DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1100 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-3006
FAX: 301-402-2071
E-mail: rmeyer@osophs.dhhs.gov

June 2, 2003

Richard C. Powell, Ph.D.
Vice President for Research and Graduate Studies
University of Arizona
Administration Building, Room 601
P.O. Box 210066
Tucson, Arizona 85721-0066

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1233 and FederalWide Assurance (FWA) 00004218

Research Project: A Multicenter, Open, Noncomparative Study to Estimate the Safety, Tolerability, and Efficacy of MK-0991 in the Treatment of Invasive Aspergillus Infections in Adults Who Are Refractory to or Intolerant of Amphotericin B, Lipid Formulations of Amphotericin B, or Azoles
Principal Investigator: Rodney D. Adam, M.D.
Protocol Number: 019-00

Research Project: A Noncomparative, Open, Multisite, Compassionate Use Study to Evaluate the Safety and Tolerability of MK-0991 for the Treatment of Oropharyngeal and Esophageal Candidiasis, Invasive Candidiasis and Invasive Aspergillus in Adults Who Are Refractory to or Intolerant of Amphotericin B or Amphotericin B Lipid Formulations
Principal Investigator: Elliot Epner, M.D.
Protocol Number: 024-01

Dear Dr. Powell:

The Office for Human Research Protections (OHRP) has reviewed University of Arizona's (UA's) May 2, 2002 report that was submitted in response to OHRP's March 18, 2002 letter to UA regarding allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

Based upon review of your May 2, 2002 report, OHRP makes the following determinations regarding the allegations presented in OHRP's March 18, 2002 letter:

(1) It was alleged that the physicians caring for the complainant's son deliberately mismanaged his son's medical care so that he would meet the eligibility criteria for the above-referenced research protocol # 019-00.

UA's May 2, 2002 report stated the following in response:

(a) "Dr. Alan List, the BMT managing physician had placed the patient on low doses of Ambisome in a preventive fashion to obviate fungal infection during the profound immunosuppression of high graft vs. host disease."

(b) "This therapeutic intervention, from 09/05 - 10/11 was managed appropriately with careful attention to fluids, electrolytes and renal function. The patient received supplemental normal saline to help prevent any renal dysfunction and in fact, at no time prior to, during, or in the post Protocol #019 period was there any renal dysfunction..."

(c) "A concern for pulmonary Aspergillosis was first raised by an abnormal chest X-Ray on 10/09 done in the face of fever. The patient was placed on higher doses of Ambisome at that time, in conjunction with saline bolus for renal protection...Given the CT findings of 10/11 and the concern for fungal pneumonia the patient was placed on higher doses of Ambisome."

(d) "Dr. Adam, after concurring with a diagnosis of Aspergillosis in a severely immunocompromised pulmonary patient who developed Aspergillosis while on Ambisome stated that the patient, 'in my medical judgement' could benefit from the investigational MK 0991 given that the patient developed his pulmonary Aspergillosis while on Ambisome."

(e) "The patient was felt to have not responded to therapy...The patient was given a choice of high dose Ambisome versus MK 0991. According to Dr. Adam, given the progression of the disease while on Ambisome the patient ultimately elected to go on protocol [Protocol #019]."

Based on the statements in (a) - (e) above and its review of other information presented in your report, including the eligibility criteria for the above-referenced research protocol # 019-00 and copies of pertinent clinical records relating to the complainant's son, OHRP finds that the above allegation was not substantiated.

(2) It was alleged that the principal investigator for the above-referenced research protocol # 019-00 sought consent from the complainant's son under circumstances that failed to minimize the possibility of coercion or undue influence, in contravention of the requirements of HHS regulations at 45 CFR 46.116.

UA's May 2, 2002 report stated the following in response:

(a) "The circumstances under which consent was sought include the following: Patient admitted to the impatient unit on 10/10/00. On 10/12/00 patient was evaluated for treatment with MK-0091. On this date, the patient's subjective evaluation included that he 'felt ok overall'. Objectively he was evaluated as alert and oriented X 3, appropriate verbal responses (Glasgow Coma Score = 15). Patient was up in the room and performing self-care."

(b) "It appears from the medical notes as well as testimony from Dr. Adams that the patient was lucid and competent to participate in the informed consent process. Confirmation by the medical record also indicates that Dr. Adam visited first to invite participation in the investigational trial. At that point, he gave the patient information and allowed time for consideration by returning later in the day. Given the nature of the disease and high possibility of quick disease progression, it may be problematic to wait for any considerable length of time. The fact that Dr. Adam returned the same day for further discussion of participation in the investigational trail (sic), supports the idea that time was an important factor in this patient's care as well as (to) give the patient time to consider his alternatives and make a decision."

(c) "Dr. Adam's consult notes on 10/12/00 included the following:

'Cytology suggestive of aspergillus, there are two options: one is to increase dose of ampho, the other is to initiate MK-991 (caspofungin) study. I have discussed with patient and will discuss further this afternoon."

(d) "In summary, the committee has concluded the following:

- The patient's disease had progressed to a point where he was severely ill.
- The patient was informed as to the progression of disease and why he was considered for participation in the investigation of trial MK-0991.
- Dr. Adam's decision to approach the patient for participation in the MK-0991 investigational trail (sic) was appropriate.
- Dr. Adam participated in a consenting process that gave the patient time to consider his alternatives that was not coercive or used undue influence.
- The patient was medically competent to sign the informed consent form."

(e) The UA institutional review board (IRB) approved informed consent document for the above-referenced research protocol # 019-00 stated the following:

> "I understand that I may ask questions at any time and that I am free to withdraw from the project at any time without causing bad feelings or affecting my medical care."

Based on the statements in (a) - (e) above and its review of other information presented in your report, including copies of pertinent clinical records relating to the complainant's son, OHRP finds that the above allegation was not substantiated.

(3) It was alleged that the informed consent process for the above-referenced research protocol # 019-00 failed to disclose appropriate alternative procedures or courses of treatment, if any, that may have been advantageous to subjects, as required by HHS regulations at 45 CFR 46.116(a)(4). In specific, it was alleged that participation in clinical trials of other investigational agents was not disclosed to the complainant's son.

UA's May 2, 2002 report stated the following in response:

> (a) "During the interview with Dr. Adam on 4/22/02, he pointed out that discussions with the patient regarding the use of therapies had taken place and that he had informed the patient that he had not successfully avoided an Aspergillosis infection while on doses of amphotericin B...Dr. Adam stated during the interview with the Panel that he felt that other investigational drugs available to him at that time of the imidazole class were not viable choices..."
>
> (b) "In summary, the committee has concluded the following:
>
> - The patient was informed as to the appropriate alternative procedures or courses of treatment, if any that may have been advantageous to him, as required by HHS regulations at 45 CFR 46.116(a)(4).
>
> - Dr. Adam's decision to inform the patient of standard treatment(s) as appropriate alternative procedures or courses of treatment for the MK-0991 investigational trail (sic) was appropriate."
>
> (c) The UA IRB approved informed consent document for the above-referenced research protocol # 019-00 stated the following:
>
> "**STANDARD TREATMENTS**
>
> The standard treatment for invasive aspergillosis includes intravenous amphotericin B or lipid forms of amphotericin B. In some cases, oral itraconazole is used to treat invasive aspergillosis. If I chose not to participate in this study, I will be offered one of the standard treatments."

Based on the statements in (a) - (c) above and its review of other information presented in your report, OHRP finds that the subject was informed of the appropriate alternative courses of treatment available to him. Accordingly, OHRP finds that the above allegation was not substantiated.

(4) It was alleged that the complainant's son was involved in a second clinical trial evaluating a salvage antifungal regimen that included MK-0991 and Ambisome®, the above-referenced research protocol # 024-01, without his legally effective informed consent, in contravention of

the requirements of HHS regulations at 45 CFR 46.116.

UA's May 2, 2002 report stated the following in response:

> "Based upon Dr. Epner's testimony, he had discussed the combined use protocol with the patient in depth during the consent process. He specifically remembered discussing alternative therapies, including other potential investigational therapies. Dr. Epner stated that the patient was lucid, coherent, asked questions about both his condition and the use of MK-0991 in combination with Ambisome®. Dr. Epner stated that he strongly believed the patient was fully competent to participate in the informed consent process. He also remembered that the patient had family members present during the consent process and that they seemed comfortable with the consent process and the plan to use the combined regimen. Ms. Meister, the social worker on the bone marrow transplant team, independently confirmed that the patient was competent to make medical decisions during the period of care that included obtaining the consent for the combined therapy."

OHRP notes that a copy of the consent form for research protocol # 024-01 signed by the complainant's son and Dr. Epner on October 31, 2000 was included in UA's May 2, 2002 report. Based on a copy of the signed consent form, the above statement and its review of other information presented in your report, OHRP finds that the above allegation was not substantiated.

As a result of the above determinations, 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 these determinations.

OHRP notes that UA's "Blue Ribbon" committee, specifically convened by UA to conduct an investigation into the allegations presented in OHRP's March 18, 2002 letter, made a number of recommendations for improving UA's human subject protection procedures. OHRP acknowledges UA's plans to implement the following investigating committee recommendations:

(1) Whenever informed consent is sought with a subject where the treating physician is also the principal investigator of the research protocol, an independent physician, with expertise in the disease entity but not associated with the research protocol as a secondary or sub-investigator, will witness and monitor the informed consent.

(2) In situations where a potential subject is at risk of death or disability and the research involves more than minimal risk a witness must be present during the consenting process. The witness would be in the position of advocate for the subject rather than a member of the investigational team. The witness would date and sign the informed consent document and also make a note in the research record that states the condition of the subject and the conditions surrounding the signing of the informed consent document.

(3) In high-risk situations with ongoing studies (i.e., not a single intervention), investigators should consider using a decision monitoring process. Personnel other than the study nurse or principal investigator should conduct decision monitoring at a date at least two days following the informed consent process. The subject should be asked simple questions regarding the nature of the study, the risks involved, the benefits (if any), and should be reminded that he or she may withdraw without prejudice. Finally, the subject should be asked if he or she still wished to participate in the study. If questions arise regarding the study or the subject is unsure of his or her decision, then he or she should be encouraged to discuss the study with the principal investigator. Decision monitoring may be conducted by telephone, but should be documented on a standard form, signed and dated by the monitor.

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

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Rebecca W. Dahl, Director, Human Subjects Protection Program, UA
Dr. David G. Johnson, Chair, UA IRB
Dr. Rodney D. Adam, UA
Dr. Elliot Epner, UA
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. Bernard A. Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Ms. Yvonne Higgins, OHRP
Ms. Freda Yoder, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Melinda Hill, OHRP