

936-5921 / 99

PD-AAM-802

ISA 29712

DEC 18, 1980

ACTION MEMORANDUM FOR THE DEPUTY ASSISTANT ADMINISTRATOR FOR HUMAN
RESOURCES DEVELOPMENT

FROM: DS/HFA, John Alden

Problem: Approval of funds for a grant to The Johns Hopkins University to support phase I clinical trials of the compound "amoscanate" as an antischistosomal drug. (Project No. 936-5921)

Discussion: From May 1976 to September 1980 the Office of Health, Development Support Bureau, AID supported the project "Research and Development of an Effective and Safe Drug for Treatment of Schistosomiasis", #931-0642, which was carried out by the Departments of Pathobiology and Pharmacology of The Johns Hopkins University, Baltimore, Maryland. Dr. Ernest Bueding, Professor in these two Departments was the senior investigator of this project. The total amount of support provided by AID over a period of four years and four months amounted to \$984,560, with \$254,000 (\$176,000 direct costs) going to The Johns Hopkins University and \$730,560 for research on primates to the Lowell University, Massachusetts under a sub-contract with The Johns Hopkins University. This project is scheduled for terminal review at the RAC meeting in March.

During this period Dr. Bueding's research was also supported by a grant from the National Institutes of Health which began on November 1, 1979 and terminated on November 30, 1980. A part of this 500,000 dollar project on the "Design of Chemotherapeutic Agents and their Metabolism" dealt with pre-clinical studies of schistosomicidal drugs, especially of amoscanate.

The original deadline of the AID contract (September 30, 1979) was postponed to September 1980 without additional funding. This extension was granted because there had been delays in receiving essential supplies and equipment for the animal experiments.

Under this previous project, the compound amoscanate was identified as an effective schistosomocide and all pre-clinical studies were completed in accordance with FDA requirements. (The amoscanate compound was patented by Giba-Geigy in 1968. All patent rights will expire in 1983, well before a drug based on amoscanate could be tested and approved for general use.) The next step in development of the drug for human use is the phase I clinical trials.

Dr. Bueding submitted a proposal to NIH for further funding of his total program for design of chemotherapeutic agents, which included further development of the schistosomiasis drug. Although the proposal was accepted

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for support by the technical peer review, NIH was not able to secure funds for it. At the suggestion of NIE, the proposal has been split into two separate segments and resubmitted. The schistosomiasis proposal is scheduled to be reviewed by NIAD's external peer review panel in March 1981 but NIH funding would not be available until July 1981, at the earliest.

In the meantime, Dr. Bueding needs financial support to keep his research team together and to undertake the next critical step for drug development and approval. The phase I clinical trials will be conducted on human volunteers receiving three different single doses of formulated amoscantate to determine the metabolism of the drug, especially with regards to any untoward side effects, including tests for carcinogenicity and mutagenicity. Favorable results from the phase I trials would allow researchers to proceed with phase II, effectiveness studies, on schistosomiasis patients. Dr. Bueding and his associates have been discussing the proposed phase I procedure with FDA and expect to submit their application for an IND (permit to use experimental drugs) within the next few weeks. We have been told, informally, by FDA officials that their conference with Dr. Bueding's group was favorable and that the probability of obtaining an IND for the phase I trials is good.

In view of the success of Dr. Bueding's research to date, the large amount of favorable publicity generated by the success of the pre-clinical phase of the project, and the continuing importance of a viable and economic anti-schisto drug for health programs in LDCs, we feel that it is in AID's interest to support these phase I clinical trials. The Johns Hopkins University considers this activity sufficiently important that they have agreed to bear the indirect and overhead costs. The funds requested from AID are for direct costs only.

This project was not included in the FY 1981 Congressional Presentation and a notification will be required before the funds can be obligated. Money is earmarked for the project in DS/HEA's approved FY 1981 OYB.

Recommendation: That you approve up to \$101,000 of FY 1981 funds for the subject activity.

Approved: *[Signature]*

Disapproved: _____

Date: *12/10/80*

Attachment: Proposal Letter
from Dr. Bueding, including Budget

DS/HEA: AABuck: cl: 12/4/80: X59823

Clearance: DS/PO: iChapnik *[Signature]* Date *12/18/80*

DS/HEA CONFIDENTIAL FILE

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH
615 NORTH WOLFE STREET
BALTIMORE, MARYLAND 21205, U. S. A.

DEPARTMENT OF PATHOBIOLOGY

November 25, 1980

Agency for International Development
Office of Health
Department of State
Washington, D. C. 20523

Gentlemen:

This is to confirm our previous request for interim funds to provide support for the clinical trial of amoscanate (Phase I studies).

One of the central goals of our effort in schistosomiasis has been the development of safe and effective agents for the mass treatment of schistosomiasis. The progress made towards this goal, achieved with the support from various government agencies - primarily AID and NIH - has led to the development of amoscanate.

Since expiration of AID contract TAC 1312, further progress has been made in reducing possible side effects. It was found that single doses of the drug rather than multiple doses (as used in China) can reduce the hepatobiliary toxicity; improved formulation reduced the single oral dose required for the complete elimination of the parasite. Only a Phase I clinical study can provide conclusive evidence that the improved single-dose, curative treatment can eliminate the risk of jaundice, observed in China with unnecessarily high and multiple doses. Another recent development is a new highly sensitive polarographic technique devised in the manufacturer's laboratories, permitting the determination of amoscanate in blood and urines. This will be of great value for pharmacokinetic studies of amoscanate in man.

As pointed out in our communication to AID, dated November 18, 1980, discussions about a (clinical) Phase I trial of amoscanate with the Food and Drug Administration and the drug manufacturer have reached a final stage. Completion and submission of an IND is scheduled within four to six weeks hence, and the start of a Phase I study in the Division of Clinical Pharmacology of The Johns Hopkins Medical Institutions is expected immediately thereafter.

Financial support is required for the Phase I study which is to be conducted on human volunteers receiving single graded doses of formulated amoscanate. The protocol for these studies will be submitted for approval by the Joint Committee on Human Investigations of the Johns Hopkins Medical Institutions. The following tests are to be carried out on individuals prior to and at intervals following drug administration.

BC/PC CONTROL

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1. Hematological profile
2. Blood chemistries
3. Urinalysis
4. Clinical tests, including electrocardiograms and electroencephalograms.
5. Measurement of drug levels and metabolites.
6. Measurements of mutagenic activity
7. Studies of dosage schedules designed to optimize the curative, and minimizing any toxic side effects
8. Examination of a possible development of drug resistant schistosomes

The above two aspects (7 & 8) require continuation of the core facility for the maintenance of the life-cycle of schistosomes.

Examination for evidence of amoscanate sensitivity in human subjects by testing:

- a. Serum (antibodies to amoscanate)
- b. Activation of lymphocytes (determination of thymidine uptake)
- c. Activation of leukocytes (histamine release)

If this Phase I trial proves uneventful, we shall proceed, as rapidly as possible, with Phase II studies (trials for effectiveness). On the basis of the experience in the People's Republic of China, there is little doubt that this drug will prove highly effective in man as it has been shown to be in experimental infections with all three major species of schistosomes in various hosts, including primates.

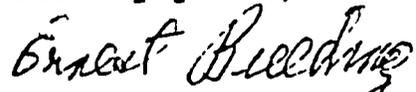
We are making considerable efforts to obtain funding, but do not expect that this can become available until the summer of 1981. For example, instead of applying for support of schistosomiasis studies within a large program-project, we now have submitted to NIH a grant proposal strictly limited to the chemotherapy of schistosomiasis. However, even if approved, funding cannot start prior to July 1, 1981. Calculation of the budget attached with this document indicates the need for a minimum of \$100,000 for the period of December 1, 1980 to June 30, 1981.

Having reached a critical point in the development of amoscanate as a promising effective and safe agent for the treatment of schistosomiasis, it would indeed be most unfortunate to stop so short of the final goal. Sudden discontinuation would compromise work conducted over the past 30 years as well as a heavy investment of government funds.

AID
November 25, 1980
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In view of this extremely serious situation this Institution will waive any request for overhead or indirect costs.

Sincerely yours,



Ernest Bueding, M.D.
Professor of Pathobiology and
Professor of Pharmacology and
Experimental Therapeutics

EB/ab

Enclosure

Budget for Interim Funding for Seven Months - Direct Costs Only

December 1, 1980 - June 30, 1981

Salaries

Professional Staff

	% Effort	
E. Bueding Professor & Program Director	20	\$ 6,204
J.G. Bourgeois Assistant Professor & Assistant Program Director	75	14,297
B.L. Nguyen Research Associate	60	6,237
J. Hawkins Research Associate	100	10,334

Non-Professional Staff

	No. of Hrs. per week	
F. Lee Lab. Technician	40	6,625
A. Baker Executive Secretary	14	2,542
H. Walters Administrative Secretary	32	5,872
E. Brown Lab. Technician	30	5,715

\$57,826

Fringe Benefits 18.5%

10,698

Total Salaries & Fringe

68,524

Animal Purchase and Care

10,500

Equipment - Polarograph

8,200

Supplies

13,000

\$ 100,224

No Indirect Cost Requested

Budgetary Justification

Personnel

The role of professionals is as follows:

E. Bueding - Program Director. Although only 20% of his salary is requested, he is expected to devote a much larger proportion of time to this project. In addition, the collaboration of two senior faculty members on this project will continue. They are P. Talalay, Distinguished Service Professor, Department of Pharmacology and Experimental Therapeutics, and P.S. Lietman, Wellcome Professor, Clinical Pharmacology and Director of the Division of Clinical Pharmacology. No salary is requested for these two colleagues, at this time, in order to keep the budget at the minimum level.

J.G. Bourgeois - Assistant Director. He will coordinate the program administration and the clinical laboratory methods (hematology, blood chemistry, urinalysis, etc.). In addition, he will continue to supervise the core facility for the maintenance of the complete life cycle of various strains of schistosomes and to supply necessary animal models for drug dosage regimens to optimize the curative, and to minimize any possible toxic side effects.

B.L. Nguyen - Research Associate. She will be responsible for the measurement of levels of amoscanate and its metabolites in blood and urine samples and for their identification using the newly developed polarographic method.

J. Hawkins - Research Associate. She will be responsible for the human blood and urine chemistry and serology.

J. Seed - Assistant Professor. He will be responsible for the toxicological examination of human urines for the presence or absence of mutagenic activity after the administration of this drug. No salary is requested for this colleague in the interests of economy.

Equipment. The polarograph is required for the measurement of the levels of amoscanate and its metabolites in blood and urine. No other method is currently available for the sensitive and specific estimation of amoscanate, and no polarograph is available in this institution.

Animals and Animal Services. Animal care facilities and programs meet requirements of Federal (89-544 and 91-579) and NIH regulations. The School has been accredited by the American Association for Accreditation of Laboratory Animal Care. The request for animal costs are based on the requirements of the Committee on Animal Care of this institution.