DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-435-8072
FAX: 301-402-2071
email: kborror@osophs.dhhs.gov

January 7, 2002

Michael Rosenblatt, M.D.
President
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215

RE: Human Research Subject Protections Under the Multiple Project Assurance (MPA) M-1544
Research Project: Grant # 1R01MH57980-01A1–"Transcranial Magnetic Stimulation (rTMS) in Depression
Principal Investigator: Alvaro Pascual-Leone, M.D., Ph.D.

Dear Dr. Rosenblatt:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) December 20, 2001 report regarding the above referenced matter.

Based upon its review of previous report, OHRP made the following determinations:

(1) In its October 10, 2001 letter to BIDMC, OHRP found that the procedures for withdrawing subjects from medications and for screening potential subjects for determination of eligibility for the research constituted human subjects research activities.

Corrective Action: OHRP acknowledges that the application and consent forms for the above-referenced project have been amended to clearly state that medication withdrawal is part of the study and cannot be initiated without the subject's prior written consent to participate in the research, and that all participants will be required to come for an initial visit at which time informed consent will be obtained. OHRP notes that this corrective action plan only addresses the above-referenced protocol. By February 8, 2002, please provide OHRP with appropriate corrective action plans to ensure that **no** research-related interventions are conducted **by any BIDMC investigator** prior to the investigator obtaining and documenting

legally-effective informed consent in accordance with, and to the extent required, by HHS regulations at 45 CFR 46.116 and 46.117.

(2) In its October 10, 2001 letter to BIDMC, OHRP found that the informed consent documents reviewed and approved by the Institutional Review Board (IRB) for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): A description of the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. The risks and discomforts of the medication withdrawal and of the neurologic, neuropsychologic, neurophysiologic, and neuroradiologic tests to be conducted, and performance of electroencephalograms were not included in the informed consent document.

OHRP also found that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects.

Corrective Action: OHRP acknowledges that the informed consent document has been revised. By February 8, 2002 please provide OHRP a copy of the revised document after it has been reviewed and approved by the IRB. Please also provide OHRP with an analysis by the IRB of any need to re-contact subjects to provide additional appropriate information regarding their participation in the research.

(3) In its October 10, 2001 letter to BIDMC, OHRP found that continuing review of research by the IRB did not appear to be substantive and meaningful.

Corrective Action: OHRP acknowledges that the IRB has recently changed its method of conducting continuing review. Please note that designation of additional IRBs under the MPA requires prior notification of and approval by OHRP.

(4) In its October 10, 2001 letter to BIDMC, OHRP found that protocol changes were implemented without IRB approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii)

Corrective Action: OHRP acknowledges that the next issue of the BIDMC's IRB newsletter to the clinical research community will include a reminder to investigators of this requirement. This corrective action appears to be adequate and is appropriate under the BIDMC MPA.

OHRP makes the following additional finding.

(5) Your September 6, 2001 report included numerous documents that were sent to

prospective subjects and their physicians, including an initial information letter to patients, information packets to physicians and to patients, a recruitment letter to physicians, initial information letter to physicians, acceptance letter to prospective subjects, an appointment confirmation letter to prospective subjects, a denial letter and a thank you letter to subjects. OHRP finds no evidence that the IRB reviewed and approved these materials before they were sent to prospective subjects and physicians.

Corrective Action: OHRP acknowledges that the principle investigator is in the process of responding to the IRB's questions and revising the above-referenced documents in accordance with the committee's request.

OHRP has the following additional questions and concerns.

(6) OHRP is concerned that the IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. See, for example, protocols #E-01-0301-FB, #E-01-0307-FB reviewed and approved on September 17, 2001; and protocol # E-01-0053-FB reviewed and approved November 19, 2001. Please respond.

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research should be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(7) HHS regulations at 45 CFR 46.110(b) require that expedited review be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. All minutes state "unless otherwise stated, the CCI Administrator and/or the CCI Revisions Coordinator will review all committee requested revisions...." Please clarify whether or not the CCI Administrator and the CCI Revisions Coordinator are experienced members of the IRB.

(8) OHRP is concerned that the following suspensions or terminations of IRB approval appear to have not been reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5):

(a) Termination of protocol #97-00-00-0295 on September 17, 2001 for non-compliance.

(b) Termination of protocol #97-00-00-0296 on September 17, 2001 for non-

compliance.

(c) Suspension of enrollment of new subjects for protocol #E-98-0162-FB on September 17, 2001for discrepancies noted during continuing review of the protocol.

Please respond.

Please provide your response to the above determinations and concerns so that OHRP receives it no later than February 8, 2002. If upon further review of the concerns and questions, BIDMC identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc Dr. Alan Lisbon, Chair, BIDMC IRBs
Dr. Alvaro Pascual-Leone, BIDMC
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA