recent pilot study of PEG-IFN plus ribavirin in 20 HIV-/HCV+ patients, mostly white men, treated for 12 months revealed a sustained response rate of 50%. Large multicenter trials are beginning to enroll that compare standard interferon and ribavirin therapy to pegylated interferon with or without ribavirin therapy in HIV-HCV coinfected patients. We propose to do a pilot study of pegylated interferon plus ribavirin in a small number of coinfected patients with advanced liver disease (stage 3 or 4 fibrosis)

The advantage of this particular county clinic is the network of peer outreach that exists to bring patients to their appointments, to counsel and teach them about treatments of HIV, HCV, and substance abuse to enhance adherence to the protocol.

HYPOTHESES:

Combination therapy with pegylated interferon alfa-2a will be safe, and will achieve clearance in some patients with HIV+ patients with chronic hepatitis C who have advanced fibrosis or compensated cirrhosis.

SPECIFIC AIMS:

To study if pegylated interferon alfa-2a plus ribavirin is safe and effective at clearing HCV (< 50 IU/mL) in patients who are HIV+ and have advanced fibrosis or cirrhosis at 24 weeks

To study what proportion of patients have sustained virologic response at 72 weeks after treatment with interferon and ribavirin for 48 weeks.

INCLUSION CRITERIA:

Age at entry 18 years or older.

A positive test for HCV RNA at the time of screening to enter the study with or without a positive test for HCV Ab.

A documented positive test for HIV by Western blot or PCR at any time in the past.

Serum ALT above 2x ULN on two occasions within past one year, one within 6 months

HIV RNA $\leq$ 30,000 for inclusion

If on HAART, therapy with no changes for at least 6 weeks before study entry

CD4 count of 150 or greater at entry.

A liver biopsy performed at least 6 months following the last course of interferon and within 6 months prior to the baseline visit, demonstrating at least stage 3 fibrosis as judged by the study pathologist.

A willingness by all women of child bearing potential to utilize adequate contraception during the entire 48 weeks of treatment and addition 12 weeks of follow-up on this study.

A willingness by all men to utilize adequate contraception during the time they are treated with interferon-ribavirin combination therapy and for 6 months thereafter.

EXCLUSION CRITERIA

Liver histology that is consistent with any other co-existent cause of chronic liver disease.

Hepatitis B surface antigen positive within 12 months of screening.

Anti-nuclear antibody titer of 1:160 or greater.

Child-Turcotte-Pugh score of greater than or equal to 7 points (See Appendix A) or any history of ascites or hepatic encephalopathy.

Any documented history of bleeding from either esophageal or gastric varices.

Platelet count of less than 75,000/mm^3.

Neutrophil count of less than 1,000/mm^3.

Hemoglobin less than 11 gm/dL.

Alpha-fetoprotein of greater than 100 ng/mL.

Evidence of a hepatic mass lesion by either ultrasound, CT or MRI that is suspicious for hepatocellular carcinoma.

Creatinine greater than 1.5 mg/dL.

Diabetes that, in the opinion of the investigator, is not controlled by diet, an oral hypoglycemic agent, and/or insulin.

Active systemic autoimmune disorders such as rheumatoid arthritis, systemic lupus, etc.

Malignancy diagnosed and/or treated within the past 2 years, except for localized squamous or basal cell cancers treated by local excision.

Serious cardiac, cerebrovascular or pulmonary disease that, in the opinion of the investigator would preclude treatment with interferon and/or ribavirin.

Underlying hematologic abnormalities that, in the opinion of the investigator, would preclude treatment with interferon.

Seizure disorder that has not been well controlled by anti-seizure medications within the past 2 years.

Pregnancy or breast-feeding.

Male partners of women who are pregnant.

Active alcohol abuse within the past 12 months.

Illicit drug use within the past 6 months.

History of severe psychiatric disease especially depression. For this study, the definition of

severe psychiatric disease includes a prior suicidal attempt, hospitalization for psychiatric disease, or a period of disability due to a psychiatric disease. (Patients whose psychiatric disease is controlled by medication and deemed psychologically stable by the investigator will be eligible for participation.)

Unable to provide informed consent.

Patients who are unable or unwilling to undergo two liver biopsies for assessment of hepatic histology during this trial.

Any other condition, which, in the opinion of the investigator, would make the subject unsuitable for enrollment, or could interfere with the subject participating in or completing the protocol.

SCREENING OF PATIENTS

Identification of potential patients.

Patients will be identified through medical records kept at the San Mateo County HIV clinics (Edison, Willow, and North county), the Stanford University Positive Care Clinic, and the Palo Alto VA HIV Clinic. We will also recruit for the study in the wider San Francisco Bay Area community via the Internet at HIV and Hepatitis C sites, promotion of study in Alameda, Costa Contra, and Sacramento counties and through outreach organizations

Patients who satisfy all preliminary entry criteria and are not excluded may enter screening.

A log of all patients screened for the trial will be maintained.

Screening for the trial is expected to last for 1 year.

Screening of patients:

The specific aims and general conduct of the protocol will be reviewed with each potential patient.

If the patient wishes to be screened for possible inclusion in this study, he or she must then sign the screening consent form.

Screening visit:

Thorough History and physical examination

Laboratory blood tests to include:

Fasting chemistries (electrolytes, BUN, creatinine, glucose, cholesterol, and triglycerides);

Liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and total protein);

Complete blood count (WBC count and neutrophil count, hematocrit, hemoglobin and platelets);

Thyroid Stimulating Hormone (TSH);

Pro-thrombin time (INR);

Alpha-fetoprotein;

Serologic screening tests to exclude other causes of chronic liver disease if these tests were either not previously performed or the results cannot be obtained (HBsAg, ANA, ferritin)

HCV RNA Quant

A urine specimen will be collected from women of childbearing potential for a pregnancy test and from all patients for the presence of protein and heme by dipstick.

Liver biopsy, if not performed within the 3 months of screening or if specimens are not available for the study pathologist to read.

Ultrasound examination of the liver if not performed within the past 3 months.

Baseline visit:

The baseline visit should be held within 8 weeks of the screening visit.

Baseline data will be obtained as shown in Table 1.

Instructions and study medications will be distributed to patients.

All patients will initially be treated for 24 weeks with pegylated interferon alfa-2a 180 µg once weekly plus ribavirin 800mg daily in two divided doses

Weeks 2-24:

During phase one, all patients will be seen and examined at regular intervals and will undergo various laboratory studies as defined in Table 1.

Week 24 visit:

Patients will be assessed for virologic response and eligibility for continuing treatment:

HCV RNA determination (<50 IU/mL)

Laboratory studies defined in table 1

Ultrasound examination of the liver

Week 28 visit:

Patients who have a virologic response (<50 IU/mL HCV RNA) at week 24 will be treated through Week 48 with follow-up through week 72.

Among responders follow up will occur every 4 weeks from week 28 until end of treatment at week 48, and both at 12 and 24 weeks after discontinuation of treatment treatment.

Blood, questionnaires, and liver biopsies will be obtained according to schedule of events (Table 1).

OUTCOME VARIABLES

PRIMARY:

HCV RNA at the end of treatment and 6 months after treatment stopped.

SECONDARY:

ALT Normalization
Improved Histopathology
Quality of life
Serious adverse events
Events requiring dose reductions.
Impact on HIV disease
- CD4 count changes
- HIV viral load changes
- Development of an opportunistic infection (AIDS Defining Event)

CESSATION OF TREATMENT

Outcomes which require permanent discontinuation of treatment:

Death from any cause
Development of hepatocellular carcinoma
Onset of ascites
Variceal hemorrhage
Hepatic Encephalopathy
Depression with suicidal ideations

DOSE MODIFICATION:

Pegylated interferon alfa-2a dosing:

Factors that will lead to mandatory reduction in the dose of peginterferon alfa-2a include:

Disabling symptoms, which, in the opinion of the investigator, are related to pegylated interferon alfa-2a treatment and prevent the patient from performing his/her occupation or daily tasks.

Rash consistent with allergic reaction or vasculitis.

Platelet count below 30,000/mm^3 (See Appendix C)

Neutrophil count below 500/mm^3 (See Appendix C)

ALT >500 (See Appendix C)

Any adverse reaction, which, in the opinion of the investigator, places the patient at increased, risks.

Consideration should be made to reduce the dose of pegylated interferon alfa-2a for:

Beck Depression Index II score of 15-28 (See Appendix B) but consider antidepressive medication

The dose of pegylated interferon alfa-2a will be reduced as follows:

3 levels for dose reduction:
1) Adjustment-135 µg

2) Adjustment-90 µg
3) Adjustment-45 µg

Once a patient's dose has been decreased, an attempt to increase the dose back to or toward the previous stable level if the following conditions are satisfied:

The event or circumstance responsible for the dosage adjustment has resolved or improved;

The patient has been at the lower dose for ≤4 consecutive doses;

≤6 total doses have been administered to the patient at the lower level during the entirety of the treatment period.

Patients who have received more than 4 consecutive or 6 total doses of pegylated interferon alfa-2a at the lower dose level should not have their dosage regimen readjusted upward. If 4 or more consecutive doses of pegylated interferon alfa-2a are held or otherwise not administered, they should consider discontinuation of study medication.

Every attempt will be made to keep those patients randomized to treatment with pegylated interferon alfa-2a on therapy by dose reduction to a minimum of 45 µg per week.

Ribavirin dosing:

The dose of ribavirin will be reduced during phase 1 as follows:

A patient without significant cardiovascular disease experiences a fall in hemoglobin to <10 g/dL and ≥8.5 g/dL

A patient with stable cardiovascular disease experiences a fall in hemoglobin by ≥2 g/dL during any 4 weeks of treatment, the ribavirin dose should be reduced to 600 mg per day (200 mg in the morning and 400 mg in the evening). Recombinant erythropoetin can be used to enhance red blood cell production at the investigator's discretion.

If a patient cannot tolerate ribavirin, then he or she can be treated with pegylated interferon alfa-2a alone and randomized at week 24, providing eligibility criteria are met.

Ribavirin should be discontinued under the following circumstances:

If a patient without significant cardiovascular disease experiences a fall in hemoglobin confirmed to be less than 8.5 g/dL.

If a patient with stable cardiovascular disease maintains a hemoglobin value <12 g/dL despite 4 weeks on a reduced dose.

In the event of ribavirin being discontinued, it can be reintroduced, at the investigator's discretion, at a daily dose of 600 mg.

If a patient becomes pregnant during the phase 1, treatment will be immediately stopped and she will not be eligible for the randomized phase of the trial.

ADVERSE EVENTS

An adverse event is any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness which occurs during the course of the trial, after treatment has started, whether the event is considered related to treatment or not.

A serious adverse event is any untoward medical occurrence that results in Death, is life-threatening (risk of death at the time of the event), requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

Data collection procedures for adverse events

At each follow-up visit, patients will be interviewed regarding medical conditions, medical changes and symptoms that have occurred since the last visit. An Adverse Event form will be completed if any adverse event is reported.

A Serious Adverse Event form will be completed for all adverse events rated as serious. All serious adverse events, for patients in both the treated and the control group will be reported to the IRB and Roche within 24 hours by telephone. This includes serious adverse events that occur from the time the patient has signed the trial informed consent to month 36

All deaths, in both the treated and in the control group will be reported to the IRB and Roche within 24 hours by telephone. This reporting includes from the time the patient has signed the trial informed consent to week 96.

SAMPLE SIZE

The study seeks to estimate the proportion of subjects who achieve virologic success after 24 weeks of treatment with Peginterferon alfa-2a. Assuming a treatment success rate of 40% with 50 patients at the end of the study, we will have 90% power to estimate this proportion of virologic success within a range of +/-20% at 95% confidence. With a drop out rate of 20% over the study period, we need to enroll 63 patients. These sample size estimates do not take into account the baseline RNA since the ultimate aim is to estimate who is undetectable at 24 and 72 weeks.

DATA MANAGEMENT AND ANALYSIS

Data Management

The protocol statistician/database manager will manage data electronically using a Microsoft ACCESS database at San Mateo County Research Unit.

The data sets created in ACCESS will be converted to SPSS. Additional data editing will be performed using SPSS.

Data Analysis

Proportion of patients with non-detectable HCV-RNA at week 24 and 72 will be estimated. The 95% confidence interval for the proportion will be reported. Logistic regression will be used to determine the characteristics that are predictive of a response to pegylated interferon alfa-2a and ribavirin.

Analyses of Secondary Endpoints

Longitudinal methods will be used to analyze changes in quality of life and other measured variables

Table 1:

Time	PE	LFT	Chem	CBC	PT	AFP	TSH	HCG[1]	UA	HCV RNA	HIV RNA	CD4	U/S	Liver Bx	SF-36[2]	BDI[3]	Pugh
Screen	X	X	X	X	X	X	X	X	X	X	X	X	X[5]	X[5]		X	X
Baseline	X	X	X	X	X			X		X	X	X			X	X	X
Week 2	X			X													
Week 4	X	X	X	X				X			X	X				X	
Week 8	X	X		X				X				X				X	
Week 12	X	X	X	X	X		X	X		X	X	X			X	X	X
Week 16	X	X		X				X								X	
Week 20	X	X		X		X		X					X			X	
Week 24	X	X	X	X	X		X	X		X	X	X			X	X	X

[1]In females of childbearing potential.

[2]Appendix D

[3]Appendix B

[4]Appendix A

[5]If none within 2 months.

Table 2: Continuation of therapy for those who respond

Visit	PE	LFT	Chem	CBC	PT	AFP	TSH	HCG[1]	HCV RNA	HIV RNA	CD4	U/S	Liver Bx	SF-36[2]	BDI[3]	Pugh[4]
Week 28	X			X				X							X	
Week 32	X			X				X							X	
Week 36	X	X	X	X				X		X	X	X		X	X	X
Week 40	X	X		X				X							X	
Week 44	X	X		X				X							X	
Week 48	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Week 60	X	X		X				X		X	X					
Week 72	X	X			X	X		X	X	X	X	X	X	X	X	X

[1]In females of childbearing potential.

[2]Appendix D

[3]Appendix B

[4]Appendix A

APPENDICES

A. Child-Turcotte-Pugh Score for Grading Severity of Liver Disease

Modified Child-Turcotte-Pugh Score				
		# of points		
Variable	**Units**	**1**	**2**	**3**
Serum albumin	(g/dL)	>3.5	2.8-3.5	<2.8
Serum total bilirubin (No Gilbert's Syndrome; No hemolytic diseases; Not receiving ribavirin)	(mg/dL)	<2.0	2.0-3.0	>3.0
Serum total bilirubin (In presence of Gilbert's Syndrome, a hemolytic disorder [e.g., patients receiving ribavirin]) ‡	(mg/dL)	<4.0	4.0-7.0	>7.0
Prothrombin Time	(INR)	<1.7	1.7-2.3	>2.3
Ascites		None	mild*	severe+
Encephalopathy		None	mild*	severe+

*Mild means readily controlled by standard medical therapies.

+Severe means difficult to control or uncontrollable by optimal, maximally tolerated medical therapies.

Prothrombin time results should be reported and used for calculations only as International Normalized Ratios (INR), because of variations in methods used and reference ranges for controls (expressed in seconds).

‡ Note that if, in the opinion of the investigator, the patient has Gilbert's syndrome or a hemolytic disorder (e.g., patients receiving ribavirin) the level of the serum total bilirubin may be increased to as high as 3.99 mg/dL without considering the total bilirubin to be sufficiently elevated for the patient to receive a score of 2 in the CTP scoring system.

The score is calculated as the sum of the scores for albumin, bilirubin, prothrombin time, ascites and encephalopathy (range 5-15). Class A is defined as 5-6, class B 7-9 and class C 10-15.

B. Beck Depression Inventory-II (BDI)

The BDI-II is a 21 item, self-administered survey used to screen for and monitor depression that takes 5-10 minutes to complete. The BDI-II has been shown to provide valid and reliable information in follow-up studies of patients with either psychiatric illness or medical illness. Although no arbitrary scores are available that can be used on all patients to classify the severity of depression, specific interpretation guidelines are available. The BDI-II was developed for the assessment of symptoms corresponding to DSM-IV criteria for diagnosing depressive disorders in 1996. The BDI-II has been extensively tested and validated and is being used in the multi-centered HALT-C protocol with a similar patient population and identical treatment.

Monitoring during treatment

1. The BDI-II is scored by summing the ratings for 21 items. Each item is rated on a 4 point scale ranging from 1-3.
2. Subjects with abnormal BDI-II scores (range: 11 to 63 with higher scores indicative of more severe symptoms) should be assessed and managed as follows:

BDI-II score	Clinical Picture
0 – 10	none to minimal
11 - 14	Mild depression
15 - 19	Mod depression
20 - 28	Severe depression
>29	Critical

C. Pegylated interferon alfa-2a Dose Adjustment Guidelines

Dose Adjustments for Low Absolute Neutrophil and Platelet Counts

Parameter	Downward Dose Adjustment
ANC (cells/mm^3)	
≥1000	None
750 - 999	Week 1 - 2*: Immediate 1 Level adjustment Week 3 - 48**: None
500 - 749	Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment Week 3 - 48: Immediate 1 Level adjustment
250 - 499	Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 2 Level adjustment Week 3 - 48: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment
<250	Stop Drug
Platelet Count (cells/mm^3)	
≥50,000	None
35,000 - 49,000	Delay or hold dose until ≥50,000 then resume dose with 1 Level adjustment
25,000 - 34,000	Delay or hold dose until ≥50,000 then resume dose with 2 Level adjustment
<25,000	Stop Drug

*Week 1-2: Signifies the abnormality was noted within the first 2 weeks of the initiation of test drug treatment.

**Week 3-48: Signifies the abnormality was noted more than 2 weeks following the initiation of test drug treatment.

Dose Adjustments for Elevated Serum ALT

Baseline Serum [ALT]	On-Treatment Serum [ALT]	Downward Dose Adjustment
≤100	<200	None
	200 - 300	Repeat test in 1 week. If ALT decreased or stable (≤10% increase), continue at present dose and follow every 1-2 weeks to assure stability. If increased by >10%, decrease dose by 1 Level and follow with weekly testing until ALT is stable or decreased.
	301 - 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
101 - 200	≤300	None
	301 - 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
201 – 300	≤400	None
	401 - 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until

		stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
301 - 500	≤500	None
	>500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to less than baseline then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
> 500	≤25% Increase	None
	>25% Increase	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to less than baseline then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.

D. SF-36 Quality of Life Survey

SF-36 HEALTH SURVEY

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent 1

Very good 2

Good 3

Fair 4

Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago 1

Somewhat better now than one year ago 2

About the same as one year ago 3

Somewhat worse now than one year ago 4

Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

EXHIBIT B

Budget

Payment Schedule

Initial Payment

Within 60 days of signing contract and upon receipt of IRB approval **$157,207.00**

Second Payment

Upon enrollment of 25 patients **$157,207.00**

Third Payment

Upon enrollment of next/final 25 patients **$157,207.00**

Final payment

Upon completion of study and submission of final report **$157,207.00**

Total Amount **$628,828.00**

COUNTY OF SAN MATEO

HEATH SERVICES
Hospital and Clinics Division

MEMORANDUM

Date: November 20, 2001

To: Priscilla Morse, Risk Management/ Pony # EPS 163 Fax # 363-4864

From: Tere Larcina, Hospital and Clinics/Pony # HOS316/Fax # 2267

Subject: Contract Insurance Approval

CONTRACTOR: Roche Pharmaceuticals

DO THEY TRAVEL: No

PERCENT OF TRAVEL TIME:

NUMBER O F EMPLOYEES: More than one.

DUTIES (SPECIFIC): Roche Pharmaceuticals will fund research for the Phase II open label treatment with Pgylated Interferon alfa-2a plus ribavirin in Patients with HCV associated cirrhosis and HIV infection-Protocol PEG086.

COVERAGE:	Amount	Approve	Waive	Modify
Comprehensive Liability:	$1m	✓		
Motor Vehicle Liability:			✓	
Professional Liability:	$1m	✓		
Worker's Compensation:			✓	

REMARKS/COMMENTS:

Priscilla Morse
SIGNATURE

TOTAL P.01

TOTAL P.01

MARSH USA INC.

CERTIFICATE OF INSURANCE

CERTIFICATE NUMBER
NYC-001246859-00

PRODUCER
MARSH USA INC.
44 WHIPPANY ROAD
P.O. BOX 1966
MORRISTOWN, NJ 07962-1966

THIS CERTIFICATE IS ISSUED AS A MATTER OF INFORMATION ONLY AND CONFERS NO RIGHTS UPON THE CERTIFICATE HOLDER OTHER THAN THOSE PROVIDED IN THE POLICY. THIS CERTIFICATE DOES NOT AMEND, EXTEND OR ALTER THE COVERAGE AFFORDED BY THE POLICIES DESCRIBED HEREIN.

COMPANIES AFFORDING COVERAGE

COMPANY A SELF-INSURED

INSURED
HOFFMANN-LA ROCHE INC.
INCLUDING ALL DIVISIONS AND
SUBSIDIARIES
340 KINGSLAND STREET
NUTLEY, NJ 07110-1199

COMPANY B N/A

COMPANY C

COMPANY D

COVERAGES This certificate supersedes and replaces any previously issued certificate for the policy period noted below.

THIS IS TO CERTIFY THAT POLICIES OF INSURANCE DESCRIBED HEREIN HAVE BEEN ISSUED TO THE INSURED NAMED HEREIN FOR THE POLICY PERIOD INDICATED. NOTWITHSTANDING ANY REQUIREMENT, TERM OR CONDITION OF ANY CONTRACT OR OTHER DOCUMENT WITH RESPECT TO WHICH THE CERTIFICATE MAY BE ISSUED OR MAY PERTAIN, THE INSURANCE AFFORDED BY THE POLICIES DESCRIBED HEREIN IS SUBJECT TO ALL THE TERMS, CONDITIONS AND EXCLUSIONS OF SUCH POLICIES. LIMITS SHOWN MAY HAVE BEEN REDUCED BY PAID CLAIMS.

CO LTR	TYPE OF INSURANCE	POLICY NUMBER	POLICY EFFECTIVE DATE (MM/DD/YY)	POLICY EXPIRATION DATE (MM/DD/YY)	LIMITS	
A	GENERAL LIABILITY	SELF-INSURED	01/01/01	01/01/02	GENERAL AGGREGATE	$ N/A
	[X] COMMERCIAL GENERAL LIABILITY				PRODUCTS - COMP/OP AGG	$ 5,000,000
	[ ] CLAIMS MADE [X] OCCUR				PERSONAL & ADV INJURY	$ 5,000,000
	[ ] OWNER'S & CONTRACTOR'S PROT				EACH OCCURRENCE	$ 5,000,000
	[X] INCLUDES PRODUCTS AND				FIRE DAMAGE (Any one fire)	$ 5,000,000
	[ ] BROAD FORM VENDORS				MED EXP (Any one person)	$ 5,000,000
	AUTOMOBILE LIABILITY				COMBINED SINGLE LIMIT	$
	[ ] ANY AUTO					
	[ ] ALL OWNED AUTOS				BODILY INJURY (Per person)	$
	[ ] SCHEDULED AUTOS					
	[ ] HIRED AUTOS				BODILY INJURY (Per accident)	$
	[ ] NON-OWNED AUTOS					
	[ ] _____				PROPERTY DAMAGE	$
	GARAGE LIABILITY				AUTO ONLY - EA ACCIDENT	$
	[ ] ANY AUTO				OTHER THAN AUTO ONLY:	
	[ ] _____				EACH ACCIDENT	$
					AGGREGATE	$
	EXCESS LIABILITY				EACH OCCURRENCE	$
	[ ] UMBRELLA FORM				AGGREGATE	$
	[ ] OTHER THAN UMBRELLA FORM					$
	WORKERS COMPENSATION AND EMPLOYERS' LIABILITY				WC STATUTORY LIMITS / OTHER	
	THE PROPRIETOR/ PARTNERS/EXECUTIVE OFFICERS ARE: [ ] INCL [ ] EXCL				EL EACH ACCIDENT	$
					EL DISEASE-POLICY LIMIT	$
					EL DISEASE-EACH EMPLOYEE	$
	OTHER					

DESCRIPTION OF OPERATIONS/LOCATIONS/VEHICLES/SPECIAL ITEMS (LIMITS MAY BE SUBJECT TO DEDUCTIBLES OR RETENTIONS)

CERTIFICATE HOLDER

SAN MATEO COUNTY HEALTH CENTER
ATTN: ANITA BOOKER
2222 WEST 39TH AVENUE
SAN MATEO, CA 94403

CANCELLATION

SHOULD ANY OF THE POLICIES DESCRIBED HEREIN BE CANCELLED BEFORE THE EXPIRATION DATE THEREOF, THE INSURER AFFORDING COVERAGE WILL ENDEAVOR TO MAIL 30 DAYS WRITTEN NOTICE TO THE CERTIFICATE HOLDER NAMED HEREIN, BUT FAILURE TO MAIL SUCH NOTICE SHALL IMPOSE NO OBLIGATION OR LIABILITY OF ANY KIND UPON THE INSURER AFFORDING COVERAGE, ITS AGENTS OR REPRESENTATIVES.

MARSH USA INC.
BY: Robert S. Fissel

MM1 (9/99) VALID AS OF: 11/26/01