DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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June 29, 2004

Michael J. Klag, M.D., M.P.H.
Vice Dean for Clinical Investigation
Johns Hopkins University School of Medicine
Turner 36
720 Rutland Avenue
Baltimore, MD 21205-2196

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011 and Federalwide Assurance (FWA) 5752

Research Project: A Phase III Open-Label, Randomized, Active-controlled Study Assessing the Efficacy and Safety of T-20/Ro 29-9800 (HIV-1 Fusion Inhibitor) in Combination with an Optimized Background Regimen, Versus Optimized Background Regimen Alone

Principal Investigator: Joel E. Gallant, M.D., M.P.H.
Project Number: 00-11-08-03

Dear Dr. Klag:

The Office for Human Research Protections (OHRP) has reviewed Johns Hopkins University School of Medicine's (JHUSM) April 24, 2003 response to OHRP's letter dated March 17, 2003 regarding the above-referenced research.

The complainant's allegations involved the following:

(1) Failure to minimize risks to subjects by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that manufacturing or packaging changes in the study drug, T-20, led to serious injury in the complainant.

JHUSM indicated in its April 24, 2003 response that the complainant's assertion to the research team that he had experienced painful and persistent injection site reactions that were attributable to a new batch of the study drug was promptly reported to the study sponsor and manufacturer. The sponsor reviewed all lots of the drug and determined that

there had been no variations in the formulation of the drug. In addition, the research team was not able to evaluate the complainant's injection site reactions because the complainant cancelled an appointment specifically scheduled in response to his complaints and declined to allow an evaluation of his reported side effects when he showed up at the clinic about three weeks later without an appointment.

Based on this and other information in JHUSM's report, OHRP is unable to substantiate the allegation that manufacturing or packaging changes in the study drug led to serious injury in the complainant.

(2) The complainant alleged that he was inappropriately withdrawn from the study.

JHUSM indicated in its April 24, 2003 response that the subject was removed from the study for failure to adhere to the protocol regimen and for failure to come in for appointments to address problems related to the subject's participation in the research. JHUSM reported that the complainant self-reported that he had stopped taking the study drug and following the background regimen for 57 days.

OHRP notes that the protocol (dated March 30, 2001, Version C) states the following in Section 7.4 on page 71: "The investigator also has the right to withdraw patients from the study if it is in the best interest of the patient." In section 7.3.1. on page 70, the protocol states that "…if the patient has missed either T-20….or all drugs prescribed in the OB regimen for more than 28 consecutive days or a cumulative total of 42 days, for any reason, including toxicology management, the patient should be discontinued from the trial."

OHRP notes that the informed consent document (dated March 20, 2001, Version C) states the following in the section titled "Termination of the Study": "Your study doctor has the right to terminate your participation in the study if you do not follow the study's instructions, or it is considered to be in your best interest." The section entitled "Procedures" states the following: "...deliberately not taking one or more of the HIV drugs or T-20 as prescribed (except when you experience side effects, as instructed by your doctor) are not allowed in the study. If you do not follow these or other conditions of the study...you may have to leave the study."

JHUSM stated the following in its April 24, 2003 response:

> The investigator and his coordinator made every effort to accommodate the complainant's concerns during the period of study participation. Unfortunately, the complainant failed to follow through on required procedures to assure appropriate monitoring of his experience as a study participant and thus disqualified himself from continued participation.

Based on the information above and other information in JHUSM's report, OHRP is unable to substantiate the allegation that the complainant was inappropriately withdrawn from the study.

3) Failure to report unanticipated problems involving risks to subjects or others to

appropriate institutional officials, the IRB, and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). In specific, the complainant alleges that his withdrawal from the study was reported as being due to noncompliance with the protocol; however, the complainant states he was compliant. In addition, OHRP has no record of receiving a report on the unanticipated problems experienced by the complainant.

OHRP notes that both the protocol and the investigator's brochure contain information on the injection site reactions experienced by subjects in previous studies using the study drug. In addition, the informed consent document specifically details the risk of injection site reactions. Based on the information reviewed, it does not appear that the injection site reactions experienced by the complainant were "unanticipated."

JHUSM indicated in its April 24, 2003 response that the complainant was withdrawn for failure to adhere to the protocol regimen (see finding #2 above) and had a "continuing record of protocol noncompliance...he cancelled study visits, stopped medications on his own initiative, and demanded changes in medications ...."

Based on the information provided in JHUSM's report, OHRP is unable to substantiate the allegation that JHUSM failed to report unanticipated problems involving risks to subjects or others to the appropriate parties.

Because OHRP is unable to substantiate the complainant's allegations above, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Karena Cooper, J.D., M.S.W.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Dr. Lewis Becker, JHM IRB #1
Dr. David R. Cornblath, JHM IRB #2
Dr. Paul S. Lietman, JHM IRB #3
Dr. Hayden Braine, JHM IRB #4
Dr. Gary Briefel, JHM IRB #5
Dr. Judy L. Stiff, JHM IRB #6
Dr. Joel E. Gallant, JHU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
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Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
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Ms. Melinda Hill, OHRP
Ms. Patricia El-Hinnawy, OHRP