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(U) BIO-MED INC COLLEGE PARK MD R C REBA ET AL. OCT 83
DAMD17--75-C-5036

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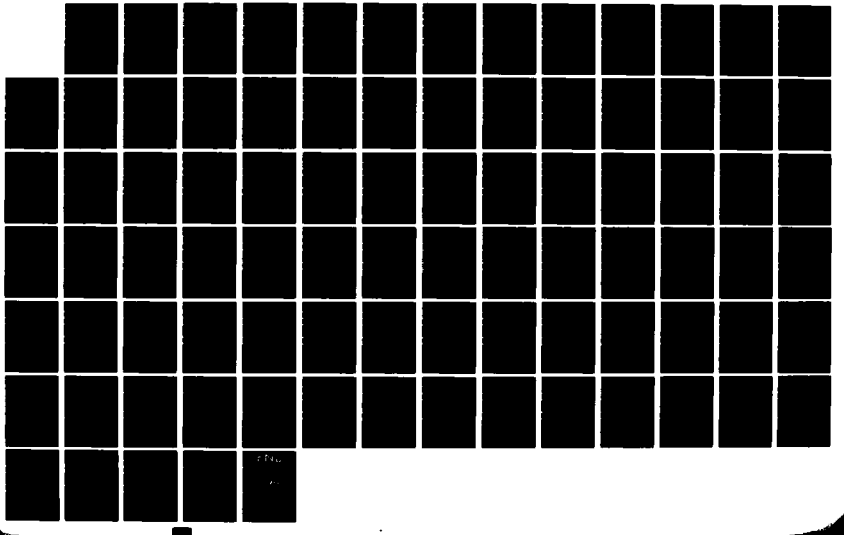

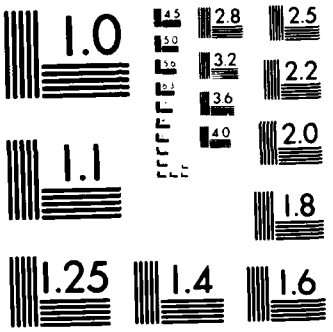

AD

Army Drug Development Program
Phase 1
Clinical Testing

Annual and Final Report

Richard C. Reba, M.D. Principal Investigator
Kevin G. Barry, M.D. Clinical Director
Leslie B. Altstatt, M.D. Associate Director

October 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrich, Frederick, Maryland 21701-5012

Contract No. DAMD17-75-C-5036

BIO-MED, Inc.
4401 Hartwick Road
College Park, Maryland 20740

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The research performed by BIO-MED, Inc., under Contract DAMD17-75-C-5036 was primarily in support of the U.S. Army Antimalarial Drug Development Program and was extended to include other drug testing appropriate to the contract. Sound scientific methodology was used for Phase I Clinical Testing and Pharmacokinetic studies of drugs. One thousand four hundred eighty nine (1,489) candidates underwent comprehensive medical evaluation for study qualification. Twenty-three experiments were performed including safety and tolerance of mefloquine administered to subjects for 52 consecutive weeks. Several Pharmacokinetic (cont'd. reverse)

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

19. cont'd.
WR 171,669; WR 229,870 (Sodium Stibogluconate); WR 6026 2HCl; SGOT; SGPT; Pyridine-methanol

20. cont'd.
studies were conducted in which the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, performed the drug assays and statistical analysis. The geographic location of BIO-MED, Inc. has permitted prompt continuing interaction between BIO-MED, staff members and the Army monitors.

AD_____

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SUMMARY

This is the final report for contract DAMD17-75-C-5036 under which BIO-MED, Inc. performed Phase I Clinical Pharmacology Studies.

When first let, the contract was a part of the Army's Antimalarial Drug Development Program. As that program was diversified to involve the development of other therapeutic agents, the subject contract was assigned a commensurately broader scope of agents to be studied.

In the period from 15 February 1975 to 18 August 1983 Bio-Med, Inc. was involved in the following activities under the terms of the contract:

1) Consultation with the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research (WRAIR) regarding drugs under development, and the anticipated requirement for Phase I Clinical Studies.

2) The development of protocols for Phase I Clinical Studies and the administrative and technical processing of these protocols including (a) appropriate scientific consultation regarding medical aspects of the studies, (b) institutional review including review of the protocol by a duly constituted Institutional Review Board, and (c) submission of the protocol(s) to the sponsoring agency for their internal review mechanisms and the incorporation of modifications indicated by such reviews.

3) The implementation of protocols which included subject recruitment, identification and medical qualification; the provision for the clinical environment for the conduct of the study including nursing, dietetic, laboratory and custodial services; the conduct of the study including the immediate medical supervision of drug administration, subject evaluation and specimen collection; the timely analysis of prescribed procedures such as ECGs, roentegenograms, etc.; and the medical follow-up of each subject and his eventual separation from the study.

4) Analysis, interpretation and reporting of the results of studies.

This report is a final compilation of the studies conducted under this research contract.

FOREWORD

Bio-Med, Inc. is a privately held medical research organization, incorporated in the District of Columbia and registered in the state of Maryland.

Contract DAMD17-75-C-5036 became effective 15 February 1975. That contract stipulated that:

"The contractor shall, for the period of this contract, and for such extensions thereof as are mutually agreed to by the parties hereto, furnish the necessary personnel, facilities, equipment and supplies to:

> Conduct Phase I Clinical Pharmacology Studies for the US Army Antimalarial Drug Development Program in accordance with the contractor's quotation...submitted in response to Request for Quotation DAMD 17-75-Q-5525."

Bio-Med, Inc commenced studies under this contract in April 1975 using clinical and office facilities at the Washington Hospital Center in Washington, D.C. The contract was extended annually until August of 1983 when a new contract was negotiated between the USAMRDC and Bio-Med, Inc. In October of 1979, the clinical and office facilities of Bio-Med, Inc. were relocated in College Park, MD. That facility has been the site of all subsequent studies under this contract.

A summary of the modus operandi of Bio-Med, Inc., including organization, scope of work, methodology, facilities and personnel, is included in the appendix.

During the reporting period, this organization has been engaged in studies of safety, tolerance and pharmacokinetics of drugs developed by or of interest to the Army Drug Development Program.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

TABLE OF CONTENTS

FINAL REPORT: DAMD17-75-C-5036

DAMD17-75-C-5036 was awarded to BIO-MED, Inc. to facilitate Phase I Clinical Testing of antimalarial drugs including pharmacokinetics, safety and tolerance. The BIO-MED mission was expanded during the contract years to include other agents of interest to the Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR). Development of methods for various drug assays in biologic fluids by WRAIR permitted increasing emphasis on pharmacokinetic studies during the later interval of the contract. BIO-MED's final reports for pharmacokinetic experiments are limited to the clinical methods and observations and do not include drug assay values.

Summaries and abstracts of studies performed under this contract are presented in numeric sequence in the appendix. The final report of Experiment #1 is included as an example of work performed and reported by BIO-MED, Inc. The report demonstrates many complexities including the presentation and solutions of problems arising during the course of the 52 week study.

WORK COMPLETED

The following studies have been designed, conducted and reported under this contract:

STUDY TITLE	PERIOD OF STUDY	NUMBER OF SUBJECTS	REPORT SUBMITTED
Experiment #1 WR 142,490 Chronic Safety and Tolerance	9/3/75- 5/7/76	50	24 June 82
Experiment #2 WR 184,806 H_3PO_4 Short-term, Safety and Tolerance			
A) Single Rising Dose Levels	4/28/75-7/28/75	40	Feb. 1976
B) Multiple Dose Levels	7/29/75-10/30/75	32	Mar. 1976
Experiment #3 WR 142,490 Short-term Safety and Tolerance, Single Dose Levels	2/2/76- 2/9/76	4	July 1976
Experiment #3, Addendum WR 142,490 HCl Short-term Safety and Tolerance, Clinical Evaluation of Two Formulations	5/10/76- 6/15/76	9	28 Aug. 76
Experiment #3, Addendum #2 WR 142,490 HCl Short-term Safety and Tolerance, Clinical Evaluation of Two Formulations	2/26/79- 7/16/79	9	15 April 80
Experiment #4 WR 142,490 HCl Safety and Tolerance Repetitive Curative Dose Levels	12/8/75- 2/2/76	12	28 Aug. 76
Experiment #5 WR 142,490 CH_3SO_3H Mefloquine Methanesulfonate? Safety, Tolerance and Pharmacokinetics of Intravenous Administration	1/10/77- 2/8/77	8	31 Oct. 77
Experiment #6 WR 184,806 H_3PO_4 Pharmacokinetics Following Oral Administration	6/21/76- 9/7/76	20	26 May 77
Experiment #7 WR 180,409 H_3PO_4 Short-term Dosage, Safety and Tolerance	9/20/76- 12/27/76	44	Feb. 77
Experiment #8 Comparative Bioavailability and Pharmacokinetics of WR 30090 HCl and WR 30090 (Oleic acid)	7/19/76- 8/23/76	4	24 Aug. 77

STUDY TITLE	PERIOD OF STUDY	NUMBER OF SUBJECTS	REPORT SUBMITTED
Experiment #9 Mefloquine (WR 142,490 HCl): Pharmacokinetics Following Oral Administration	3/28/77-12/12/77	21	9 May 78
Experiment #10 Comparative Bioavailability and Pharmacokinetics of WR 142,490 HCl (Mefloquine Hydrochloride) and Mefloquine Hydrochloride HLR	1/30/78-4/10/78	13	9 Jan. 79
Experiment #11 WR 149,024 Short-term Dosage, Safety and Tolerance	3/6/78-2/22/79	25	16 May 79
Experiment #12 WR 194,965 H_3PO_4: Short-term Dosage, Safety and Tolerance, Single Oral Dose, Rising Dose Levels	8/1/77-1/3/78	48	24 April 78
Experiment #13 WR 172,435 CH_3SO_3H: Short-term Dosage, Safety and Tolerance, Single Oral Dose, Rising Dose Levels	5/1/78-7/24/78	6	6 Dec. 78
Experiment #13, Addendum WR 172,435 CH_3SO_3H: Short-term Dosage, Safety and Tolerance: Effect on the Total and Differential Leukocyte Counts Following a Single Oral Dose	10/15/79-11/12/79	12	15 April 80
Experiment #13, Addendum #2 WR 172,435 CH_3SO_3: Short-term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels	10/6/80-10/20/80 5/10/82-7/5/82	32	19 Jan. 83
Experiment #14 Pharmacokinetics of WR 180,409 H_3PO_4 (a Pyridine-methanol) Following Oral Administration			
A) Part I, Pilot Study	6/11/79-7/9/79	4	
B) Part II, Comparative Bioavailability	8/20/79-10/22/79	12	2 Feb. 81
Experiment #15 Continuation of Single Dose, Rising Dose Level Studies with Orally Administered WR 171,669: Short-term Safety and Tolerance, Preliminary Pharmacokinetics	3/31/80-8/19/80	28	3 Feb. 81

STUDY TITLE	PERIOD OF STUDY	NUMBER OF SUBJECTS	REPORT SUBMITTED
Experiment #16 WR 229,870 (Sodium Stibogluconate Injection BP) Pharmacokinetics Following a Single Intravenous Dose	4/28/80- 5/27/80	8	4 Sept. 80
Experiment #17 WR 180,409 H_2PO_4: Short-term Multiple Doses, Safety, Tolerance and Pharmacokinetics	3/2/81- 5/26/81	32	16 Aug. 82
Experiment #18 WR 194,965 H_2PO_4: Short-term Safety and Tolerance to Three Divided Doses, Rising Dose Levels	6/8/81- 5/10/82	44	17 Jan. 83
Experiment #21 WR 6026 2HCl: Short-term Dosage, Safety and Tolerance Study: Single Oral Dose, Rising Dose Levels	1/10/83- 5/31/83	44	under review
Experiment #22 The Effect of Low and High Calorie Diets Upon the SGOT and SGPT of Normal Human Subjects	9/20/82-11/29/82 5/23/83-8/8/83	27 19	

With the exception of Experiment #22 which may require further investigation, final reports of each of the above studies have been submitted as stipulated by the contract. The interested reader is referred to the respective reports for technical details of the work cited. Abstracts and summaries of these reports appear in the appendix.

APPENDIX

1. BIO-MED, Inc. Modus Operandi

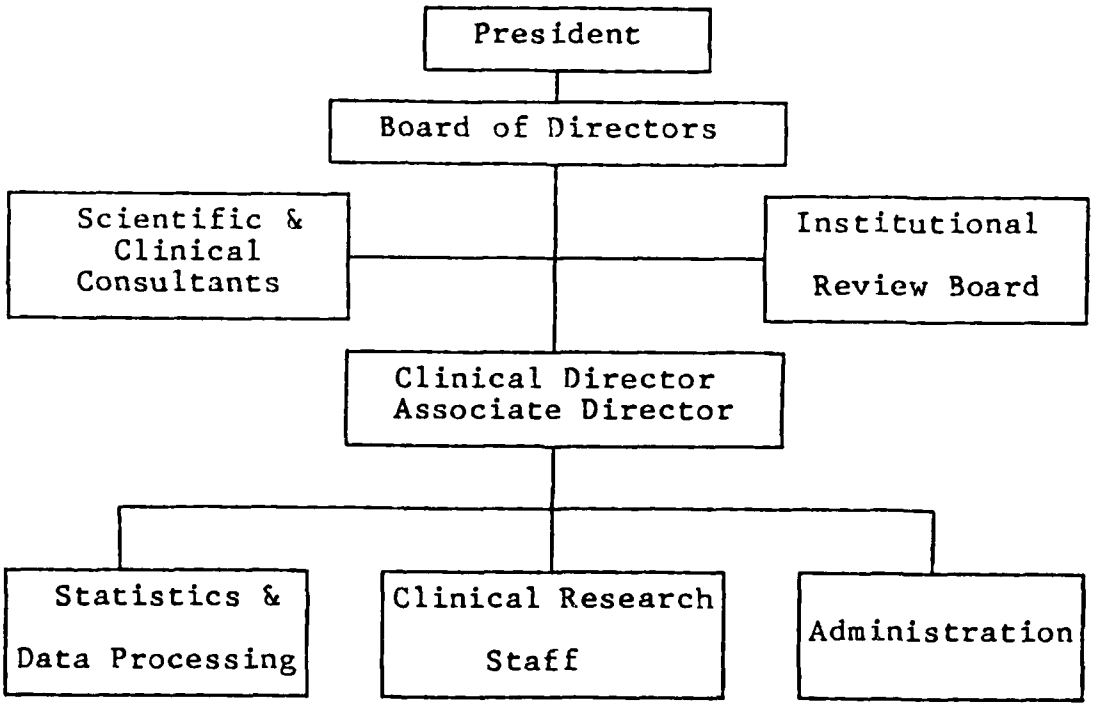
2. Final Report: Experiment #1, WR 142,490 Chronic Safety and Tolerance

3. Study Summaries and Abstracts

BIO - MED, Inc.

4401 Hartwick Road · College Park Maryland 20740 · Telephone: (202) 882-0977

Below is the organizational chart for BIO-MED, Inc.



I. Introduction

The administration of a new drug to humans is one of the most critical events in drug development. Use of human subjects for research purposes raises ethical issues.

The decision to carry the experimental work into humans rests in part upon a number of assumptions:

1) that pre-clinical studies can produce useful inferences about the risk/benefit ratio of the drug in man;

2) that risks to subjects are minimal and that an average person can understand the study adequately and render a free and informed consent to participate;

3) that information gained by administering the drug to normal subjects is essential for further development of the drug.

There have been some sincere differences of opinion regarding the scientific and ethical features associated with each of these assumptions. It is important that these discussions continue. Nevertheless, these assumptions are the basis for continuing evaluation of safety, tolerance and pharmacokinetics of drugs in man, or what have been termed "Phase I Clinical Studies".

BIO-MED, Inc. has been designing, performing and interpreting the results of Phase I Clinical Studies since 1974 when this organization was formed. BIO-MED, Inc. has found that with critical and cautious application, the above assumptions are useful.

The following narrative is presented to indicate the means by which Phase I Clinical Studies of new drugs are conceived and conducted by BIO-MED, Inc. In all matters the scientific requirements of the sponsoring agency, the regulatory requirements of the federal, state and local governments, and the interests of the subject participants are coordinated to meet the overall objectives of each research protocol.

II. Scope of Work

Phase I Clinical Studies involve the administration of drugs to human subjects for the determination of safety, tolerance and pharmacokinetics. The scope of work covers all aspects of the design, implementation and interpretation of the clinical studies that precede studies of efficacy in humans. Included are:

1. the review and interpretation of preclinical work leading to the contemplated work in humans. Knowledge of the principles and practices of preclinical studies is needed by the clinical investigator who would test the drug in man.

2. the design of clinical studies. Early safety and tolerance studies typically are a two by two rising dose, double-blind design, where the dose will be carried to intolerance or to a pre-designated level. Studies such as these depend principally upon an appreciation of the limitations of experimental design in clinical settings and upon having well-defined and appropriately sensitive criteria for detecting intolerance. Studies of the Maximum Tolerated Dose may require crossover designs or repetitions of the dose in multiple groups. Here, ideal designs in terms of mathematical elegance and efficiency must be carefully weighed against what is achievable in the study population. Pharmacokinetic studies will test the mathematical model under consideration. Such studies require close coordination between the kineticist and the clinical investigator.

3. the implementation of clinical studies. Steps in the conduct of clinical studies are detailed in the section "Methodology".

4. the analysis and interpretation of data. Phase I studies require a variety of statistical procedures that range from simple parametric tests to complex mathematical computer programs.

BIO-MED, Inc. has extensive experience with the design, conduct and analysis of Phase I Clinical Studies.

The most challenging and consequential aspect of the scope of work is the requirement for using humans as experimental subjects. Subjects in Phase I Clinical Studies clearly meet the definition of "subjects at risk" and virtually all drugs to be studied under this contract are to be used under a "Notice of Claimed Investigational Exemption for a New Drug (IND)". As is the case with current Army contract Phase I studies, BIO-MED, Inc. continues to take responsibility for safeguarding the rights and welfare of subjects placed at risk. BIO-MED, Inc. has filed with the United States Army Medical Research and Development Command (USAMRDC) a written assurance that it will abide by the policy for the protection of Human Subjects as contained in Title 45, Part 46 of the Code of Federal Regulations, as amended. This assurance, which also requires compliance with AR 70-25, "The Use of Human Subjects in Research", has been accepted by the USAMRDC. Investigational drugs are used at BIO-MED, Inc. in compliance with Title 21, Part 312 of the CFR. Before implementation, all studies must be approved by the Institutional Review Board of this organization and by the Human Use Review Office of HQS, USAMRDC.

III. Methodology

The following represents the methods and practices by which Phase I Clinical Studies are planned and conducted at BIO-MED, Inc.

The sponsor advises us of a requirement for a Phase I Clinical Study of a drug under development. Representatives of BIO-MED, Inc. meet with the sponsor to review information that has led to the proposed study. Preclinical and any existing clinical data are evaluated.

BIO-MED, Inc. prepares a clinical research protocol designed to meet the requirements of the sponsor. After discussion, a mutually acceptable final version of the protocol is prepared. The protocol is then submitted to the Institutional Review Board (IRB) of BIO-MED, Inc. This IRB reviews the protocol.

If approved by the IRB, the protocol is referred on to the sponsor where it is processed by the regulatory bodies of the agency. No studies are conducted at BIO-MED, Inc. without the approval of the FDA.

When a protocol has been processed as described, it is scheduled for implementation at BIO-MED, Inc. Equipment, facilities and supplies are readied to meet the requirements of the study. Subject employee applicants are solicited through the classified pages of metropolitan newspapers.

Applicants respond by telephone and undergo initial screening. Applicants are then scheduled for medical evaluation at the clinical facility. There, they are informed of the nature and scope of the research planned as a part of a group discussion. Applicants are then interviewed individually; if the investigator is satisfied that the applicant fully understands the risks and benefits to the subjects in the study, and that the individual has no discernible disqualifying characteristics, the applicant is allowed to sign the informed consent document (see Appendix, p. VII-A-4).

Each applicant then has a comprehensive medical evaluation. The evaluation consists of a medical history, a complete physical examination, hematologic and biochemical tests with urinalysis, an ECG and a roentgenogram of the chest. Applicants must meet acceptability criteria described in the protocol.

Qualified applicants (including alternates) are admitted to the clinical facility, the medical evaluation is repeated, and final selection of subjects is made. On the first day of dosing, subjects sign a "reaffirmation of consent" and are given the test substance as prescribed by the protocol. Subjects remain in the facility under observation as prescribed and are released after medical evaluation. The length of follow-up period is defined by each protocol, but always continues until any abnormalities noted return to normal or until a satisfactory medical disposition is made. Subjects are instructed to return at any time that they feel a problem has developed as a result of their study participation.

An individual record is maintained for each subject. The record consists of signed consent forms, the subjects medical history, qualifying and protocol examinations, certificates of drug administration, nurses' notes, EGG's, laboratory results and follow-up letters. This record is retained permanently at BIO-MED, Inc. Laboratory data are also entered into a master log and into the sponsor's computer-operated data file. All requisitions and dispositions of experimental drugs are recorded.

IV. Facilities

BIO-MED, Inc. occupies a modern, fireproof, steel and concrete structure adjacent to the University of Maryland in College Park. The Clinical Facility uses 4500 square feet of the ground floor of that building. Of the floor space, most is committed to subject housing. In the present configuration, nine beds are set aside for dormitory-like facilities for the subjects, and four beds are set aside in a separate area for acute studies and continous physiological monitoring. The facility can be reconfigured to accomodate sixteen to twenty subjects simultaneously.

BIO-MED, Inc. is equipped, staffed and trained to deal with medical emergencies. A portable cardiac defibrillator is available. Subjects in emergent need would have their immediate problems attended to and would then be transported by ambulance to nearby Doctor's Hospital of Prince George's County which is ten minutes away by emergency vehicle. There is a peramedical and rescue station three blocks away from the clinical facility in College Park.

The laboratory has facilities for bloodletting, urinalysis, specimen processing and a walk-in freezer for storage. BIO-MED, Inc. has contracted with National Health Laboratories, Inc. of Vienna, Virginia to perform all routine hematologic and biochemical tests. Urinalysis is performed in the clinical facililty. A microscope, UV light for phototoxicity studies and both a table-top and a floor model refrigerated centrifuge are included. The adjoining physician's examining room is fully equipped.

The laboratory and physician's examining room open onto the intensive observation area which contains four hospital beds and a four channel cardiac monitor with telemetry option.

Subject records are maintained in locked cabinets in the nursing station. Other facilities include a complete kitchen, a dining area and a subject lounge.

The adminstrative office houses a MICOM 2000 word processor which has been used for the generation of most documents. In the Director's office is a TRS 80 Model III Micro-Computer System including hard disc drive, printer, graphics modification and telecommunications equipment. This system provides local ADP support and interfaces with any system with comparable equipment. All clinical data can be stored in this system and can also be entered directly into any other system with telecommunications capability. There is also a Tektronics 4051 graphics computer with two disk drives, a hard copier and a printer which is capable of providing rapid, sophisiticated statistical support.

V. Past Performace

Since its formation in 1974, BIO-MED, Inc. has continually performed Phase I Clinical Studies under the supervision of the same Clinical Director, Kevin G. Barry, M.D. The original Principal Investigator, Richard C. Reba, M.D., remains with the program. Since 1979, Leslie B. Altstatt, M.D., has served as Associate Clinical Director and full-time attending physician at BIO-MED, Inc. Curricula vitae for each of these individuals have been previously submitted. It should be noted that among them, they have over eighty years of teaching, research and patient care experience, with a special empasis on Phase I Clinical Studies in the past seven years.

Since 1974, BIO-MED. Inc. has conducted Phase I Clinical Studies involving the participation of volunteer subjects for periods varying from one week to one year. These studies include: 1) chronic studies of drug effect for one year; 2) acute studies of oral tolerance; 3) acute studies of tolerance and pharmacokinetics with drugs administered intravenously and drugs given intramuscularly; and 4) crossover studies comparing formulations and routes of administration. All protocols were prepared by BIO-MED, Inc. with the advice and assistance of the sponsor's scientific representatives.

BIO-MED, Inc. has had two contracts with the government:

DAMD 17-75-C-5036, "Army Drug Development Program: Phase I Clinical Testing". Term: 15 February 1975 - 18 August 1983. Project Officer: Richard C. Reba, M.D.

DAMD 17-81-C-1139, "Safety, Tolerance and Biovailability of the Ayerst formulations of 2-PAM chloride, Studies I and II". Term: 17 August 1981 - 16 May 1982. Project Officer: Richard C. Reba, M.D.

BIO-MED, Inc. has conducted medical evaluations of over 1200 applicants and has used representative samples of that data to establish its ranges of normal values. Some of these data are from "placebo-volunteers" collected over a period of one year and provide a dynamic view of variations in laboratory values within normal subjects over time.

We believe that it is a measure of the care with which protocols were developed and executed that no serious adverse reactions occured in subjects in any of the studies conducted and there is no evidence that any subject experienced lasting harm from study participation. Many candidates are referred by word of mouth attesting to our favorable reputation among young men in this area.

BIO-MED, Inc. has been most fortunate in the membership of its Institutional Review Board. All members of this board have continually served without compensation since BIO-MED, Inc. was moved to College Park in 1979. The board members include 1) a practicing physician from this area, 2) the Chief of Economic Botany from the Department of Agriculture in nearby Beltsville, Maryland, 3) a graduate student in the Department of Chemistry at the University of Maryland, 4) the executive secretary of the Medical Society of Prince George's County and 5) a lawyer who formerly served with the Food and Drug Administraction. The composition, function and organization of this board have been reviewed and approved by the FDA in connection with their overall evaluation of this facility in 1980.

VI. Personnel

Principal Investigator: Richard C. Reba, M.D. served as Principal Investigator for most studies. There was an interim during which John A. Johnson, M.D. served as Principal Investigator. Dr. Reba is Board Certified in Internal Medicine and Nuclear Medicine andd licensed for the handling of radioisotopes. In the past nine years, he has been Prinicipal Investigator on at least fifteen different Phase I Clinical Studies. As Principal Investigator, he has been directly responsible for the scientific validity of protocols,for the ethical and competent execution of such protocols and for the prompt and accurate reporting of studies accomplished.

Clinical Unit Director: Kevin G. Barry, M.D. served as Clinical Unit Director. Dr. Barry, a highly experienced Internist and Nephrologist, has held corporate responsibility for all work done at BIO-MED, Inc. since the formation of the organization. He ascertained that all activities were consistent with company policy, good medical practice and applicable local, state and federal regulations. Because of his extensive clinical experience and expertise, he advised on all medical matters related to the qualification of subjects, including the need for obtaining specialized opinion. He attended all drug administrations that required the use of the intensive observation unit. He had final approval authority for all documents and reports emanating from the facility.

Associate Clinical Director: Leslie B. Altstatt, M.D. served as Associate Clinical Director. He is a board certified Pediatrician with extensive experience in hematology, tropical medicine and clinical research. He has spent the past four years exclusively in the design, implementation and interpretation of Phase I Clinical Studies. In addition to his participation in the research and design of studies conducted, he was responsible for the minute to minute conduct of the studies including interview and medical qualification of subject candidates, drug administration and proper medical supervision of subjects while they were in the clinical facility and during the follow-up periods. These responsiblities extended to 24 hours of each day, 7 days a week.

Nurses: Four nurses were employed at any one time: a charge nurse and three staff nurses. BIO-MED, Inc. has always been distinguished by its stable and superior nursing staff. All nurses are registered and licensed in the State of Maryland. Each staff nurse has extensive experience with BIO-MED, Inc. The charge nurse is a person of outstanding achievement in her field. A full-time cook and housekeeper also worked under the supervision of the charge nurse.

Information processor: One individual was responsible for the collection, formatting, storage and retrieval of data collected during the preparation and execution of studies. This individual operated the electronic data processing systems described above. The individual devoted 100% of his time to the projects.

Bookkeeper: The services of an individual capable of maintaining financial records were required. This individual managed financial records for all employees, including the subjects (who were temporary employees).

Secretary: Services of a part-time secretary were required for report preparation.

Administrator: Gisela R. Barry has been the administrator since 1974. Services of a part-time administrator were required to coordinate fiscal policy and procedures. The administrator met on a regular basis with the Associate Clinical Director to assure smooth, efficient operation of the Clinical F
The administrator closely supervised the support staff. The administrator signed all contracts and voucher submissions. The administrator maintained correspondence with the Contracting Officer and the Contracting Officer's Representative.

BIO - MED, Inc.

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ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 1

FINAL REPORT

TITLE: WR 142,490
CHRONIC SAFETY AND TOLERANCE

BIO - MED, Inc.

4401 HARTWICK ROAD · COLLEGE PARK MARYLAND 20740 · TELEPHONE: (202) 882-0977

ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 1

FINAL REPORT

TITLE:	WR 142,490 CHRONIC SAFETY AND TOLERANCE
CLINICAL DIRECTOR:	KEVIN G. BARRY, M.D.
PRINCIPAL INVESTIGATOR:	RICHARD C. REBA, M.D.
ASSISTANT TO THE DIRECTOR:	PAMELA G. GUHA, M.D.
CONSULTING AND ORGANIZATIONAL REVIEW COMMITTEE MEMBERS:	JAMES A. CURTIN, M.D. STUART H. DANOVITCH, M.D. HOWARD BERNSTEIN, M.D. MERVYN ELGART, M.D.

Abstract:

A clinical trial was carried out to assess the safety and tolerance of the antimalarial drug WR 142,490. With the protocol (inclosure 2) approved by the appropriate review boards, free-standing male subjects between the ages of 21 and 45 years who were in good health as demonstrated by normal blood chemistries, complete blood counts, urinalysis, electrocardiogram, chest x-ray, medical history and clinical evaluation including a physical examination were recruited from the Washington, D.C. Metropolitan area through classified advertising in local papers.

Subjects were enrolled and started in the study in 5 groups, 10 subjects to each group. By lottery, subjects were assigned to drug or placebo treatment groups. At final enrollment, 23 subjects were assigned to the drug group and 25 to the placebo group. Subjects returned weekly for evaluation over a period of 52 weeks. The test substance was given weekly and periodic clinical evaluations were performed. Eighteen subjects in each group completed the study. Treatment was discontinued in two subjects receiving drug because of the possibility of hair loss due to medication. The remaining five subjects receiving drug withdrew for a variety of reasons, none related to drug effect. Review of records at the end of the study when treatment codes were broken showed identical study days of participation for each group. No consistent nor significant differences between drug and placebo groups were identified by routine clinical observation (weekly interviews, BP, weight), laboratory tests (including urinalyses), physical exam and ophthalmic evaluations. There is an unlikely possibility that two subjects had accelerated loss of hair from the head as a result of drug administration.

This study showed WR 142,490 to be well tolerated and safe over a one year period of administration of 500 mg weekly.

Laboratory Data for Subject ____ are compiled and displayed in the following pages. Discreet laboratory values were entered by keyboard into a data file specifically created for this study on a Tektronics Model 4051 Graphics Computer. Data sets for each laboratory test for each subject were printed out in tabular form (following two pages) and these data were visually checked for accuracy against the Master log of data. Verified/corrected data were then displayed as serial points against a background of a mean plus or minus two standard deviations. These displays follow the tabulated data.

TITLE:

WR 142,490 CHRONIC SAFETY AND TOLERANCE

PURPOSE:

To determine tolerance and safety of the anti-malarial drug WR 142,490 in normal human subjects during administration for 52 weeks.

RATIONALE:

Malaria remains a leading cause of death among the world population. During the Vietnam conflict, malaria casualties exceeded the number of battle casualties. Therefore, the search for an effective prophylactic therapy maintains a high priority in the field of research. Only chloroquine/primaquine has been approved for suppression of falciparum malaria. Chloraquine/primaquine is not totally effective in the suppression of falciparum malaria and its use is limited by clinical intolerance. Consequently, an urgent need exists for an effective malaria suppressant.

WR 142,490 is an investigational quinoline methanol which has undergone trials in human subjects. The initial trial showed that all 10 subjects who received 250 mg of WR 142,490 weekly for 8 weeks were protected when exposed to mosquitoes who were heavily infected with multi-drug resistant P. falciparum. The possibility that WR 142,490 is effective in the prevention and treatment of falciparum malaria warrants investigation of its tolerance and safety when administered to normal human subjects for 52 weeks as for suppressive therapy.

Subject Selection:

The study was performed at the Washington Hospital Center. The subjects were males between 21 and 43 years of age.

Approximately 100 applicants were screened to secure the subjects needed. Applicants had a complete medical history, physical examination and urinalysis. Applicants passing the initial screening had a final clinical laboratory screening which included PA chest x-ray, electrocardiogram, triglycerides, cholesterol, glucose, BUN, creatinine, uric acid, sodium, potassium, chloride, CO_2, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, direct bilirubin, total protein, albumin, globulin, A/G ratio, calcium, phosphorous, white cell count and differential, red cell count and morphology, hematocrit, hemoglobin, MCV, MCH, MCHC, platelets and G6PD.

Fifty subjects meeting qualifications of the study were identified. Within five blocks of ten subjects per block, subjects were sequentially assigned to drug or placebo treatment groups by lottery. The codes identifying drug and placebo were sealed and the contents remained unknown to the subjects and the investigators with the few specific exceptions noted below in "Results".

In the fifth block of ten subjects two subjects withdrew before the first dose was given. Both of these subjects had been assigned to the drug group. Thus at the conclusion of the study, the drug group had only 23 subjects while the placebo group had 25 subjects.

Accepted subjects received an in-depth explanation of the study and all questions were answered fully and clearly prior to the subject granting written informed consent. Each subject was hired as a temporary employee during his participation in the study. Any subject was able to withdraw from the study at any time. Each subject was assigned a study number and was provided with a wallet card indicating he was receiving an investigational drug with the telephone number to be called for emergency complications.

METHODS:

1. Twenty-three subjects were assigned to the group receiving 500 mg of the test drug and 25 were assigned to the placebo group. Doses were to be given weekly for 52 consecutive weeks.

2. Assignment to treatment groups (drug or placebo) was random through lottery with the code sealed and available only for emergencies to the investigator and his staff.

3. The coded capsule was ingested weekly by each subject in the presence of a member of the investigating team. The subject signed the signature identification log at the time of capsule ingestion.

4. Non-directed interviews, physical and laboratory examinations were performed according to the attached schematic.

5. Emergencies: Arrangements were made to notify the Army Clinical Monitor and the Washington Hospital Center authorities immediately by telecom and by written communication if medical emergencies occurred.

SPECIMEN MANAGEMENT:

Each blood sample consisted of 37 ml of venous blood. Each sample was centrifuged, the serum obtained was divided into 2 aliquots. Aliquot number 1 was coded with the appropriate subject code and sent for analysis the day the specimen was obtained. Aliquot number 2 was coded appropriately and stored in the freezer for later determinations of drug concentrations. The lysed red cells were also stored in the freezer for the same purpose.

The urine specimens obtained were analyzed immediately. If any abnormalities were found the subject was recalled prior to further drug administration.

LABORATORY DATA:

All laboratory data were recorded weekly by test via subject identification code. Any deviation from normal was immediately brought to the attention of the investigator and the monitor from Army Research Command. All laboratory determinations were performed in duplicate on consecutive days and repeat specimens were obtained and evaluated as appropriate prior to further drug administration.

RECORDING:

Individual worksheets were maintained for each subject recording BP and pulse, weight, laboratory results, subjective

symptoms, physical examination and laboratory specimen codes. A cumulative master log was also kept which included laboratory data and the results of a non-directed symptomatology check. This provided for ongoing availability at all times to the Research Committee, Washington Hospital Center, and the Army Research and Development Command.

RESULTS:

Forty-eight subjects were enrolled in the study. The study was commenced on September 16, 1975 and completed April 27, 1977.

Subject compliance is depicted in Figure 1. Thirty-six subjects completed 52 weeks of the study. Twelve withdrew at various intervals. The times and reasons for their resignations are shown in Table II.

Of the thirty-six subjects completing the study, 18 received drug and 18 the placebo. The group that received drug had a total of 6566 subject days; the group that received placebo had 6566 subject days.

The elements of subject participation are outlined in Table I, "Schedule of Procedures".

In Table III, times and reasons for the withholding of medication are listed.

Weekly Visits: Subjects returned for evaluations weekly, with the exceptions shown in figure 1. A checklist was prepared for each subject which outlined the elements of subject participation for each of the 52 weeks.

A summary of each subject's compliance with the dosing schedule alone shows the doses of medication given week by week, and gives the reason for doses missed. These summaries are also in the Appendix.

A summary of the scheduled physical examinations, including temperature, blood pressure and weight, is also included in the Appendix.

Laboratory Results: The complete panel of laboratory examinations* was performed on each returning subject on weeks 1 through 8, and weeks 10, 12, 14, 16, 19, 23, 27, 31, 35, 39, 43, 47, 51 and 52.

The discreet values for each laboratory test for each subject were compiled. These are displayed in tabular form by subject number in the Appendix.

* Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alka. Phos., SGOT, SGPT, LDH, T. Bilirubin, CBC, differential and indices, Platelets, Urinalysis.

The discreet values for each laboratory test for each subject are also displayed serially against a background depicting the mean and the normal* range for this study. These displays are in the Appendix by subject number.

The laboratory results were reviewed as they were reported. On several occasions, the results led to omission of specific doses of drugs, (Table II), and in one instance led to the subject being dropped from the study because of constitutional hyperbilirubinemia (Table III).

All data displays were reviewed for trends. In no subject did laboratory abnormalities consistently increase in frequency with increased subject time in the study.

The occurrence of abnormalities in each laboratory test were summarized for the drug and placebo groups. Those findings are displayed in Table IV. The data for each laboratory test were fitted to a 2 x 2 contingency table and Fisher's exact probability for each data set was calculated and displayed in the table.

The frequencies of urinary abnormalities are displayed in Table V.

Physical Examinations:

Subjects were scheduled for physical examinations during the qualification period and at weeks 8, 20, 32, 40 and 52.

The details of these physical evaluations are recorded in the appendix. Temperature, pulse, blood pressure, height and weight at each examination are shown. Only those physical abnormalities thought to be related to study participation were transcribed to these summary pages.

Complete physical evaluations revealed no abnormalities which could be related to receiving the drug or to study participation.

Electrocardiograms: Rhythm strips were obtained and evaluated on the occasion of each physical examination. A 12-lead electrocardiogram was obtained at the end of the study. No significant change in electrocardiograms were noted.

Eye Examinations: Eye examinations of each subject were conducted during the weeks 13, 26, 41 and 52.

The examination included best corrected visual acuity, external and slit lamp examination, evaluation of media and

* Normal ranges based on laboratory data from 100 Normal Subjects.

fundi, visual fields and retinal threshold. Fundus photography was performed prior to study day one and at the conclusion of the study.

No significant abnormalities were detected in the eye examinations.

DEPARTURES FROM PROTOCOL:

Dermatologic Problems: After about six months of participation in the study, one subject complained of loss of hair from the head.

The subject was referred to a dermatologist who made the diagnosis of "telogen effluvium" (excessive loss of normal hair from normal follicles) possibly associated with the taking of the anti-malarial drug.

The code was broken, and the subject was taking the drug. The drug was discontinued for this subject. (Table II)

The forty-one subjects then participating in the study had dermatologic evaluation. One other subject was found to have telogen effluvium. That subject was also receiving the drug, which was discontinued for that subject(Table II). All other subjects were found to be normal.

Results of the scalp examinations are summarized in Table V.

Each subject who completed the study had a final dermatologic evaluation.

No significant abnormalities were detected.

Reproductive and Toxicity Studies in Male Rats Receiving WR 142,490: While this study was in progress, the sponsoring agency received a report of a toxicity study implicating Mefloquine as a cause of "a decrease in reproductive performance" and "moderate degenerative changes" in the epididymis in rats.

The information regarding the toxicity studies and the actions taken are summarized in the communication "To: All Subjects Participating in Experiment No. 1: WR 142,490 Chronic Safety and Tolerance". (Inclosure 1)

That communication informed the subjects of the findings and their evaluation. Subjects were offered the opportunity to have sperm counts performed if they so desired.

No subject withdrew from the study as a result of this new information being made available.

Discussion:

The design of this study rested on the assumption that clinically important side effects from the chronic ingestion of WR 142,490 would be detected in a double-blind study of 48 subjects followed over a period of 52 weeks. The sensitivity to the detection of drug effect was optimized by weekly interviews, frequent blood and urine tests and periodic physical examinations. The double-blind design of the study provided for the specificity in identifying real drug effect. It was assumed that a study of such sensitivity and specificity following 48 subjects over 52 weeks would have sufficient power to meet the requirements of a Phase I Clinical Study.

There is adequate precedent to support the above assumptions.

Compliance was excellent for a one year study, and was equivalent in drug and placebo groups.

Forty-eight subjects were enrolled in the study. Assignment to study groups was random, by lottery. Twenty-three were assigned to the Drug group, twenty-five to the Placebo group.

Subject resignations (P=7, D=5) resulted in groups of equal sizes completing the study (P=18, D=18) and, remarkably, identical subject days of participation for each group (6566 subject days).

However, compliance in terms of medication administered was less in the drug group.

	Drug	Placebo
Doses Received	1107	1278
Doses Missed	89	22

The non-compliance in the drug group was largely due to the elective discontinuance of subjects 5, 15 and 32 from receiving drug (= total of 79 missed doses) because of alopecia (5, 15) and constitutional hyperbilirubinemia (32). Subjects 5 and 15 were followed for the full 52 weeks and their cumulated data were included in the final analysis. These decisions regarding subject disposition and data did not affect the outcome of the study.

Aside from possibly accelerated hair-loss in two subjects (see below) all abnormal physical findings were attributable to pre-existing normal variations or to temporary intercurrent illness or injury.

No eye abnormalities attributable to drug were identified in a very thorough program of evaluation by the consulting ophthalmologist.

The differences in the frequency of abnormalities in blood glucose and BUN were significantly greater in the placebo group; the frequency of serum potassium and serum albumin abnormalities were significantly greater in the drug treatment group. These differences are judged to reflect no underlying physiological process; they are "statistically significant", but not important.

The scheduled examinations and observations showed no consistent differences between the drug and placebo groups. The absence of persistent symptoms or physical findings in either group attests to the continuous good health of both groups.

In concluding that drug administration produced no discernible effect, the risk of a Type I error is not considered since the null hypothesis of "no difference" is retained. The risk of a Type II error is the risk that the cited clinical observations over one year could not detect a real difference. That risk is not quantifiable and must therefore be a matter of clinical judgement. In our judgement, it is highly unlikely that significant effects could be missed.

There is finally the possibility that the chronic administration of WR 142,490 produces hair loss in males. In support of that possibility, Telogen Effluvium was diagnosed in 2 of 23 males receiving drug. However, the placebo group had no cases of Telogen Effluvium and thus no valid comparison between the rates in the two groups can be made.

CONCLUSION:

We conclude that healthy males can ingest 500 mg of WR 142,490 at weekly intervals for 52 weeks safely and without significant symptomatology.

TABLE I

"SCHEDULE OF PROCEDURES"

STUDY WEEK(S)	ACTIVITY
-4 to 0	Subject Qualification
1 thru 52	Weekly Visit (Interview, Dosing, Weight, Blood Pressure)
1,2,3,4,5,6,7,8, 10,12,14,16,19,23, 27,31,35,39,43,47, 51,52	Laboratory tests
13,26,41,52	Eye Examination
8,20,32,40,52	Physical Examination

TABLE II

SUBJECT WITHDRAWAL: TIMES AND REASONS

SCN	D/P	WEEK OF FINAL VISIT	REASON
1	D	25	Found full-time work
7	D	9	Unknown
14	P	41	Moved to California
19	P	44	Moved out of town
23	P	16	Moved to Texas
29	P	35	Job transfer
32	D	8	Elevated bilirubin
33	D	28	Personal reasons
35	D	9	Family illness out of town
38	P	33	Attending school out of town
39	P	15	Moved out of town
49	P	16	Unknown

TABLE III

DOSES WITHHELD DUE TO MEDICAL CONDITIONS

SCN	D/P	WEEK(S) WITHHELD	REASON
2	P	28	On medication for abscessed tooth
4	P	16	2-day history of non-specific gastroenteritis
5	D	36-52	Hair loss. Elevated WBC and Platelets.
6	D	22	Ill with flu.
8	P	19	Cold
9	D	28,29,32,40	Allergic reaction to fish(40); LDH elevated(28); Enzymes elevated(29 and 32).
12	P	11	URI
15	D	30-52	Hair loss (Alopecia).
17	P	3,9-11,48-52	Elevated SGPT
18	P	4,5	Taking erythromycin for sore throat
19	P	28	Complained of diminished and clouded distant vision
25	D	52	SGOT, Alkaline phosphatase, triglycerides, NA, Cl - elevated
28	P	52	Back injury - did not keep appointment
26	P	2	Broken nose in rugby - did not come in
29	P	20	On penicillin for cycle accident
30	D	48	Elevated SGPT, Albumin
32	D	9-52	Dropped from study - elevated bilirubin
36	P	4	On tetracycline
38	P	5	Cold, slight fever (99^6), aching
41	P	43,47-52	(43)stomach illness, vomiting, (47-52)scalp exam abnormal.
42	D	45	Possible Alopecia.
43	D	44	On medication for asthma attack one day prior.
45	P	29-31,52	(29-31)Appendectomy, (52) Abnormal labs (BUN 22, Uric acid 9.2, Cholestorol 282, Triglycerides 314, SGPT 139)

TABLE IV

Comparison of the Frequency of Abnormal Laboratory Values in the Drug and Placebo Groups

Laboratory Test	Drug Group		Placebo Group		
	#abn/ total	%abnormal	#abn/ total	%abnormal	Fisher's* Test
Glucose	30/473	6.3	58/521	11.1	.0051
BUN	13/472	2.7	29/521	5.6	.0196
Creatinine	10/469	2.1	8/521	1.5	.3210
Sodium	10/470	2.1	9/521	1.7	.4092
Potassium	12/473	2.5	2/521	0.4	.0036
Chloride	6/473	1.3	10/521	1.9	.2887
CO_2	39/473	8.2	33/521	6.3	.1495
Uric Acid	26/473	5.5	26/521	4.9	.4140
T. Protein	18/473	3.8	14/521	2.7	.2067
Albumin	58/473	12.3	29/521	5.6	.0001
Calcium	9/473	1.9	11/521	2.1	.4983
Phosphate	17/473	3.6	12/521	2.3	.1541
Cholesterol	37/473	7.8	23/521	4.4	.0169
Triglycerides	34/472	7.2	38/521	7.3	.5276
Alka. Phos.	15/473	3.2	17/521	3.3	.5400
SGOT	6/475	1.3	2/521	0.4	.1153
SGPT	7/474	1.5	10/521	1.9	.3865
LDH	4/473	0.8	2/521	0.4	.2990
T. Bilirubin	15/473	3.2	10/521	1.9	.1455
Hematocrit	18/472	3.8	14/521	2.7	.2049
Hemoglobin	9/472	1.9	14/521	2.7	.2737
RBC	13/472	2.7	6/521	1.1	.0532
WBC	26/472	5.5	20/521	3.8	.1359
Lymphs	14/472	2.9	11/521	2.1	.2557
Segs	6/472	1.3	4/521	0.8	.3170
Platelets	3/472	0.6	3/521	0.6	.6092

* Fisher's Exact Probability

TABLE V

Comparison of the Frequency of Abnormal Urine Values in the Drug and Placebo Groups

EXPERIMENT 1

DRUG

SCN	# ABN	# UA	%
1	1	14	7.1
5	1	22	4.5
6	2	22	9.0
7	0	8	0
9	1	22	4.5
13	1	21	4.8
15	0	21	0
16	0	21	0
20	0	21	0
21	1	22	4.5
22	0	22	0
24	2	22	9.0
25	2	22	9.0
30	0	22	0
31	7*	22	32
32	0	8	0
33	5*	15	33
34	1	22	4.5
35	1	7	14
42	0	22	0
43	1	22	4.5
44	3	22	14
47	0	22	0

PLACEBO

SCN	# ABN	# UA	%
2	1	19	5.3
3	0	22	0
4	2	22	9.0
8	1	22	4.5
10	2	22	9.0
11	1	20	5
12	6	20	30
14	1	18	5.5
17	3	21	14.3
18	3	21	14.3
19	0	19	0
23	0	12	0
26	0	21	0
27	1	22	4.5
28	0	22	0
29	0	17	0
36	0	22	0
37	0	22	0
38	14*	15	93
39	5*	11	45
40	0	22	0
41	2	21	9.5
45	0	21	0
48	2	22	9.0
49	0	12	0

* > 5 WBC's/HPF

TABLE VI

EXPERIMENT #1: WR 142,490 CHRONIC SAFETY AND TOLERANCE

Scalp Examinations

Grp.	SUBJ. CODE NO.	STUDY[1] WEEK	TE[2]	HEMOSTAT TEST[3] TOTAL HAIRS	% T	A/T	HAIR[4] LOSS
I	1	No Subject					
	2	38	0	9	00	9/0	32
	3	35	0	20	10	18/2	20
	4	35	0	5	00	5/0	75
	5	35	X	6	67	2/4	100
	6	35	0	5	00	5/0	10
	7	No Subject					
	8	35	0	10	10	9/1	45
	9	35	0	6	00	6/0	50
	10	35	0	4	25	3/1	25
II	11	31	0	17	12	15/2	15
	12	41	0	9	11	8/1	10
	13	31	0	17	12	15/2	30
	14	31	0	9	11	8/1	10
	15	30	X				162
	16	31	0	11	09	10/1	30
	17	31	0	11	36	7/4	200
	18	31	0	7	00	7/0	80
	19	32	0	11	18	9/2	10
	20	31	0	15	13	13/2	40

[1]Study Week = number of weeks from 1st weekly drug administration.

[2]TE = telogen effluvium: excessive hair loss of normal club hairs from normal resting hair follicles.

[3]Hemostat Test = a cluster of hairs is removed by hemostat and counted differentiating telogen (T) from anagen (A) hairs. Anagen hairs have a growing hair follicle whereas telogen have a resting follicle which gives the extracted hair a "club" appearance. The % telogen hairs (%T) in this test is usually less than 40%.

[4]Hair Loss: subjects were requested to collect all hair loss from combing, pillows, and other practical sources for 2-3 days *before the examination* to be counted by the dermatologist. In this table, estimates are omitted and actual counts tabulated as loss per day. Greater than 75 is considered excessive.

Scalp Examinations (Cont'd) - Page 2

Grp.	SUBJ. CODE NO.	STUDY[1] WEEK	TE[2]	HEMOSTAT TEST[3] TOTAL HAIRS	% T	A/T	HAIR[4] LOSS
III	21	31	0	9	11	8/1	15
	22	36	0	10	20	8/2	50
	23	No Subject					
	24	35	0	14	21	11/3	10
	25	31	0	10	10	9/1	0
	26	31	0	19	16	16/3	15
	27	31	0	11	09	10/1	4
	28	36	0	14	07	13/1	10
	29	34	0	6	17	5/1	0
	30	31	0	6	00	6/0	10
IV	31	22	0	8	13	7/1	0
	32	No Subject					
	33	No Subject					
	34	22	0	9	11	8/1	20
	35	No Subject					
	36	22	0	8	13	7/1	10
	37	22	0	6	17	5/1	10
	38	25	0	12	17	10/1	10
	39	No Subject					
	40	27	0	7	14	6/1	20
V	41	7	0	7	14	6/1	0
	42	7	0	20	15	17/3	0
	43	7	0	6	00	6/0	0
	44	7	0	12	08	11/1	10
	45	7	0	6	17	5/1	10
	46	No Subject					
	47	7	0	7	00	7/0	30
	48	7	0	13	15	11/2	0
	49	7	0	8	13	7/1	10
	50	No Subject					

Enclosure 1

BIO - MED, Inc.

Tel: (202) 882 0977

DATE: September 22, 1976

TO: All Subjects Participating in Experiment No. 1
WR 142,490 Chronic Safety and Tolerance

FROM: Kevin G. Barry, M.D., Clinical Director AMDPG

SUBJECT: Reproductive and Toxicity Studies in Male Rats Receiving WR 142,490 (Mefloquine)

The superiority of mefloquine over other antimalarial drugs has resulted in expanded toxicologic studies in animals and an increased number of studies of safety and effectiveness in humans.

One of the animal toxicologic studies included observations of the effect of increasing dosage of mefloquine administered to rats on reproductive function. Groups of male rats received 5, 20 and 50 mg mefloquine per kilogram body weight per day for 91 days. The total dose per kilogram at 5 mg/kg per day for 91 days (455 mg/91 days) exceeds that administered to subjects in the 52-week study during the entire 364 days (average 364 mg/364 days). In rats at the 5 mg/kg/day dose level, there were no toxic effects observed in the laboratory examination of blood, growth rates or reproductive performance.

Rats receiving 20 mg/kg/day for 91 days (total dose per kilogram 1820 mg/91 days as compared to 364 mg/364 days in our human subjects) developed definite toxicity manifested by anemia, but there was no effect on growth rate OR reproductive performance. Microscopic examination of the reproductive organs and sperm delivery ducts (epididymis and vas deferens) showed minimal changes in the cells lining the epididymis. The epididymis is composed of a large number of ducts and deliver the sperm from the testes to the vas deferens which is another duct.

No microscopic changes were observed in the other reproductive organs. The epididymal changes were not associated with any decrease in reproductive performance and at this dose level clinical toxicity was manifested by anemia.

In rats receiving 50 mg/kg/day for 91 days (total dose per kilogram 4550 mg/91 days as compared to 364 mg/364 days in our subjects), multiple toxic effects were observed:

a) significant anemia;

b) changes in white blood cell differential count;

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c) increase in SGOT serum enzyme concentration;

d) decrease in growth rate measured by body weight change;

e) suggestion of decreased reproductive capability manifested by 16 of 20 exposures to females resulting in conception as compared to 20 of 20 in controls and rats receiving the drug at 5 and 20 mg/kg/day dose levels.

Microscopic examination of the reproductive organs and sperm delivery ducts in the rats receiving 50 mg/kg/day for 91 days showed changes in the epididymis of 18 of the 20 treated rats not present in controls. The major change was moderate alteration of the cells lining the epididymal ducts. No changes were observed in the rest of the reproductive system.

The relative dose levels between subjects in the 52-week study and the foregoing rat study may be expressed as follows:

	MG/KG/BODY WEIGHT			CLINICAL
	PER DAY	PER WEEK	PER 91 DAYS	TOXICITY
Subjects	1	7	91	0
5 mg/kg Rats	5	35	455	0
20 mg/kg Rats	20	140	1820	Anemia
50 mg/kg Rats	50	350	4550	Significant Anemia Changes in white blood cell differential counts Increase in SGOT serum enzyme concentration Decrease in growth rate measured in body weight change Suggestion of decreased reproductiv capability manifest by 16 of 20 exposur to females resultin in conception as co pared to 20 of 20 i controls and rats r ceiving the drug at and 20 mg/kg/day do levels

The contracting agency, Organizational Review Committee and Human Subject Committee recommended that you be informed of the current status of the rat study. While the other agencies and committees do not feel a sperm count *at this time* is indicated, the Human Subject Committee has recommended we offer a sperm count to any subject requesting it.

If you wish to have your sperm count performed, notify us and we will arrange it.

Additionally, an extract of a memo from the Office of the Director of the Division of Medicinal Chemistry, Walter Reed Army Institute of Research including their recommendations which BIO-MED will follow, is enclosed as an appendix.

We will keep you current concerning ongoing toxicologic studies.

Sincerely,

Kevin G. Barry

Kevin G. Barry, M.D.
Clinical Director, AMDPG

KGB:evm
Appendix

SGRD-UWM-C
MFR

15 September 1976

1. No epididymal lesions have been reported in any previous animal studies.

a. Subacute rat toxicity. It was concluded that repeated daily oral doses of 5 mg/kg/day of WR 142,490 for 28 consecutive days to male rats was nontoxic, 30 mg/kg/day caused minimal lymphocytopenia and 150 mg/kg/day was lethal in some animals. The target organs were the myocardium, skeletal muscle and lymphoid tissues, with no changes in the testes or epididymus.

b. Subacute dog toxicity. Repeated oral doses of 5 mg/kg/day of WR 142,490 for 28 consecutive days were nontoxic to dogs. Doses of 30 mg/kg/day for 28 days caused occasional diarrhea and emesis and lesions in the lymphoid tissue and/or the liver. Doses of 150 mg/kg/day for 28 days caused various toxic signs, erythroid depression of the bone marrow, lesions in the lymphoid tissues, and death in some animals. No epididymal lesions were reported.

c. Chronic toxicity in rats. At the completion of 52 weeks, weekly doses of 5 mg/kg did not cause any adverse effects. However, 25 or 125 mg/kg/week reduced the rate of weight gain, but did not cause any toxic signs, any changes in peripheral blood elements, clinical blood chemistry or urinalysis or any pathologic tissue lesions.

d. Chronic toxicity in dogs. At the completion of 52 weeks, weekly doses of 5, 25 or 125 mg/kg did not cause any toxic signs, any changes in peripheral blood elements, clinical blood chemistry or urinalysis, or any pathologic tissue lesions.

2. The male rats in the reproductive study under discussion received 5, 20 and 50 mg/kg/day for 91 consecutive days; 5 mg/kg/day was nontoxic. However, histologic changes occurred in the epididymus of rats which received 20 or 50 mg/kg/day. There was also a decreased reproductive index in rats which received 50 mg/kg/day. It was noted that other toxic changes also occurred in both groups, i.e., reduced RBC count, Hgb and Hct and increased SGOT in the blood.

3. In order to evaluate and compare the drug exposure in these studies, the available estimates of biologic half life in single dose experiments were reviewed (2 days, 14 days and 16 days in the rat, dog and man respectively).

Blood levels of drug were not obtained in the multiple dose animal toxicology studies. However, the measured blood levels in subjects currently in the 52 week study reached plateau after 6-8 doses

and were well within the predicted range based on a 16 day biologic half-life.

The current status of Experiment #1 was briefly reviewed. The first group of 10 subjects have completed 50 weeks of the study. The last group of 10 was started about 3 months ago. No adverse effects have as yet been discovered, though two individuals were discontinued because of hair loss, possibly drug related, and are being followed by a dermatologist.

4. Sperm examinations of the subjects participating in Experiment #1 was thought inadvisable because of the lack of any baseline evaluation in these individuals (ref. Dr. Mattis' letter).

Conclusion

After considering the above information regarding toxicological data in rats and dogs, available pharmacokinetic data in rats, dogs and man, and the advice of Drs. Paul Mattis and Walter Modell, the following conclusions were reached.

1. Epididymal lesions in male rats occurred in conjunction with other signs of toxicity and were related to the frequent high doses and prolonged duration of administration in the reproductive study.

2. Therefore, the results of the reproductive study do not imply any substantial increase in risk to the participants and Experiment #1 should be allowed to continue.

3. A copy of the reproductive study in rats and this memorandum will be forwarded through the AIDRB to FDA, as also recommended in Dr. Mattis' letter of 30 August 1976.

4. We advised Dr. Barry to continue the study and provide the participating subjects with this new information in the interest of maintaining their informed consent.

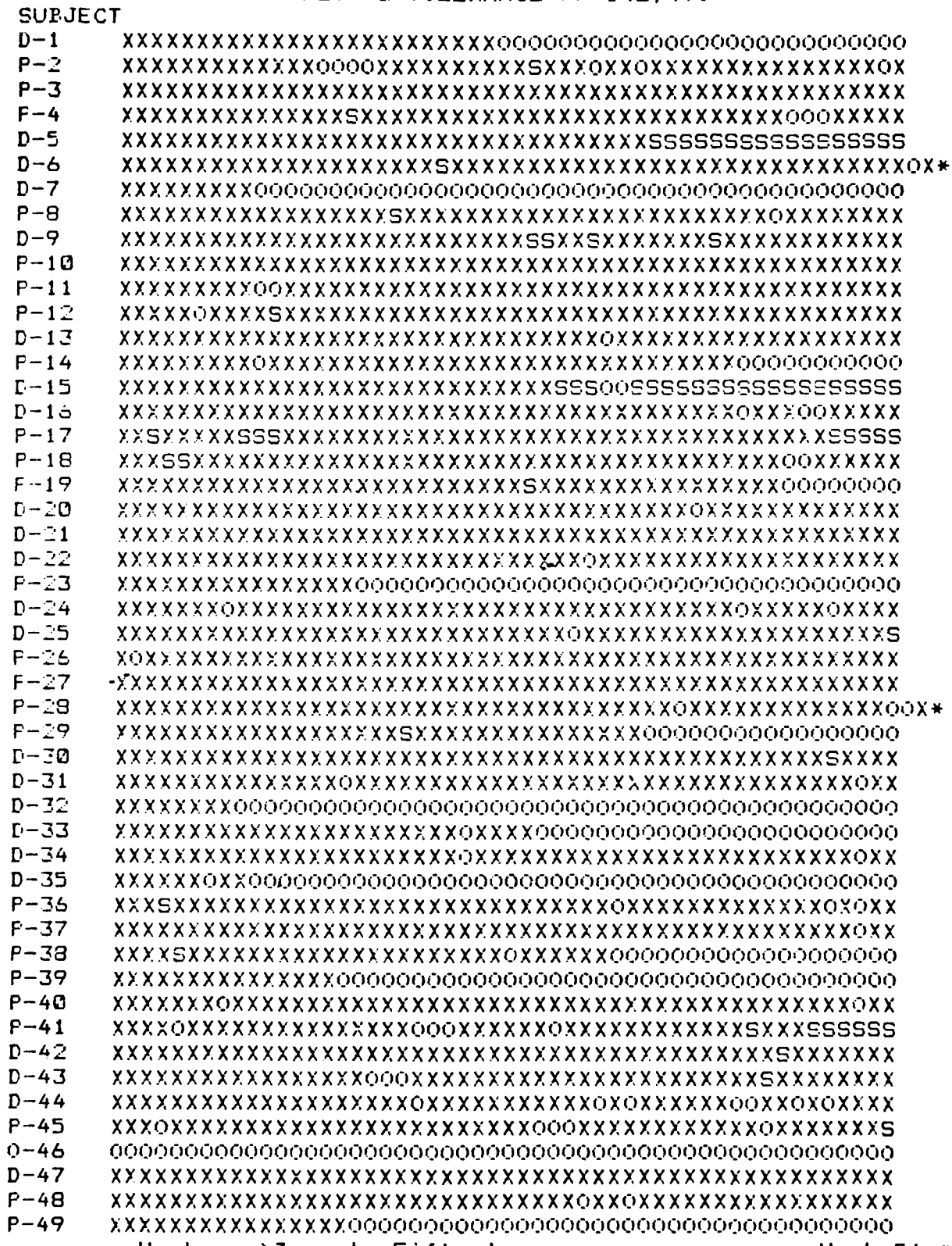
5. We will request that Dr. Barry provide us with a copy of his letter to the subjects for inclusion in the IND and this letter will likewise be forwarded through the AIDRB to FDA.

6. All parties, Bio-Med, Inc., the participating subjects, the Ad Hoc Clinical and Preclinical Pharmacology Advisory Committee, the AIDRB and FDA will be advised of the results of ongoing reversibility studies or any other pertinent data as soon as these become available.

FIGURE 1

SUBJECT COMPLIANCE

CHRONIC SAFETY & TOLERANCE:WR 142,490



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EXPERIMENT NO. 2: WR 184,806·H_3PO_4
SHORT TERM DOSAGE SAFETY AND TOLERANCE
MULTIPLE DOSE LEVELS
STUDY SUMMARY

INTRODUCTION:

In Single dose studies previously reported, no intolerance to WR 184,806·H_3PO_4 was observed below the 1000 mg dose level. At higher dose levels, lightheadedness with associated difficulties concentrating and focusing, headache, nausea and sleep disturbances occurred. There were no associated objective findings and the symptoms were of less than twenty-four hours duration. This study was performed to determine the short term safety and tolerance of WR 184,806·H_3PO_4 administered orally in multiple doses. A total of eight study levels were used to administer drug or placebo to 29 subjects. The dose levels ar assignment to receive drug or placebo for each subject are detailed on pages11 and 12 (Table 1).

SUBJECTS:

The subjects were recruited from the Washington, D.C. metropolitan area and were hired as temporary employees. Advertisements in university newspapers provided initial contacts with potential subjects. This method plus positive recommendations by participating subjects to their classmates enlarged the candidate pool. Approximately 80% of the subjects were university students with superior motivation, understanding and compliance.

Screening:

Candidates for employment underwent qualifying examinations to obtain the subjects for study. The initial evaluation included a complete history and physical examination, chest x-ray, electrocardiogram and the following tests: urinalysis white blood cell and differential count, red blood cell count hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, Na^+, K^+, Cl^-, CO_2, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin and G6PD. Laboratory tests were performed in duplicate by National Health Laboratories, Inc. using standard methods. Chest x-rays were performed in the Department of Radiology at the Washington Hospital Center. Electrocardio-

grams were performed by trained personnel using a Cambridge VS-4 portable electrocardiographic machine. Urinalyses were performed by physician investigators in the research unit laboratory using standard methods.

Informed Consent:

Qualified candidates were presented with a complete explanation of the background and rationale for the study as well as procedures to be used as shown on pages 7 through 9. Candidates were interviewed in a group and individually. At individual interviews it was ascertained that the candidate understood the study and personal risk factors. Qualified candidates were asked to read and permitted to sign the consent statement as shown on page 10.

Human Subject Committee:

The composition and function of the Human Subject Committee is shown on page 33. A member of the Human Subject Committee participated in the consent interviews and made frequent visits to the research unit to monitor the study and assure the subjects' health and welfare were given primary consideration. Each subject clearly understood that he could termina his participation in the study at any time.

HOUSING:

Subjects were housed on the Clinical Research Unit of the Washington Hospital Center, utilizing semi-private rooms with modern facilities. A lounge area was available which contained television, reading materials, games, chairs and desks. Subjects, supervised by the investigating team, were allowed to use the tennis courts, swimming pool and recreational facilities at the Washington Hospital Center. A choic of meals was made available to each of the subjects by the Food Service Department at the Washington Hospital Center. Each subject underwent serial physical examinations in the unit examing room and specialty areas within the hospital.

METHODS:

The dosing schedule and number of subjects in each study peri are tabulated on page 11 and 12. Sixteen subjects received drug and 13 placebo (Table 1).

Clinical and laboratory evaluations:

The schematic table detailing the sequence of tests during each study interval is shown on page 5.

RESULTS:

Symptoms and physical findings:

The onset, duration and description of symptoms and physical findings on all subjects are presented on pages 13 through 18. Mild symptoms of transient diarrhea, constipation, lethargy, flushing and disturbing dreams occurred in both control and subjects receiving drug. Two subjects, receiving 3600 mg dru (1200 mg daily for 3 days) complained of vague tremulousness and lightheadedness similar to that observed when 1200-1400 mgs of WR 184,806·H_3PO_4 were administered as a single dose in a previous study. Two other subjects receiving 600 and 750 mg of drug daily experienced sleep disturbances. In all subjects the above noted symptoms were mild, temporary and without associated physical or laboratory abnormalities. All symptoms and findings are shown in Table 2.

Physical Examination:

One subject receiving 3000 mg drug developed a maculopapular rash 10 days after completion of drug administration which was also associated with the subject's use of a commercial soap for the first time. The rash disappeared upon discontin ation of use of the soap and was considered a soap precipitat contact dermatitis by the consulting dermatologist.

Mild sunburn in 2 subjects and swimming pool chemical conjunctivitis in one subject were not considered drug related. All physical abnormalities detected are tabulated on pages 20 through 22 (Table 3).

Laboratory tests:

Abnormal hematologic and biochemical values are tabulated on pages 26 through 28 (Table 4). Eighty-three percent of the subjects had at least one abnormality. Abnormalities were distributed with equal frequency amongst subjects administered drug and placebo. No abnormalities were ascribed to drug ingestion.

Ten subjects had abnormal urinalyses, 6 of these received drug Glycosuria (1+) with a normal blood sugar was detected on days 2 and 4 in one subject receiving 900 mg of drug. Intermittent trace proteinuria was detected in one subject receivin drug as well as one who received placebo. Increased numbers of red and white cells in the urinary sediment in control and drug administered subjects demonstrated no pattern and are not considered study related. No subject had cylindruria. All findings are tabulated on page 30 (Table 5).

The results of electrocardiography and phototoxicity testing are described on pages 31 and 33. No electrocardiographic changes attributable to drug ingestion were observed. Phototoxicity was not produced under conditions of this study.

Individual Summary Sheets:

Individual summary sheets, for each subject, are shown on pages 36 through 73.

CONCLUSION:

Possible intolerance to multiple doses of WR 184,806·H_3PO_4 was detected. Some subjects receiving drug, as well as controls, experienced flushing, vivid dreams and other symptoms considered potentially drug related in the previous single dose study. Tremulousness and lightheadedness occurred on the last day of dosing in two subject receiving 3600 mg total dose. The late onset of these symptoms and similarity to symptoms of intolerance at 1200 and 1400 mg single dose levels suggests they may be drug related. Gastrointestinal symptoms occurred in the control subjects as well as those receiving drug. In the latter, the symptoms did not persist or increase in severity with continued drug administration. No physical or laboratory abnormalities were ascribed to drug ingestion.

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FINAL REPORT
EXPERIMENT NO. 3: WR 142,490·HCl SHORT TERM SAFETY AND TOLERANCE
Single Dose Levels

STUDY SUMMARY

INTRODUCTION:

WR 142,490·HCl is an investigative quinoline methanol which has undergone extensive tolerance and efficacy studies in human subjects. As of 23 July 1974 112 volunteers have received various doses of WR 142,490. A 2 by 2 rising dose double blind Phase I tolerance study in volunteers has been performed to a maximum dose of 2 gm administered as a single dose. Occasional subjects at this dose of the drug complained of transitory "dizziness." This included subjects receiving placebos as well as subjects receiving test drug. There were no physical abnormalities detected and laboratory tests were normal in these subjects.

The purpose of this study was to determine the top tolerated single oral dose of WR 142,490.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects. The selection methodology, qualifications and acceptability criteria for study entry are presented on Pages 4 and 7.

Drug Administration:

A double blind method was used as presented on Page 7. The initial dose level was 1.75 grams.

Clinical and Laboratory Evaluations:

The schematic table detailing the sequence of tests during each study interval is shown on Page 9.

RESULTS:

General:

Intolerance occurred in both subjects receiving WR 142,490 at the initial dose level of 1.75 grams. Therefore, the study was suspended pending further investigation.

Symptoms and Physical Findings:

Subject Code Nos. 97 and 100, who ingested WR 142,490·HCl at the first dose level of 1.75 gm, developed symptoms after drug administration. Subject Code Nos. 98 and 99, who ingested placebo, were asymptomatic throughout the study.

Subject Code No. 97 experienced nausea and mild epigastric discomfort 30 minutes after drug ingestion followed 30 minutes later by a loose watery stool. The nausea and abdominal discomfort lessened after passage of a 2nd watery stool 2½ hours after drug ingestion but persisted for a total duration of 3½ hours. The subject then felt well until 24 hours after drug ingestion when, following breakfast, he had a single unexpected emesis. Thereafter he remained asymptomatic.

Subject Code No. 100 developed mild abdominal cramping followed by watery diarrhea 30 minutes after drug ingestion. During the following 5 hours the subject had another six watery stools and thereafter was asymptomatic.

The observations upon physical examination remained unchanged in both subjects during and after the symptoms noted.

Clinical Laboratory Studies:

Hematologic and Biochemical: There were no significant alterations attributed to drug ingestion. The abnormal test results are shown as Table 2, Page 21.

Urinalysis: No abnormalities were detected.

Electrocardiography and Phototoxicity Testing: No rhythm strip electrocardiographic changes or phototoxicity were produced under conditions of the study.

Individual Summaries: Summaries for each subject are presented as Pages 27 through 30.

CONCLUSION:

The administration of 1.75 grams WR 142,490·HCl under conditions of this study was accociated with temporary nausea, vomiting, abdominal cramps and watery diarrhea. The intolerance to this dose level as compared to tolerance at higher dose levels in previous studies is attributed to the use of a new formulation (Lot B512) in place of the formulation (Lot E443) used in the previous studies.

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ADDENDUM TO EXPERIMENT 3: WR 142,490·HCL SHORT TERM SAFETY AND TOLERANCE
Clinical Evaluation of Two Formulations

STUDY SUMMARY

INTRODUCTION:

WR 142,490·HCL, Mefloquine Hydrochloride, is an investigational quinoline methanol which has been shown to be effective in the treatment and prophylaxis of humans with chloroquine resistant strains of Plasmodium falciparum.

The purpose of this study was to determine the relative tolerance and bioavailability of two formulations of the antimalarial drug mefloquine HCl (WR 142,490·HCl) administered orally to healthy subjects.

Phase I testing, in volunteers, showed that the drug was well tolerated in single doses up to 2,000 mg. Transient lightheadedness occurred in both dosed and control subjects at single oral doses of 1,500 and 1,750 mg but not at 2,000 mg. An additional study was designed to extend the Phase I tolerance study to 2,500 mg in a rising dose double blind study. This study was initiated at an oral dose of 1,750 mg, a previously tolerated dose, because the study was to be conducted in a different study population using a more rapidly dispersing coated tablet formulation manufactured by INTERx, Lawrence, Kansas (Lot B512) instead of the previous tablet formulation manufactured by Lafayette Pharmacal, Inc., Lafayette, Indiana (Lot E443). Gastrointestinal intolerance occurred in two subjects at the initial 1,750 mg dose manifested by watery diarrhea 30-45 minutes after the drug was administered and continuing for 3 to 4 hours. A further study, Experiment No. 4 entitled "WR 142,490·HCl Safety and Tolerance, Repetitive Curative Dose Levels" was designed and conducted to test the tolerance of the INTERx formulation WR 142,490·HCl when the drug was administered orally on Days 1 and 7. Single repetitive oral doses of 1,000, 1,250, and 1,500 mg were given to 3 groups of subjects using a 2 x 2 rising double blind method. In this study, diarrhea starting 30 to 60 minutes after dosing and lasting ½-3 hours, occurred in all four subjects receiving the 1,250 and 1,500 mg dose. In the 2 subjects ingesting 1,500 mg, diarrhea occurred after both administrations. Diarrhea occurred after both doses of 1,250 mg in one subject but only after the first dose in the other subject.

An accurate chemical analysis for mefloquine in serum specimens is now available. The analysis is currently in use in the laboratories of the Department of Pharmacology, Division of Medicinal Chemistry at Walter Reed Army Institute of Research. Therefore, it is practical to determine if a correlation exists between symptoms and serum drug concentrations. A comparative study of human tolerance and bioavailability between the two available formulations has been done.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects. The selection methodology, qualifications and acceptability criteria for study entry are presented on Pages 4, 7, and 8.

Drug Administration:

A 2 x 2 balanced latin square crossover design was used in this study (see Page 3).

Clinical, Laboratory and Drug Assay Schedules:

The schematic detailing the study schedule and testing times are presented on Page 9.

RESULTS:

Compliance:

One subject terminated participation for personal reasons and was not administered B512. Another was terminated because of pharyngitis six days after receiving B512 and did not receive E443. Therefore, 6 subjects completed the "crossover" as planned and 7 administrations of each formulation was accomplished. The two withdrawals did not affect the balance of the 2 x 2 latin square design since 3 subjects in each group, A & B, completed both parts of the study.

Symptoms and Physical Findings:

The description, onset and duration of all symptoms and findings for the entire study group are presented on Pages 16 through 21. Symptoms ascribed to drug administration are shown as Table 2B, Pg. 22. Administration of both formulations of WR 142,490·HCL as a single 1,750 mg oral dose was associated with combinations of mild and temporary, nausea, abdominal cramps

and loose stools. Additionally, non-incapacitating lightheadedness occurred in four instances in 3 subjects: following administration of E443 on two occasions and B512 on two occasions.

Physical Examination:

Subject Code No. 204 developed pharyngitis and otitis externa accompanied by temporary enzyme elevation following B512 administration on Day 7 of the 1st study interval. Subject Code No. 206 developed a left otitis externa following a weekend at the beach. The physical abnormalities were not considered drug related.

Laboratory Tests:

Abnormal hematologic and biochemical values are tabulated on Pages 26 through 27 (Table 3). There is no pattern suggesting the minor abnormalities observed were drug related. The following abnormalities warrant comment: Subject Code No. 204 developed pharyngitis, otitis externa and temporary elevation of SGPT, SGOT and LDH 6 days following administration of B512 and was not administered E443. Urinalyses (Page 28) were abnormal on three occasions in 3 different subjects. Subject Code Nos. 203 and 207 had trace glucosuria and trace proteinuria respectively. Subject Code No. 208 developed temporary microscopic hematuria on Day 7 of the first study interval following trauma. Electrocardiographic rhythm strips did not change significantly in any subject following drug administration (Page 30).

Individual Final Summaries:

Final summaries for each subject are presented as Pages 31 through 42.

CONCLUSION:

WR 142,490·HCl as formulated in Lots B512 and E443 are not tolerated at a single oral dose of 1,750 mg as administered in this study. Intolerance was manifested by combinations of nausea, abdominal cramps and loose stools. These symptoms were mild and temporary. Additionally, three subjects complained of non-incapacitating lightheadedness: one following administration of each formulation and one each following B512 and E443. It should be noted that the intolerance was not of sufficient magnitude to preclude use of the

dose level and formulations as tested if the clinical need existed. In such an instance E443 appears to be preferable as the frequency and duration of symptoms were less than following administration of the B512 formulation.

FINAL REPORT

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3

WR 142,490·HCl: SHORT-TERM SAFETY AND TOLERANCE: SINGLE DOSE LEVEL: Clinical Evaluation of Two Formulations

ABSTRACT

The study reported herein was conducted to compare the safety, tolerance and bioavailability of two formulations of WR 142,490·HCL. The two formulations, designated Lot E-443 and Lot B-512 were administered in a 1000 mg single oral dose.

Nine healthy volunteer subjects were alternately given each formulation in a 2 x 2, latin square crossover design with a 6 week "wash-out" period. Physical findings, symptoms, laboratory values and electrocardiograms were monitored. Blood samples for pharmacokinetics were collected and submitted to WRAIR.

In this study, no adverse reactions to either formulation were detected. Decisions regarding these formulations at the dose level given should be based on comparative bioavailability.

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EXPERIMENT NO. 4: WR 142,490·HCL SAFETY AND TOLERANCE
Repetitive Curative Dose Levels

STUDY SUMMARY

INTRODUCTION:

Mefloquine hydrochloride, WR 142,490, has been shown to be a highly effective antimalarial when administered as a single oral dose, in humans ill with chloroquine resistant strains of P. falciparum. Twelve of fourteen non-immune subjects infected with chloroquine resistant strains of P. falciparum and administered mefloquine hydrochloride, were cured with single doses of 1.0-1.5 gm. Recrudescence occurred in the two remaining individuals, one of whom was cured with a repeat 1.0 gm dose of mefloquine.

Phase III mefloquine clinical studies, in Thailand, with naturally acquired P. falciparum infections appear promising. However, two recrudescences following treatment occurred. It is anticipated repeat dosing in individuals who recrudesce after initial clearing of parisitemia may be necessary.

This study was performed to determine tolerance and safety of WR 142,490·HCL, administered orally to healthy human subjects, when predicted curative single dose levels are repeated on the 7th day following initial dosing as outlined in the protocol on Pages 5 through 8 A total of three consecutive rising dose levels were used in a double blind study. Four subjects participated at each dose level. The dose levels and assignment, to receive drug or placebo, are detailed on Pages 8 and 10.

A capsule formulation had been used for most previous WR 142,490·HCL studies. For this study a more rapidly dispersing coated tablet formulation designated Lot B512 was used.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects. The selection methodology, qualifications and acceptability criteria for study entry are presented on Pages 4 and 5.

Drug Administration:

A double blind method was used as presented on Page 6 and tabulated on Page 14 .

Clinical, Laboratory and Drug Assay Schedules:

The schematic detailing the sequence of testing is presented on Page 8 .

RESULTS:

Symptoms and Physical Findings:

One control subject (#89) had transient abdominal cramps and passed one loose watery stool thirteen hours after placebo administration.

Five of the six subjects receiving drug had gastrointestinal symptoms. At the 1000 mg dose level Subject #87 experienced transitory nausea followed by passage of a loose, brown, watery stool within the first hour after the first drug administration. Subject #85 tolerated both drug administrations and Subject #87 tolerated the second administration without any symptoms.

The symptoms at the 1250 mg dose level were more frequent and of longer duration. Although Subject #92 tolerated the second administration without symptoms, three watery stools were passed starting 30 minutes after the initial dosing and ending 180 minutes later. Subject #90 developed symptoms 30 minutes after each dosing including 3-5 watery stools during a 2-3 hour interv

At the 1500 mg dose level, both subjects were intolerant of the drug each time it was administered. Subject #94 developed slight nausea and passed a watery stool 30 minutes after the initial dose. The nausea persisted for 1 hour. Following the second dose, nausea was absent, but the subject passed four watery stools during the interval of 60 minutes to 150 minutes after dosage. Subject #95 became nauseated 90 minutes following the initial dose immediately after breakfast and vomited the breakfast 30 minutes later. No loose stools were passed. Following the second administration of drug, nausea was absent but four watery stools were passed during the interval of 1½ hours to 3 hours after drug administration.

The description, onset, and duration of all symptoms and findings for the entire study group are shown in Table 2, Pages 17 and 18.

Physical Examination:

No significant abnormalities developed during the study period.

Laboratory Tests:

Hematologic and biochemical tests are tabulated on Pages 21 and 22. There were no significant alterations in these tests attributable to drug ingestion.

Urinalyses - Results of urinalyses are tabulated on Page 23. There were no significant alterations in urine protein, glucose, or changes in urine sediment attributed to drug ingestion.

Electrocardiography and Phototoxicity - Findings are detailed on Pages 25 and 26. No ECG rhythm changes were observed. Phototoxicity did not occur in the course of this study.

Individual Final Summaries:

Summaries for each subject are shown on Pages 29 through 40.

DISCUSSION:

Previous Phase I testing with mefloquine, Lot E443 (Lafayette Pharmacal, Inc.) in humans, at the Statesville Penitentiary, established that the drug was well tolerated in single oral doses of 2000 mg. However, in the present study a different formulation of WR 142,490·HCL, Lot B512 (INTERx, Inc.), was used. This formulation is designed as a more rapidly dispersing coated tablet as compared with the capsules and tablets used in most earlier clinical trials. Tolerance of the two formulations appears to be quite different.

Since only one control subject developed gastrointestinal symptoms following placebo ingestion, it is suggested that the symptoms observed in this study were induced by active drug or the combination of drug and excipient.

It should be noted that symptoms occurred in only 1 of 4 administrations of the 1000 mg dose. The frequency and duration of loose stools were approximately the same at the 1250 and 1500 mg dose level, but nausea and emesis occurred only at the 1500 mg dose level. It is undetermined whether or not the drug was returned in the one episode of emesis that occurred, but it may be inferred since diarrhea did not occur following that administration, but did occur following the second administration to that subject.

CONCLUSION:

Intolerance to the INTERx formulation of WR 142,490·HCL, designated Lot B512, occurred at the three dose levels tested. Intolerance was minimal at the lowest dose tested (1000 mg) and consistent at the highest (1500 mg). Intolerance was manifested primarily by passage of one to five watery stools starting 30 to 90 minutes after drug ingestion and lasting for ½ to 3 hours. Mild nausea occurred in 3 of 12 trials. Emesis occurred once and may have included all or part of the administered drug. No other symptoms, physical or laboratory abnormalities of significance occurred in the subjects during the study.

RECOMMENDATIONS:

It is recommended that cross over investigations be performed between WR 142,490·HCL formulations for comparative tolerance and bioavailability.

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EXPERIMENT NO. 5: WR 142,490·CH_3SO_3H: MEFLOQUINE METHANESULFONATE SAFETY, TOLERANCE, AND PHARMACOKINETICS OF INTRAVENOUS ADMINISTRATION

ABSTRACT

Single oral doses of mefloquine hydrochloride are effective against human infections with multidrug-resistant P. falciparu malaria. Animal studies have also shown this drug to be activ intravenously, curing infections with P. falciparum malaria in Aotus monkeys after a single intravenous dose.

The present study was designed to determine the safety, tolerance, and pharmacokinetics of mefloquine methanesulfonate administered intravenously.

Eight subjects received mefloquine methanesulfonate intravenou ly. The study was discontinued because of the occurrence of local symptoms during the infusion in six subjects followed by evidence of periphlebitis and phlebitis.

An interesting finding of undetermined cause was an apparent de crease of serum haptoglobin on study day 2 compared with level recorded on study day 0, prior to infusion of the drug, in each subject.

The occurrence of local irritation associated with intravenous infusion of mefloquine methanesulfonate precludes further clinical testing of the current formulation.

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EXPERIMENT NO. 6: WR 184,806·H_3PO_4

PHARMACOKINETICS FOLLOWING

ORAL ADMINISTRATION

ABSTRACT

WR 184,806·H_3PO_4, a substituted quinoline methanol antimalarial was administered as a single oral dose to four groups of five subjects each to obtain specimens for pharmacokinetic data. Tablets were administered at dose levels of 250, 500, and 1000 mg and a cherry syrup suspension at a dose level of 250 mg WR 184,806·H_3PO_4.

For drug assay, urine collections were obtained as 24-hour specimens immediately prior and for the first 3 days after drug administration; Venous blood was obtained prior to and serially following drug administration for a total of 15 days. Drug assay results are not available at this time.

Two of the five subjects administered 1000 mg WR 184,806·H_3PO_4 experienced light-headedness of one-hour duration with onset thirty minutes after drug ingestion in one subject and eight hours after dosing in the other. Two of the twenty subjects experienced mild headache of four hours duration with onset seven (subject receiving 250 mg drug) and six (subject receiving 500 mg drug) hours after drug administration. No other symptoms or clinical observations were considered potentially drug related. Conclusions await drug assay reports and analysis.

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EXPERIMENT NO. 7: WR 180,409·H_3PO_4

SHORT TERM DOSAGE SAFETY AND TOLERANCE

RISING SINGLE DOSE LEVELS

ABSTRACT

WR 180,409·H_3PO_4, a new antimalarial agent was administered orally as a single dose to 22 subjects in a Phase I double-blind, rising dose level study. Intolerance manifested by combinations of nausea, vomiting, dizziness, mild mental "fuzziness", occurred in 3 of the 4 subjects at the 1000 mg dose level and also in 3 of the 4 subjects administered 1250 mg drug. Both subjects administered 1500 mg WR 180,409·H_3PO_4 developed nausea, vomiting, dizziness, mental fuzziness (1 subject) and insomnia (1 subject).

No physical or laboratory abnormalities were attributed to drug. A single low platelet count with normal counts subsequently was reported in one subject administered 1250 mg drug. It was concluded that the occurrence was possibly but not probably drug related.

The symptoms of intolerance were mild and of less than 48 hours duration in all subjects. It was concluded that WR 180,409·H_3PO_4 should be considered for multiple dose testing and bioavailability studies.

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EXPERIMENT NO. 7: WR 180,409·H_3PO_4

SHORT TERM DOSAGE SAFETY AND TOLERANCE

RISING SINGLE DOSE LEVELS

STUDY SUMMARY

INTRODUCTION:

The study was performed to determine the short term dosage safety and tolerance of WR 180,409·H_3PO_4 administered orally to human subjects as outlined in the protocol on pages 1 through 10. A total of 11 study intervals were used to administer drug or placebo to 43 subjects. The dose levels and assignment to receive drug or placebo for each subject are detailed in Table 1, page 11.

SUBJECT:

Recruitment:

Subjects were healthy males aged 21 to 45 years weighing between 50-100 Kg. They were recruited from the Washington, D.C. metropolitan area and were hired as temporary employees.

Screening:

Candidates for employment underwent qualifying examinations to obtain the subjects for study. The initial evaluation included a complete history and physical examination, chest x-ray, electrocardiogram and the following tests: urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, Na^+, K^+, Cl^-, CO_2, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin. Laboratory tests were performed by National Health Laboratories, Incorporated using standard methods. Chest x-rays were performed in the Department of Radiology at the Washington Hospital Center. Electrocardiograms were performed by trained personnel using a Cambridge VS-4 portable electrocardiograph machine. Urinalyses were performed in the research unit laboratory using standard methods.

Informed Consent:

Qualified candidates were presented with a complete explanation of the background and rationale for the study as well as procedures to be used as shown on pages 7 through 9. Candidates were interviewed as a group and individually. At individual interviews it was ascertained the candidate understood the study

and personal risk factors. Qualified candidates were asked to read and permitted to sign the consent statement as shown on page 10.

Human Subject Committee:

The committee is composed of individuals from the community including previous subjects. A member of the human subject committee participated in the consent interviews and made frequent visits to the research unit to monitor the study and assure the subjects' health and welfare were given primary consideration. Each subject clearly understood that he could terminate his participation in the study at any time.

HOUSING:

Subjects were housed in the clinical research unit of the Washington Hospital Center, utilizing semi-private rooms with modern facilities. A lounge area was available which contained television, reading materials, games, chairs, and desks. Subjects, supervised by the investigating team, were allowed to use the tennis courts, swimming pool and recreational facilities of the Washington Hospital Center. Each subject underwent serial physical examinations in the unit examining room and special tests were performed in specialty areas within the hospital.

METHODS:

Drug administration:

Drug lots used, dosing schedules, number of subjects in each study period and incremental increases in doses are tabulated on pages 5 and 6. Twenty-two subjects received drug and 21 placebo.

Clinical and laboratory evaluations:

The schematic table detailing the sequence of tests during each study interval are shown on page 8.

RESULTS:

Symptoms and physical findings:

The onset, duration and description of symptoms and physical findings on all subjects are presented on pages 17 through 20. A tabulation of the occurrence of symptoms compatible with but not attributed in all cases to drug intolerance in all instances is presented as Table 2a, pages 21 through 24. The two subjects receiving 1500 mg and 3 of the 4 subjects receiving 1250 mg as well as 3 of the 4 receiving 1000 mg had symptom patterns suggestive of intolerance including combinations of nausea, vomiting, light-headedness, mental fuzziness and inability to concentrate. In all subjects the symptoms were mild, not incapacitating and of less than 48 hours duration.

Physical examinations:

No abnormalities occurred during the course of the study which were attributable to participation in the study.

Laboratory tests:

Hematologic and biochemical tests are presented as Table 3, pages 28 through 32. Subject Code #160 receiving 1250 mg WR 180,409·H_3PO_4 was reported to have 10,000 platelets on a blood specimen drawn approximately 22 hours after drug ingestic There was no associated purpura or petechiae produced with the tourniquet test and repeat platelet counts 44 hours after drug ingestion were normal. This finding is possibly but not probab drug related. Only 4 of the 43 subjects were without at least one abnormal laboratory value in the hematologic or biochemical testing. The abnormalities observed were random, inconsistent or marginal. None of the abnormal values reported except as noted above were considered possibly drug related.

Urinalysis was normal at all times and in all subjects except for the following: Subject Code #124 receiving 5 mg drug had 9 WBC's per high powered field in the urinary sediment on day 3 only. Subject Code #161 receiving 1000 mg of drug had pyuria day 3 of 27 WBC's per high powered field and on day 7, 7 WBC's per high powered field. The urinalysis on the days of pyuria were otherwise normal and were completely normal on all other test days. The intermittent pyuria observed is not attributed to drug ingestion as it has been seen during previous studies with equal frequency in both drug and placebo administered subjects.

Individual Summary Forms:

Individual summary forms for each subject are presented on page 35 through 77.

CONCLUSION:

It was concluded that intolerance to single dose oral administration of WR 180,409·H_3PO_4 was manifested by combinations of nausea, vomiting, light-headedness and mental fuzziness. Intolerance was marginal at the 750 mg dose and definite but not universal at the 1250 mg dosage. The two subjects receivin 1500 mg both had multiple symptoms of intolerance. In no instance was the intolerance incapacitating and it was of less than 36 hours duration in all subjects.

RECOMMENDATIONS:

WR 180,409·H_3PO_4 is well tolerated in single oral dose administration at dose levels which may be efficacious. The intolerance manifestations to the drug are mild and not incapacitating. Therefore, it is recommended that bioavailability studies following single dose oral administration be performed.

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EXPERIMENT NO. 8: COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF WR 30090·HCl AND WR 30090·(OLEIC ACID)

ABSTRACT

WR 30090·HCl is an effective antimalarial against chloroquine resistant strains of P. falciparum. However, clinical usefulness is limited by the frequency of inadequate absorption following oral administration. WR 30090·(Oleic Acid) was formulated to improve absorption. Animal studies demonstrated an eightfold increase in absorption of the Oleic Acid as compared with the HCl formulation. The purpose of this study was to compare the bioavailability and pharmacokinetics of the two formulations.

Four subjects participated in the crossover study. Two subjects received 250 mg WR 30090·HCl followed 2 weeks later by 35 mg WR 30090·free base oleic acid. The sequence of drug administration was reversed for the other two participants.

Both formulations were well tolerated clinically in all subjects and no adverse reactions attributed to drug were observed.

The study was suspended following completion of the initial dose levels when it became evident additional refinement of the drug assay procedure was required.

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EXPERIMENT NO. 9:

MEFLOQUINE (WR 142,490·HCl): PHARMACOKINETICS FOLLOWING ORAL ADMINISTRATION

ABSTRACT

Mefloquine (WR 142,490·HCl), a substituted quinoline methanol is an effective, well tolerated single dose agent for the prevention and treatment of chloroquine resistant falciparum malaria.

Initial studies indicate the drug has a prolonged biologic hall life of 15-25 days in man. This study was performed to define the pharmacokinetic model for the absorption and elimination kinetics of orally administered single doses of mefloquine by nonlinear regression analysis of sequential blood levels of pa ent compound. In this double blind randomized study four grou of four subjects each received 250, 500, 1000, or 1500 mg mefl quine as tablets. A fifth group of 4 subjects received 500 mg mefloquine as an aqueous suspension. Sequential blood levels were measured during the 84 days following drug administration.

Symptoms compatible with drug effect were present in some subjects at all dose levels. The symptoms were fleeting and mild except at the highest dose level. Mefloquine was poorly tolerated at the 1500 mg dose level. At this dose level one subject had incapacitating rotational vertigo for two hours and all su jects had temporary symptoms including combinations of light-headedness with difficulty focusing and concentrating, dysphor headache, and gastrointestinal complaints. Fleeting and mild light-headedness occurred in three of the four subjects receiving 1000 mg mefloquine.

All subjects completed the 84 day study. Drug assay results and their statistical analysis are not available at the time of reporting.

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EXPERIMENT NUMBER 10

COMPARATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF WR 142,490·HCl (MEFLOQUINE HYDROCHLORIDE) AND MEFLOQUINE HYDROCHLORIDE·HLR*

ABSTRACT

Mefloquine hydrochloride, a substituted quinoline methanol, has been shown to be an effective single dose agent in the treatment of chloroquine-resistant P. falciparum malaria and effective for prophylaxis. The drug administered to human subjects in single doses up to 1000 mg was well tolerated. Intolerance at higher doses was manifested by temporary light-headedness, diarrhea, abdominal cramps, occasional nausea and/or vomiting. Symptoms were considered dose related and mild in all cases.

A variety of formulations have been used in previous tolerance and therapeutic studies. Clinical results in infected volunteers and blood level determinations in a limited number of pharmacokinetic studies indicate considerable variation in the bioavailability of these formulations. The use of a new formulation in field studies, such as the HLR formulation, must therefore be supported by prior demonstration of adequate bioavailability.

A study for comparative bioavailability of the HLR formulation and an established effective formulation, WR 142,490·HCl, was done. A classical two way balanced crossover design including 3 groups of 4 subjects each was used. Symptoms were absent or mild and temporary. Symptomatology attributed to drug ingestion included gastrointestinal symptoms and headache following ingestion of both formulations. Lightheadedness occurred only following administration of the WR formulation. No significant changes in physical examination or laboratory values attributed to drug administration were observed. In conclusion, WR 142,490·HCl and the F. Hoffmann-La Roche, & Co. formulation were both well tolerated under conditions of this study. Drug assay analysis is not yet available and will be reported separately at a later date by the responsible institution.

*F. Hoffmann-La Roche, & Co.

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FINAL REPORT

EXPERIMENT NUMBER 11

WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

ABSTRACT

WR 149,024 is 1, 18-diamino-6, 13-diaza-9, 10-dithiaoctadecane tetrahydrochloride.

$$(H_2N(CH_2)_5NHCH_2CH_2S-)_2 \cdot 4HCl$$

Preclinical studies have demonstrated the efficacy of WR 149,024 in the treatment of endotoxic, hemorrhagic, anaphylactic and traumatic injury shock in animal models. The mechanism of action appears to be reversible alpha adrenergic blockade.

This safety and tolerance study was performed to initiate testing in human subjects. Twenty-five subjects received from 1 mg to 720 mg WR 149,024 diluted in normal saline to a volume of 120 cc administered intravenously during a 120 minute interval. Drug infusion was discontinued in one subject because of ECG variation present prior to drug infusion. One subject developed temporary erythema and pruritis of the skin overlying the infusion vein during the infusion. No definite systemic drug effect was demonstrable, although 2 subjects at the higher dose levels had nausea (1 with emesis) and moderate, temporary orthostatic intolerance immediately upon completion of the infusion. The frequency of orthostatic intolerance at most dose levels, both prior to and upon completion of the infusion, does not permit attribution of orthostatic intolerance to drug effect. No changes related to infusion of WR 149,024 were observed in other physical, hematologic, or biochemical testing.

WR 149,024 was well tolerated and safe under conditions of this study. There was no evidence of pharmacologic effect. It is recommended more sensitive methods to detect WR 149,024 pharmacologic activity be used for future studies.

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FINAL REPORT

EXPERIMENT NUMBER 12

WR 194,965·H_3PO_4: SHORT TERM DOSAGE, SAFETY AND TOLERANCE: SINGLE ORAL DOSE, RISING DOSE LEVELS

ABSTRACT

WR 194,965·H_3PO_4 is an antimalarial agent classified as a "Mannich base". In pre-clinical studies it was more effective than SN 7744, another "Mannich base" which had been tested in human subjects.

WR 194,965·H_3PO_4 clinical testing was initiated in this study using a standard double-blind, rising single dose level method. Forty-six subjects participated, 24 subjects received drug and 22 received placebo. Nine dose levels were used ranging from 5 mg through 1250 mg.

Mild transient light-headedness, probably drug related, occurred in 2 of 4 subjects at the 1000 mg dose level. Approximately 3 hours after drug administration, 1 of the 2 subjects who received 1250 mg of drug developed light-headedness, anorexia, nausea, and emesis. These symptoms were moderately incapacitating for 11 hours then diminished and disappeared by 32 hours after onset. This subject also had recurrent elevation of serum bilirubin and marginal eosinophilia. There were no other significant abnormalities in either physical or laboratory findings. Another subject who received placebo in the same study group also had elevations of serum bilirubin reported on the same days as the subject who received drug. The other subject who received 1250 mg WR 194,965·H_3PO_4 had no symptoms, changes in physical findings or laboratory deviations that suggested adverse drug effect.

In conclusion, WR 194,965·H_3PO_4 was well tolerated up to the 1250 mg dose level. At this dose level one subject had significant symptomatology that can be related to drug administration. We recommend testing additional subjects at 1250 mg and appropriate higher dose levels to better define the top tolerated dose of WR 194,965·H_3PO_4.

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FINAL REPORT

EXPERIMENT NUMBER 13

WR 172,435·CH_3SO_3H: SHORT TERM DOSAGE, SAFETY AND TOLERANCE: SINGLE ORAL DOSE, RISING DOSE LEVELS

ABSTRACT

WR 172,435·CH_3SO_3H is an antimalarial agent classified as a pyridine methanol. In pre-clinical studies it was similar in effectiveness against P. falciparum malaria in the Aotus monkey to WR 180,409·H_3PO_4, another pyridine methanol, and appeared to be less toxic than WR 180,409·H_3PO_4 when administered to rodents.

WR 172,435·CH_3SO_3H clinical testing was initiated in this study using a standard double-blind, rising single dose level method. Eighteen administrations of drug and of placebo were used in a 2 x 2 design study. Eight dose levels were used ranging from 5 mg through 1000 mg.

Transient light-headedness or gastrointestinal symptoms occurred occasionally in subjects administered either placebo or drug at the lower dose levels. Temporary mild gastrointestinal symptoms were the only symptoms attributed to drug and occurred in 1 of 2 subjects receiving 800 mg and 2 of 4 subjects receiving 1000 mg WR 172,435·CH_3SO_3H. Leukocytosis without change in the differential count occurred in 9 study subjects. Seven of these received WR 172,435·CH_3SO_3H. Three of 4 subjects receiving 1000 mg had leukocytosis 24 hours post dosing which returned to normal by 48 hours.

WR 172,435·CH_3SO_3H was well tolerated up to the 1000 mg dose level. Symptoms at this dose level were not incapacitating and of less than 12 hours duration. The cause of transient leukocytosis is indeterminate. Safety and tolerance studies at and above the 1000 mg dose level may be undertaken if other considerations warrant additional testing.

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FINAL CLINICAL REPORT

ADDENDUM TO EXPERIMENT NUMBER 13

WR 172,435·CH_3SO_3H: SHORT TERM DOSAGE, SAFETY AND TOLERANCE· EFFECT ON THE TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE

ABSTRACT

WR 172,435·CH_3SO_3H is a pyridine methanol with demonstrated anti-malarial activity.

In Phase I clinical testing (BIO-MED, Inc. Experiment 13, Final Report, 6 December 1978,) administration of this drug was associated with leukocytosis - an increase in both neutrophils and lymphocytes. Leukocytosis was observed on day 2 with a return to normal on day 3. While the observations suggest a drug effect, the observations were retrospective.There was also an apparent association of gastrointestinal symptoms with drug administration

It was determined that a study specifically designed to detect leukocytosis and gastrointestinal symptoms was indicated. Therefore, Twelve volunteer subjects were divided into 3 groups of 4 subjects each. In a double blind study, by random assignment, 2 subjects of each group received a single 1000 mg oral dose of dru and two received a placebo.

Subjects were observed for symptoms, and white blood cell counts and differential counts were performed on each subject immediatel before dosing and at 5 minutes, 4, 8, 12, 24, 48 and 72 hours an at 14 days.

White blood cell counts rose to over 10,000 mm^3 in all subjects receiving the drug, marked by an absolute increase in neutrophils The white cell count increased in all subjects receiving the placebo, but none increased to 10,000 mm^3, and in only one instance did the absolute neutrophil count increase, and that to marginal degree. All subjects receiving 1000 mg of the drug developed gastrointestinal symptoms; none of the placebo group developed gastrointestinal symptoms.

It is concluded that WR 172,435·CH_3SO_3H, given in single 1000 mg dose per mouth in the formulation provided produced leukocytosis, marked by a neutrophil response, and gastrointestinal symptoms in 6 of 6 normal male subjects. Leukocytosis and symptomatology wer of less than 48 hours duration.

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ADDENDUM 2 TO EXPERIMENT NUMBER 13

WR 172,435·CH_3SO_3H: SHORT TERM DOSAGE, SAFETY AND TOLERANCE: MULTIPLE ORAL DOSES, RISING DOSE LEVELS

ABSTRACT

In a study of safety and tolerance with special emphasis on white blood cell elevations, the prospective antimalarial WR 172,435.CH_3SO_3H was given to 28 subjects in a 2 x 2, double-blind rising dose level experiment. The drug was administered in 3 divided doses over 24 hours at 4 total dose levels of 1200, 1400, 1600 and 1800 mg respectively.

The drug was well tolerated at the 1400 mg dose level (given 600,400,400). At higher levels, or with the 800, 600 schedule, subjects had one or more of a variety of complaints including abdominal pain and cramps, diarrhea,headaches, light-headedness and fatigue. At the 1800 mg dose level, these symptoms were debilitating. At every dose level, in at least one subject there was a transient increase in the total WBC with an increase in the number of mature circulating neutrophils.

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FINAL REPORT

EXPERIMENT NUMBER 14

PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART I

ABSTRACT

WR 180,409·H_3PO_4, a substituted pyridinemethanol, was administered as a single oral dose of 750 mg to four subjects in a pilot study. Two subjects each received a capsule formulation (Lafayette E-556) and two a new tablet formulation (INTERx D-522). This pilot study was performed to obtain preliminary absorption and elimination data from which optimum dosage scheduling and blood sampling times could be computed for subsequent parts of the study.

Gastrointestinal symptoms occurred in all subjects. Administration of the capsule formulation was associated with mild abdominal discomfort and passage of one loose stool in both subjects. One subject receiving the capsules also noted slight light-headedness and difficulty concentrating. Following administration of the tablet formulation, one subject passed a voluminous liquid stool and the other passed four stools with associated borborygmus. The latter subject also had a nightmare following drug administration.

The gastrointestinal signs and symptoms are considered drug related. The neurologic symptoms are considered possibly drug related.

No physical changes were observed. All subjects had two or more deviations of laboratory values beyond two standard deviations. A moderate SGOT elevation in one subject 24 hours after tablet ingestion is considered possibly, but not probably, drug related.

FINAL REPORT

EXPERIMENT NUMBER 14

PHARMACOKINETICS OF WR 180,409·H_3PO_4: (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION, CLINICAL OBSERVATIONS

PART II

ABSTRACT

Two formulations of WR 180,409·H_3PO_4 were compared for tolerance and pharmacokinetics using 12 subjects in a randomized order, crossover design.

The formulations were given as a single oral dose of 750 mg with a dosing interval of 28 days.

Significant gastrointestinal intolerance was observed with equivalent frequency and severity with both formulations.

Blood samples for drug assay have been submitted to the sponsor.

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FINAL REPORT

EXPERIMENT NUMBER 15

CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

ABSTRACT

WR 171,669, a phenanthrene methanol, has demonstrated good activity against chloroquine-resistant P. falciparum malaria. In the experiment reported here, the drug was tested in healthy, volunteer subjects to determine the maximum tolerated single dose and to study the pharmacokinetics.

Twenty-eight subjects, assigned to 7 groups of 4 subjects each, were given single doses of the drug by mouth in amounts ranging from 750 to 2000 mg in a 2 x 2, double-blind, rising dose level design. Clinical observation and pharmacokinetic samplings were conducted over a period of two weeks for each subject.

No disabling or disruptive symptoms occurred. No abnormal physical findings developed. Biochemical and hematologic abnormalities in the drug and placebo groups were equivalent. However, the temporal pattern of SGPT elevation in two subjects suggested transient hepato-toxicity.

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FINAL CLINICAL REPORT

EXPERIMENT NUMBER 16

WR 229,870 (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE

ABSTRACT

In accordance with the approved protocol "WR 229,870 (Sodium Stibogluconate Injection, BP): Pharmacokinetics Following a Single Intravenous Dose", eight volunteer male subjects received 600 mgm of Sodium Stibogluconate Injection intravenously over a period of ten minutes. No acute intolerance was seen. Blood specimens and urine specimens appropriate for antimony assay were collected at the designated intervals for determination of the pharmacokinetics of sodium stibogluconate. Antimony assays had not been done at the time of this report.

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 17

WR 180,409·H_3PO_4: SHORT TERM MULTIPLE DOSES, SAFETY, TOLERANCE AND PHARMACOKINETICS

ABSTRACT

In a double-blind study of safety and tolerance, 32 healthy male subjects were each given from 750 to 1500 mg of the drug WR 180,409·H_3PO_4, or placebo, in 3 doses over a period of 24 hours. Blood specimens were collected at the designated times and sent to the Department of Pharmacology, Walter Reed Army Institute of Research, for determination of the pharmcokinetics of WR 180,409·H_3PO_4 in multiple doses.

Although mild gastrointestinal symptoms or lightheadedness were observed in one of every four subjects receiving the drug, there was no apparent dose/response relationship and equivalent symptoms were also encountered in subjects receiving placebo. No clear-cut signs of intolerance were noted at any dose level administered.

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 18

WR 194,965·H_3PO_4: SHORT TERM SAFETY AND TOLERANCE TO THREE DIVIDED DOSES, RISING DOSE LEVELS.

ABSTRACT

In a double-blind study of safety and tolerance, 44 healthy male subjects were each given from 1000 to 2500 mg of the drug WR 194,965·H_3PO_4, or placebo, in 3 doses over a period of 24 hours. Symptomatology, physical status, laboratory tests, phototoxicity and electrocardiographic rhythm strips were used to study the safety and tolerance of the drug.

At the highest dose level, one subject who received the drug had moderately debilitating gastrointestinal symptoms; the other had marked "light-headedness". Mild, non-debilitating symptoms were noted in drug recipients at the lower dose level. Placebo subjects had the expected array of non-specific complaints. The other variables observed showed no consistent differences between drug and placebo subjects.

The drug was well-tolerated at 2000 mg with no reported symptoms; it appeared to produce mild symptoms at 2250 mg and significant symptoms at 2500 mg.

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 21

WR 6026 2HCl: Short Term Dosage, Safety and Tolerance Study Single Oral Dose, Rising Dose Levels

ABSTRACT

Under DAMD Contract 17-75-C-5036, 44 healthy subjects were given increasing single oral doses of WR 6026 2HCl or placebo (1 mg - 60 mg, 11 dose levels) in a double blind study of safety and tolerance. There were no physical abnormalities and no symptoms that could be attributed to drug effect. No abnormalities were reported in serial methemoglobin and haptoglobin concentrations. Variations from normal in CO_2, total protein, globulin and the reticulocyte count were greater in the subjects receiving drug than in the subjects receiving placebo. These variations are judged to be not clinically significant. WR 6026 2HCl, given orally up to 60 mg in a single dose, was safe for healthy males under the conditions of this experiment. The drug was well tolerated up to and including 60 mg/dose.

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