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Army Drug Development Program
Phase I
Clinical Testing

Annual Report

John A. Johnson, M.D.

February 1981

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, 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)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A148 919	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Army Drug Development Program Phase I Clinical Testing		5. TYPE OF REPORT & PERIOD COVERED Annual Report Feb 1980 - Jan 1981 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) John A. Johnson, M.D.		8. CONTRACT OR GRANT NUMBER(s) DAMD 17-75-C-5036
9. PERFORMING ORGANIZATION NAME AND ADDRESS BIO-MED, Inc. 4401 Hartwick Road College Park, Maryland 20740		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 63764A.3M463764D995.AA.041
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Development Command Fort Detrick, Frederick, Maryland 21701-5012		12. REPORT DATE February 1981 13. NUMBER OF PAGES 214
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release;
distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Phase I Clinical Testing, Antimalarial, Antileishmanials, Human Subjects, Pharmacokinetics, Comparative Bioavailability, WR 229,870, WR 171,669, WR 180,409, WR 172,435, WR 194,965, Automatic Data Processing.

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

From February 1980 through January of 1981, research was continued at BIO-MED, Inc. under contract DAMD 17-75-C-5036 "Phase I Clinical Studies: The Army Drug Development Program". Programs and Activities under this contract include:

Experiment No. 16: WR 229,870: (Sodium Stibogluconate Injection BP) Pharmacokinetics Following a Single Intravenous Dose

(cont'd)

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. Abstract (continued)

Experiment No. 15: Continuation of Single Dose Rising Dose Level Studies with Orally Administerd WR 171,669: Short Term Safety and Tolerance.

Experiment No. 14: Pharmacokinetics of WR 180,409·H_3PO_4: (A Pyridinemethanol) Following Oral Administration.

Addendum No. 2 to Experiment No. 13: WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels.

Experiment No. 17: WR 180,409·H_3PO_4: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.

Experiment No. 18: WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

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

SUMMARY

In this reporting period, BIO-MED, Inc. continued to design and implement Phase I clinical studies in support of the Army's drug development program.

Studies of WR 180,409 H_3PO_4, a Pyridinemethanol with promising antimalarial activity, were completed. In a study (Part I, Experiment #14) of tolerance and bioavailability of a capsule and a tablet preparation, all subjects developed mild gastrointestinal symptoms after receiving 750 mg of the drug orally. In a further comparative experiment (Part II, Experiment #14), tolerance and pharmacokinetics were studied using twelve subjects in a crossover design with each subject receiving a tablet and a capsule formulation containing 750 mg. Significant gastrointestinal intolerance was observed with equivalent frequency and severity with both formulations.

The intolerance to a single 750 mg dose of this drug led to the development of Experiment #17 wherein it is proposed that the drug be administered in three divided doses in a rising dose schedule to the level of intolerance. That protocol has been approved by the Institutional Review Board of BIO-MED, Inc. and has been submitted to the sponsor for their approval.

WR 171,669, a phenanthrene methanol with demostrated activity against chloroquine resistant P. Falciparum malaria, was studied in a single dose, double-blind, rising dose schedule in 28 subjects ~~(Experiment #15)~~. Doses up to 2000 mg produced no symptoms. SGPT elevations in two subjects admit the possibility of mild, transient hepatotoxicity.

In a study of the pharmacokinetics of WR 229, 870 (Sodium Stibogluconate Injection, BP) a single intravenous dose of 600 mg of Pentostam® was given to eight subjects. No acute intolerance developed. Blood and urine specimens were collected as scheduled and submitted to the sponsor for antimony assay. Preliminary reports show excellent pharmacokinetic data.

BIO-MED, Inc. had previously reported that the oral administration of a single 1000 mg dose of WR 172,435 was associated with a transient neutrophilic leucocytosis. A study was implemented (Addendum 2 to Experiment #13) to study the safety and tolerance of the three divided doses of the drug given at 12 hour intervals. After one group of four subjects had been studied, this project was suspended because of problems with the drug formulation. (See "Progress Report", Addendum 2 to Experiment #13).

In previous studies of WR 194,965·H_3PO_4 (an antimalarial of the Mannich base class), the top tolerated single dose in man was found to be less than the dose that cured 100% of Aotus monkeys infected with falciparum malaria. A protocol (Experiment #18) has been developed at BIO-MED, Inc. and approved by their Institutional Review Board which would establish the highest well-tolerated dose of the drug in three divided doses.

FOREWORD

Phase I clinical studies of drugs under development by the U.S. Army Research and Development Command (USAMRDC) were performed at the clinical facility of BIO-MED, Inc. under the terms of the contract DAMD17-75-C-5036. All protocols were jointly reviewed by BIO-MED, Inc. and the Division of Experimental Therapeutics of the Walter Reed Army Institute of Research, and approved by the Institutional Review Board of BIO-MED, Inc. and the Human Subjects Research Review Board, Office of the Surgeon General, Department of the Army before implementation at BIO-MED, Inc.

Special assurance for the conduct of these studies has been extended from the Headquarters of the USAMRDC to BIO-MED, Inc.

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

TABLE OF CONTENTS

TITLE	PAGE
Title Page	1
Report Documentation (DD1473)	2
Summary	5
Foreword	7
Objectives	9
Methods and Results	9
Conclusions	9

Study Reports and New Protocols:

1. Final Report: Experiment No. 14: Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration.

2. Final Report: Experiment No. 15: Continuation of Single Dose Rising Dose Level Studies with Orally Administered WR 171,669: Short Term Safety and Tolerance.

3. Final Report: Experiment No. 16: WR 229,870:(Sodium Stibogluconate Injection BP) Pharmacokinetics Following A Single Intravenous Dose.

4. Progress Report: Addendum No. 2 To Experiment No. 13:WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels.

5. Protocol: Experiment No. 17: WR 180,409·H_3PO_4: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.

6. Protocol: Experiment No. 18: WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

Distribution List

OBJECTIVES

General: The general objective of this contract was to continue to provide support to the Army Drug Development Program by conduction Phase I studies of safety, tolerance and pharmacokinetics following procedures which fully conform with DHW guidelines for the protection of the health and rights of human subjects.

Specific: The specific objectives for each study conducted are detailed in the attached reports.

METHODS AND RESULTS

The Methods and Results are detailed in the attached reports. At the time of this submission, pharmacokinetic data from the studies conducted were not available. As the data become available, interim supplementary reports will be submitted.

CONCLUSIONS

1. WR 180,409·H_3PO_4 is not well tolerated in man in a single oral dose at the estimated curative level. Tolerance to divided doses should be studied.

2. WR 171,669 was subjectively well tolerated in man up to the 2000 mg single oral dose level. Further consideration of a possible drug related SGPT elevation is required.

3. Optimal dose schedules for Sodium Stibogluconate can be determined when the pharmacokinetic analysis is complete. A single intravenous dose of 600 mg given over 10 minutes is well tolerated in the normal subject.

4. WR 172,435 should be reformulated, and studied further to determine tolerance with multiple doses.

5. WR 194,965·H_3PO_4 should be further studied to establish tolerance to multiple doses.

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FINAL REPORT

ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 14

PART I

TITLE:	PHARMACOKINETICS OF WR 180,409·H_3PO_4: (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PRINCIPAL INVESTIGATOR:	JOHN A. JOHNSON, M.D.
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FINAL REPORT

EXPERIMENT NUMBER 14

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

PART I

TABLE OF CONTENTS

SUBJECT	PAGE
ABSTRACT	13
INTRODUCTION	14
METHODS AND MATERIALS	15
RESULTS	20
DISCUSSION	21
CONCLUSIONS AND RECOMMENDATIONS	21
Table III - Symptoms	23
Table IV - Laboratory Abnormalities Table	24
Individual Subject Final Summary Sheets	25-28

APPENDIX: a. Explanation for Potential Subjects
b. Consent Form

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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.

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FINAL REPORT

EXPERIMENT NUMBER 14

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

INTRODUCTION:

WR 180,409·H_3PO_4, a substituted pyridinemethanol, is the first compound of this chemical class to be tested in the U.S. Army Antimalarial Program. It represents a potential new class of antimalarial drug. In animal test systems the compound was exceptionally well tolerated and had excellent antimalarial activity. The acute oral LD_{50} was 900 mg/kg in mice. In rats, the acute LD_{50} was 500 mg/kg. Clinical and pathological examination of rats 72 hours after a single oral dose of 100 mg/kg detected no adverse effect; a single oral dose of 300 mg/kg caused some decrease in weight; and 900 mg/kg caused weight loss, bleeding around the eyes, depression of lymphoid tissue and degenerative changes in the liver. When administered to beagle dogs, doses of 37 mg/kg or higher frequently caused vomiting. The drug was curative against the chloroquine-resistant Vietnam Smith strain of Plasmodium falciparum in the Aotus monkey when administered orally at a dose of 2.5 mg/kg/day for 7 days, at a dose of 12 mg/kg/day for 3 days, and as a single oral dose of 35 mg/kg.

A clinical Phase I safety and tolerance study with WR 180, 409·H_3PO_4 was recently completed. Single doses of 5 to 1500 mg were administered to a total of 22 subjects in a double-blind rising dose study. Intolerance to the drug was manifested by nausea, vomiting, dizziness and "mental fuzziness."

One or more of these symptoms occurred in 3 of the 4 subjects receiving 1000 mg and 3 of the 4 subjects taking 1250 mg. Two subjects administered 1500 mg of WR 180,409·H_3PO_4 as a single dose experienced similar symptoms. Onset of symptoms was generally within 8 hours of drug administration, though 1 individual who took 1500 mg vomited 24 hours later. In all cases, the symptoms had subsided by 32 hours after dosing. There were no physical abnormalities or laboratory abnormalities attributed to the drug.

In this pilot study, 2 formulations were compared, and more definitive data concerning the relative bioavailability and pharmacokinetics of the drug was obtained following analysis of the drug assay specimens.

METHODS AND MATERIALS:

Subject Qualification

Four male subjects, 21-34 years of age, weighing between 61 and 79 kg and within 10% of their ideal body weight, were employed for the study. They were recruited from the Washington, D.C. metropolitan area. Subjects were hired by BIO-MED, Inc. as temporary employees for study purposes.

Candidates for employment were presented with a complete explanation of the background and procedures to be used in the study and of all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually in the presence of an investigator and a member of the Human Use Committee. Each participant was given the opportunity to ask questions. The consent form was then read and signed in the presence of a witness, investigator and a member of the Human Use Committee.

Candidates were screened to obtain subjects for the study. The medical evaluation included a comprehensive history and physical examination, chest X-ray, 12 lead electrocardiogram, urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin and G6PD.

Subject acceptability criteria was based upon the precept that the risks of participation should be slight and comparable for all subjects. Following this guideline, certain candidates were rejected routinely: for example, candidates with organic heart murmurs, splenomegaly or active lesions on chest X-ray.

The presence of conditions which did not increase risk or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes were not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean were cause for rejection. Deviations between 2 and 3 standard deviations from the mean were generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/kg would have caused rejection, whereas a serum sodium of 153 mEq/L of itself would not.

In addition to the above qualifications, no candidate having received the drug WR 180,409·H_3PO_4 previously was permitted to participate in this study.

Whenever doubt existed concerning the eligibility of a candidate, a decision was made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates were given full consideration and the integrity and ethics of the Research Team protected.

Procedures:

Four subjects were admitted, beginning 1 day prior to drug administration, and housed for a period of 4 days in a controlled environment in Nursing Unit 5W of the Washington Hospital Center. Two of the subjects were given the tablet formulation (INTERx D-522) and two were given the capsule formulation (Lafayette E-556).

Physical examinations, interviews, vital sign measurements, laboratory tests, and drug assay samplings were conducted according to the Schematic Study Plan (Table I) and the Assay Specimen Collection Schedule (Table II). On study day 4, the subjects were released from the controlled environment, returning for the various evaluations and blood samplings as indicated through study day 21, the last day of observation. On study day 21, final physical and laboratory evaluations were conducted. All abnormal findings caused follow-up until normalcy, stabilization, or proper medical disposition was secured.

The clinical and laboratory evaluation of the subjects is outlined below.

TABLE I

SCHEMATIC STUDY PLAN

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	14 Mon	21 Mon
Dose		X						
Physical Exam	X		X					X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Laboratory Tests+	X		X					X
Blood for Drug Assay++		X	X	X	X	X-----	X	X
Immunologic Studies+++	X		X					

*Controlled Environment

+ Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis.

++ Drug Assay: Each subject immediately prior to drug administration and after dosing at 1, 2, 4, 6, 8, 12, 16, 24, 28, 30, 36, 40, 44, 48, 60, 72 hours; and on study days 5, 7, 8, 14, and 21.

+++ In addition to the blood samples listed above, 10 ml clotted blood and 20 ml heparinized blood were drawn on day 0 (prior to drug administration) and again on day 2 (1 day after drug administration). The 20 ml sample was drawn through a 19 gauge needle into a heparin-rinsed syringe containing <0.5 ml heparin. It was stored in the syringe at room temperature, and transported to the Department of Gastroenterology, Walter Reed Army Institute of Research. The heparinized samples were used to determine the proportion of circulating T-lymphocytes (E-rosettes) and B-lymphocytes (EAC-rosettes). These results were reported directly to the Contracting Officer Technical Representative.

Drug Administration:

WR 180,409·H_3PO_4 was supplied as 250 mg tablets (INTERx D-522) and capsules (Lafayette E-556). Assigning subject code numbers for drug formulation was done by lottery. Each subject received 750 mg of the drug on day 1. The drug was ingested in the presence of a staff nurse. Subject code no. 345 was dosed 7 days later than the other 3 subjects.

On the day of drug administration, the subjects fasted from 2400 to 0600, at which time they were given 360 ml Sustacal (Mead Johnson product) containing a total of 360 calories. They drank water ad lib until 6 hours after dosing, at which time they ate a light lunch. Nine hours after dosing they resumed a regular diet which they selected from the hospital menu.

Laboratory Tests Specimen Collection:

On study days 0, 2, and 21 hematologic and biochemical blood profiles were conducted. For these profiles, 27 ml venous blood were obtained before breakfast. Seven ml of blood were used for determination of white blood cell and differential count, red blood cell count, hematocrit, hemoglobin, MCH, MCV, MCHC, and platelet count. Twenty ml of the venous blood were centrifuged and the serum separated into 2 samples. One sample was used on the day obtained to determine the values for serum glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin. The other sample was stored in the refrigerator as a "back-up" until the biochemical lab report was received. Thereafter, it was stored in the freezer until released by the investigator.

Urinalysis was conducted for each subject on study days 0, 2, and 21, consisting of pH, glucose, protein, specific gravity, white blood cell count, red blood cell count, and presence of amorphous sediment. Laboratory results are presented on page 11.

Drug Assay Specimen Collection and Time Schedule:

Ten ml of venous blood were drawn by a staff nurse for each drug assay. Six ml of the blood were transferred to a heparin-rinsed teflon capped glass tube and stored at -20°C pending transport to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. The drug was assayed as a parent compound by high pressure liquid chromatography. Four ml of the blood were centrifuged and the serum separated. The serum was transported to the Department of Pharmacology, WRAIR, for bioassay of antimalarial activity.

EXPERIMENT NUMBER 14 PART I

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

TABLE II: ASSAY SPECIMEN COLLECTION SCHEDULE

DAY OF STUDY	SPEC. NUMBER	SPEC. TIME	SPEC. VOLUME
Day 1	1	-15 min.	10
Tuesday	2	1 hr.	10
	3	2 hrs.	10
	4	4 hrs.	10
	5	6 hrs.	10
	6	8 hrs.	10
	7	12 hrs.	10
Day 2	8	16 hrs.	10
Wednesday	9	20 hrs.	10
	10	24 hrs.	10
	11	28 hrs.	10
	12	30 hrs.	10
	13	36 hrs.	10
Day 3	14	40 hrs.	10
Thursday	15	44 hrs.	10
	16	48 hrs.	10
	17	60 hrs.	10
Day 4 Friday	18	72 hrs.	10
Day 5 Saturday	19	96-98 hrs.	10
Day 7 Monday	20	144-146 hrs.	10
Day 8 Tuesday	21	168-170 hrs.	10
Day 14 Monday	22	312-314 hrs.	10
Day 21 Monday	23	480-482 hrs.	10
		Total	230 ml

RESULTS:

Symptoms:

Signs and symptoms possibly attributable to drug ingestion are presented as Table III, page 10.

All subjects had gastrointestinal signs and symptoms. Following administration of formulation E-556, subject code no. 345 had mild abdominal discomfort starting 1 hour after drug administration and terminating with the passage of 1 loose stool 2 hours and 10 minutes after drug administration. Subject code no. 347, also receiving capsule formulation E-556, evacuated 1 loose stool with associated mild abdominal discomfort 3 hours and 15 minutes after drug administration. Additionally, this subject experienced recurrent light-headedness for 10 minutes starting 7 hours after dosing followed by difficulty concentrating when reading which persisted for approximately 7 hours.

The 2 subjects receiving the D-522 tablet formulation also had gastrointestinal symptoms. Subject code no. 348 evacuated 1 voluminous liquid stool 3 hours and 30 minutes after drug administration and subject code no. 346 passed 2 semiformed and then 2 liquid stools with borborygmus starting 1 hour and 30 minutes after dosing and ending 50 minutes later. Subject code no. 346 also had a nightmare 16 hours following drug administration.

The symptoms were mild, not incapacitating, and of less then 8 hours duration.

Laboratory Values:

Laboratory value deviations were minimal or inconsistent. Subject code no. 346, with an SGOT value of 37 U/L on day 0, had an isolated elevation to 58 U/L 24 hours after drug administration with a normal value of 29 U/L reported on the next determination on day 21. See Table IV: Laboratory Abnormalities.

DISCUSSION:

The occurrence of loose stools in all subjects suggests a drug effect independent of the specific formulation: capsule and tablet administration were both followed by loose stools with associated abdominal symptoms between 1.5 and 3.5 hours following administration. The neurologic symptoms of light-headedness and difficulty concentrating while reading observed by subject code no. 347 after ingestion of capsule formulation E-556 is considered possibly drug related since similar symptoms were present at higher dose levels in other studies. Finally, the nightmare experienced by subject code no. 346 after administration of tablet formulation D-522 is considered possibly but not probably drug related since sleep disturbances have occurred in both control and drug administered subjects in previous studies.

Mild elevation of the SGOT value (58 U/L) isolated to the determination 24 hours after ingestion of the tablet (D-522) for subject code no. 346 is considered probably not drug related as no pattern of SGOT elevation was observed in a previous safety and tolerance study[1].

CONCLUSIONS AND RECOMMENDATIONS:

The administration of WR 180,409·H_3PO_4, both as a tablet (2 subjects) and capsule (2 subjects), was followed by the passage of one or more loose stools and associated abdominal discomfort between 1 hour and 30 minutes and 3 hours and 30 minutes following oral ingestion of 750 mg drug. These gastrointestinal signs and symptoms are considered drug related. The occurrence of transient light-headedness and more prolonged difficulty in concentrating experienced by one subject receiving the E-556 capsule formulation, is considered possibly drug related. The sleep disturbance in 1 subject following administration of D-522 tablets and the minimal elevation of SGOT occurring 24 hours after drug administration in this subject are both considered possibly but not probably drug related.

[1] Experiment No. 7: WR 180,409·H_3PO_4: Short Term Dosage Safety and Tolerance, Rising Single Dose Levels

Administration of the capsule formulation E-556 in a previous safety and tolerance study (reference: BIO-MED, Inc. Final Report No.7) was not associated with frequent loose stools, even up to doses of 1500 mg. In that study only 1 subject had a loose stool. That subject received 750 mg drug. It is possible that lower gastrointestinal tract signs and symptoms associated with the administration of both formulations would be prevented if the drug were administered with food.

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART I TABLE III: Symptoms

Group	CODE NUMBER	FORMULATION	Nausea		Emesis		Loose Stool		Other	
			Onset *	Duration+	Onset	Duration	Onset	Duration	Onset	Duration
I	345	E-556 capsules					1 loose stool 2.2	<0.1	Vague abdominal sensation,"queasy",relieved w/stools 1.0	1.2
I	346	D-522 tablets					1.5 semiformed 1.8 semiformed 2.2 liquid 2.3 liquid	<0.1 <0.1 <0.1	Nightmare 16.0	
I	347	E-556 capsules					1 loose stool with mild discomfort 3.25	<0.1	Mild abd. discomfort assoc. w/stools 3.5 Light-headedness 7.0 Difficulty concentrating when reading 8.0	<0.1 0.2 7.0
I	348	D-522 tablets					1 voluminous liquid stool 3.5	<0.1		

* Onset hrs. after dosing + Duration hrs. after onset

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART I TABLE IV: Laboratory Abnormalities Table

Group	Lot No. Dose 750 mg	Code Number	Tests	Study Days Scr	0	2	21	Normals
I	Lafayette E-556	345	Glucose	97	94	137H	102	66 - 114 mg/dl
			Uric Acid	8.7H	8.5H	7.3	7.7	4 - 8 mg/dl
			Alka.Phos.	80	69	69	95H	29 - 94 U/L
I	INTERx D-522	346	SGOT	16	37	58H	29	0 - 47 U/L
			Gamma A globulin	--	320H	310H	--	60 - 297 mg/dl
			Gamma G globulin	--	770	550L	--	635 -1400 mg/dl
I	Lafayette E-556	347	Glucose	76	78	88	58L	66 - 114 mg/dl
			Albumin	4.9	4.7	5.2H	4.9	4.1 - 5.1 mg/dl
			Gamma M globulin	--	410H	240	--	41 - 248 mg/dl
			Mono	4	10	10	12H	0 - 10 %
I	INTERx D-522	348	Total Protein	6.7	6.3L	6.6	6.9	6.4 - 8.0 g/dl
			Globulin	1.7L	1.7L	1.8	2.1	1.8 - 3.4 g/dl
			Eosin	5	7H	7H	7H	0 - 5 %
			Gamma A globulin	--	52L	56L	--	60 - 297 mg/dl
			Gamma M globulin	--	37L	38L	--	41 - 248 mg/dl

KEY: H - high L - low -- not done

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART I

TOTAL DOSE: 750 mg DOSING DATE: 6/19/79 CODE: 345 AGE: 35
DOSE PER Kg: 9.94 mg/kg TIME DOSED: 0900 GROUP: I-A
FORMULATION: E-556 HEIGHT: 176.53 cm WEIGHT: 75.41 kg

ABNORMALITIES

DATE: 1979	6/14	6/18	6/19	6/20	6/21	6/22	6/25	7/2	7/9
STUDY DAY:	Scr	0*	1*	2*	3*	4	7	14	21
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X	X		X					X
6. CBC									
7. Platelets									
8. Immunoglobulins									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	21	Normal Range
Glucose	97	94	137H	102	66-114 mg/dl
Uric Acid	8.7H	8.5H	7.3	7.7	4-8 mg/dl
Alka.Phos.	80	69	69	95H	26-94 U/L

KEY: H - high L - low

Symptoms and Physical Findings: Starting 1 hour after drug administration the subject experienced a vague abdominal sensation which slowly increased and was defined as a "queasy" sensation at 2 hours followed 10 minutes later by a loose stool. Immediately after stooling the subject became and remained asymptomatic. Physical examination was unchanged throughout the study interval.

Abnormalities Comment: Laboratory abnormalities were minimal or inconsistent and not considered related to study participation.

Conclusion: Abdominal symptoms initiated 1 hour after drug administration and ending with passage of a loose stool 2 hours and 10 minutes after drug administration considered related to ingestion of formulation E-556 of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART I

TOTAL DOSE: 750 mg DOSING DATE: 6/12/79 CODE: 346 AGE: 26
DOSE PER Kg: 9.53 mg/kg TIME DOSED: 0800 GROUP: I
FORMULATION: D-522 HEIGHT: 184.15 cm WEIGHT: 78.70 kg

ABNORMALITIES

DATE: 1979	6/6	6/11	6/12	6/13	6/14	6/15	6/18	6/25	7/2
STUDY DAY:	Scr	0*	1*	2*	3*	4	7	14	21
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry				X					
6. CBC									
7. Platelets									
8. Immunoglobulins		X		X					

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	21	Normal Range
SGOT	16	37	58H	29	0-47 U/L
IgA	-	320H	310H	-	60-297 mg/dl
IgG	-	770	550L	-	635-1400mg/dl

KEY: H - high L - low -- not done

Symptoms and Physical Findings: The subject passed 2 semiformed stools between 1.5 and 2 hours after drug administration. This was followed during the next 20 minutes by 2 liquid stools with associated gastrointestinal "rumbling". Therefore the subject had a total of 4 stools beginning 1.5 hours and ending 2 hours and 20 minutes after drug administration. The subject also experienced a nightmare approximately 16 hours after drug administration. There were no other symptoms during the study interval and the physical examination remained unchanged.

Abnormalities Comment: Slight SGOT elevation to 58 U/L was reported on day 2 with normal values preceding and following that isolated elevation. Minimal deviations in immunoglobulins is not considered study related.

Conclusions: SGOT elevation isolated to the day following drug administration and the nightmare occurring approximately 16 hours after drug administration possibly but not probably drug related. Gastrointestinal symptoms with the passage of 4 stools beginning 1.5 hours after drug administration considered related to ingestion of Formulation D-522 of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART I

TOTAL DOSE: 750 mg DOSING DATE: 6/12/79 CODE: 347 AGE: 21
DOSE PER Kg: 12.34 mg/kg TIME DOSED: 0800 GROUP: I
FORMULATION: E-556 HEIGHT: 164.46 cm WEIGHT: 60.78 kg

ABNORMALITIES

DATE: 1979	2/1	6/11	6/12	6/13	6/14	6/15	6/18	6/25	7/2
STUDY DAY:	Scr	0*	1*	2*	3*	4	7	14	21
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry				X					X
6. CBC									X
7. Platelets									
8. Immunoglobulins		X							

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	21	Normal Range
Glucose	76	78	88	58L	66-114 mg/dl
Albumin	4.9	4.7	5.2H	4.9	4.1-5.1 mg/dl
Monocytes	4	10	10	12H	0-10 %
IgM	-	410H	240	-	41-248 mg/dl

KEY: H - high L - low - not done

Symptoms and Physical Findings: Three and one-quarter hours after drug administration the subject passed 1 loose stool with associated mild abdominal discomfort. No further gastrointestinal symptomatology occurred. Seven hours after drug administration, for an interval of 10 minutes, the subject felt "lightheaded off and on". One hour later the subject noted a nonspecific "difficulty concentrating when reading". This symptom persisted for approximately 7 hours. Thereafter the subject was asymptomatic. The physical examination remained unchanged during the study.

Abnormalities Comment: Minimal laboratory deviations reported are not considered of clinical significance nor related to study participation.

Conclusion: Neurologic symptoms possibly related to drug administration. The loose stool with mild abdominal discomfort occurring 3.5 hours after administration of Lafayette lot number E-556, WR 180,409·H_3PO_4, probably drug induced.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART I

TOTAL DOSE: 750 mg DOSING DATE: 6/12/79 CODE: 348 AGE: 26
DOSE PER Kg: 11.17 mg/kg TIME DOSED: 0800 GROUP: I
FORMULATION: D-522 HEIGHT: 174.62 cm WEIGHT: 67.13 kg

ABNORMALITIES

DATE: 1979	5/29	6/11	6/12	6/13	6/14	6/15	6/18	6/24	6/25	7/2
STUDY DAY:	Scr	0*	1*	2*	3*	4	7	13	14	21
1. Symptoms			X					X		
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry	X	X								
6. CBC		X		X						X
7. Platelets										
8. Immunoglobulins		X		X						

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	21	Normal Range
Total Protein	6.7	6.3L	6.6	6.9	6.4-8.0 g/dl
Globulin	1.7L	1.7L	1.8	2.1	1.8-3.4 g/dl
Eosinophils	5	7H	7H	7H	0-5 %
IgA	-	52L	56L	-	60-297 mg/dl
IgM	-	37L	38L	-	41-248 mg/dl

KEY: H - high L - low - not done

Symptoms and Physical Findings: Three and one-half hours after administration of INTERx lot D-522 the subject passed a voluminous liquid stool without associated symptoms and without recurrence. Twelve days following drug administration, and for approximately 3 days, the subject had symptoms of the common cold without fever. The subject was otherwise asymptomatic and physical examination was unchanged throughout the study interval.

Abnormalities Comment: Minimal eosinophilia present before and after drug administration not considered study related. Other minimal laboratory deviations present before and after drug administration not considered significant or related to study participation.

Conclusion: One voluminous liquid stool 3.5 hours post drug administration attributed to administration of formulation D-522, WR 180,409·H_3PO_4.

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EXPLANATION
ANTIMALARIAL DRUG PROJECT
EXPERIMENT NUMBER 14
Pharmacokinetics of WR 180,409·H_3PO_4
(A Pyridinemethanol) Following Oral Administration

GENTLEMEN:

This document explains the nature of the study, its purpose, procedures, risks, and benefits. You will be given the opportunity after reading it to ask additional questions. The present study will be conducted in three parts. If you choose to participate as a research subject, you may select only one of the three parts of the study.

The study for which you have applied involves taking by mouth the antimalarial drug WR 180,409·H_3PO_4, (A Pyridinemethanol). WR 180,409·H_3PO_4, a substituted pyridinemethanol, is the first compound of this chemical class to be tested in the U.S. Army Antimalarial Program. It represents a potential new class of antimalarial drug. In animal test systems, the compound was exceptionally well tolerated and had excellent antimalarial activity.

A Clinical Phase I safety and tolerance study with WR 180,409·H_3PO_4 was recently completed. Single doses of 5 to 1500 mg were administered to a total of 22 subjects in a double-blind rising dose study. Intolerance to the drug occurred at the 1000 mg dose level. One or more symptoms occurred including nausea, vomiting, dizziness and "mental fuzziness". Onset of symptoms was generally within 8 hours of drug administration, though one individual who took 1500 mg vomited 24 hours later. In all cases, the symptoms had subsided by 32 hours after dosing. There were no physical abnormalities or laboratory abnormalities attributed to the drug.

There are no data from human studies concerning the absorption and elimination pattern of this drug. In order to design further Phase I and Phase II studies with WR 180,409·H_3PO_4 additional information is needed to accurately determine the pattern in which the drug is absorbed and excreted. Therefore, the present study will be conducted in three parts.

Part I.

An initial pilot study will be conducted in which 750 mg of the drug will be administered orally to four subjects. Two will be given the drug in the form of a 250 mg capsule formulation and two will be given the drug in the form of a 250 mg tablet formulation. Ten ml of blood will be drawn at the times specified in Table I-A, page 13, to measure the drug serum concentrations to determine rates of absorption and elimination.

The schedule for Part I of the study is presented in the following schematic.

TABLE I

SCHEMATIC STUDY PLAN FOR PART I - PILOT STUDY

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	14 Mon	21 Mon
Dose		X						
Physical Exam	X		X					X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Laboratory Tests[+]	X		X					X
Blood for Drug Assay[++]		X	X	X	X	X——X		X
Immunologic Studies[‡]	X		X					

*Controlled Environment

[+]Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

[++]Drug Assay: Each subject immediately prior to drug administration, and after dosing at 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 30, 36, 40, 44, 48, 60, 72 hours; and on study days 5, 7, 8, 14, and 21. (See Table I-A, page 13)

[‡]In addition to the blood samples listed in the protocol, 10 ml of clotted blood and 20 ml of heparinized blood will be drawn on Day 0 (prior to drug administration) and again on Day 2 (1 day after drug administration). The 20 ml sample will be drawn through a 19 gauge needle into a heparin rinsed syringe containing < 0.5 ml heparin. It will be stored and transported in the syringe at room temperature. These specimens will be used to measure serum IgG, IgM, and IgA, and to determine the proportion of circulating T-lymphocytes (E-rosettes) and B-lymphocytes (EAC-rosettes).

TABLE I-A: WR 180,409·H_3PO_4 (A Pyridinemethanol)
Specimen Collection Schedule for Drug Assay
PART I

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME		BLOOD VOLUME (ml)
Day 1	1	0	Prior to Dosing	10
	2	1 hr	9:00 AM	10
	3	2 hr	10:00 AM	10
	4	4 hr	NOON	10
	5	6 hr	2:00 PM	10
	6	8 hr	4:00 PM	10
	7	12 hr	8:00 PM	10
	8	16 hr	MIDNIGHT	10
	9	20 hr	4:00 AM	10
Day 2	10	24 hr	8:00 AM	10
	11	28 hr	NOON	10
	12	30 hr	2:00 PM	10
	13	36 hr	8:00 PM	10
	14	40 hr	MIDNIGHT	10
	15	44 hr	4:00 AM	10
Day 3	16	48 hr	8:00 AM	10
	17	60 hr	8:00 PM	10
Day 4	18	72 hr	8:00 AM	10
HOME				
Day 5	19	96-98 hr	8:00-10:00 AM	10
Day 7	20	144-146 hr	8:00-10:00 AM	10
Day 8	21	168-170 hr	8:00-10:00 AM	10
Day 14	22	312-314 hr	8:00-10:00 AM	10
Day 21	23	480-482 hr	8:00-10:00 AM	10
			TOTAL	230 ml

Part II.

This study will employ 3 groups of 4 subjects for a simple two-way cross-over administration. Four (4) subjects will be admitted to the unit as a group. Two subjects will be given the tablet formulation and two will be given the capsule formulation at the initiation of the study. You will receive one dose of each of the drug formulations designated according to the sequence shown in the table below.

PART II
SEQUENCE OF DRUG ADMINISTRATION

GROUP	SUBJECT	1st DOSING	2nd DOSING
A	1	E-556*	D-522
A	2	E-556	D-522
A	3	D-522+	E-556
A	4	D-522	E-556
B	5	E-556	D-522
B	6	E-556	D-522
B	7	D-522	E-556
B	8	D-522	E-556
C	9	E-556	D-522
C	10	E-556	D-522
C	11	D-522	E-556
C	12	D-522	E-556

*Lafayette Pharmacal, Inc. - 250 mg capsules

+INTERx - 250 mg tablets

The schedule for Part II of the study is presented in the schematic on page 16.

TABLE II

SCHEMATIC STUDY PLAN FOR PART II
COMPARATIVE BIOAVAILABILITY

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri*	7 Mon	~3-7 x $T_{\frac{1}{2}}$+ Mon
Dose		X					
Physical Exam	X		X				X
Interview	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Laboratory Tests++	X		X				X
Blood for Drug Assay+++							

*Controlled Environment

+The entire sequence will then be repeated after an interval of ~3-7 times the elimination half-life determined in Part I, with each subject taking the same dose of the opposite formulation of WR 180,409·H_3PO_4 the second time.

++Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

+++Drug Assay: The schedule of blood sampling will be determined by information obtained from Part I of the study. A total of approximately 36 samples of 10 ml each will be drawn over a period to include 3-7 times the elimination half-life of the drug.

Blood (10 ml) will be drawn at specific times after you take the drug to measure the amount of drug present. In addition, we will collect all of your urine during the first four days you are on the unit.

TABLE IIA: Schematic Drug Administration and Assay Specimen Collection Schedule

Dose: 750 mg WR 180,409·H_3PO_4
sequence as per explanation pg.15

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME		SPECIMEN VOLUME (ml)
Day 1 Tuesday	1	0	Prior to Dosing	10
	2	1 hr	9:00 AM	10
	3	2 hr	10:00 AM	10
	4	4 hr	NOON	10
	5	6 hr	2:00 PM	10
	6	8 hr	4:00 PM	10
	7	12 hr	8:00 PM	10
	8	16 hr	MIDNIGHT	10
Day 2 Wednesday	9	22 hr	6:00 AM	10
	10	28 hr	NOON	10
	11	34 hr	6:00 PM	10
	12	40 hr	MIDNIGHT	10
Day 3 Thursday	13	48 hr	8:00 AM	10
	14	56 hr	4:00 PM	10
	15	64 hr	MIDNIGHT	10
Day 4 Friday	16	72 hr	8:00 AM	10
HOME				
Day 5 Saturday	17	96 hr	8:00 AM	10
Day 7 Monday	18	144 hr	8:00 AM	10
Day 9 Wednesday	19	192 hr	8:00 AM	10
Day 11 Friday	20	240 hr	8:00 AM	10
Day 14 Monday	21	312 hr	8:00 AM	10
Day 17 Thursday	22	384 hr	8:00 AM	10
Day 21* Monday	23	480 hr	8:00 AM	10
			TOTAL	230 ml

*Day 0 for study interval 2nd drug administration

Part III.*

An additional four subjects will be needed to complete part three of the study. The information obtained from Parts I and II of the study will determine which formulation will be used in Part III. You will be given single doses of the drug on three separate occasions. Three different doses will be administered to each individual. It is anticipated that these doses will be 250 mg, 500 mg, and 750 mg pending results of Part II of the study. Two of you will receive the three doses in increasing order (250, 500, 750 mg), and two of you will receive the drug in decreasing order (750, 500, 250 mg). The specifics for Part III of the study are presented in the schematic below:

TABLE III

SCHEMATIC STUDY PLAN FOR PART III

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	~3-7 x $T_{\frac{1}{2}}$+ Mon
Dose		X					
Physical Exam	X		X				X
Interview	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Laboratory Tests++	X		X				X
Blood for Drug Assay+++							

*Controlled Environment

+The entire sequence will be repeated twice beginning each time after an interval of ~3-7 times the elimination half-life of the drug as determined in previous studies. The subject will receive a total of 3 different single oral doses either in increasing or decreasing order.

++Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

* Part III of Experiment #14 was cancelled.

+++Drug Assay: The schedule of blood sampling will be determined by information obtained from previous parts of the study. A total of approximately 20 samples of 10 ml each will be drawn over a period to include 3-7 times the elimination half-life of the drug.

You have already had many of the examinations listed in the Schematic Study Plans as part of your qualification examination.

No matter which part of the study you select to participate in, you will be admitted to the research unit for the first 4 days. You will be seen on brief visits thereafter for a period of time specific to your portion of the study. On the last day of your part of the study you will have a complete physical examination.

During the interval in the research unit the entire group will remain together with a member of the Unit Staff and will function according to their direction. Facilities provided while participating in the study include room and board with a study-lounge area.

On the day the drug is to be administered, you will have a liquid breakfast (Sustacal) at 6:00 a.m. and lunch will be withheld. You will be given the drug at 8:00 a.m.. You may have water as you wish until 2:00 p.m., at which time you may have a light lunch. Beginning at 5:00 p.m. you may resume the normal diet you select from the hospital menu until you are discharged from the unit.

At your discretion, 15 minutes before drug administration, a small teflon catheter can be placed in 1 of your arm veins. This will be used to obtain blood samples during the day you are dosed. In this way, repeated venipunctures may not be necessary on that day.

Ten ml of venous blood will be drawn by a staff nurse for each drug assay. Six ml of the blood will be transferred to a heparin-rinsed teflon capped glass tube and stored at -20°C pending transportation to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. The drug will be assayed as a parent compound by high pressure liquid chromatography. This method has previously been employed for drug assay in animal blood samples and spiked human samples and is working well. Four ml of the blood will be centrifuged and the serum separated. The serum will be transported to the Department of Pharmacology, WRAIR, for bioassay for antimalarial activity.

It is important that the blood be obtained as nearly as possible to the times specified in your part of the study. On the days you come in for blood drawing, it is important that you eat a light breakfast (i.e., cereal, milk, juice, coffee, bread -- no eggs or bacon). It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs, and lack of proper sleep may affect the level of drug in your blood on any given day.

The Human Use Committee is also looking after your safety. They insure that you are not subjected to undue risk and discomfort. A member of this committee will be available to speak with you at the Washington Hospital Center. After members of the investigating team and the Human Use Committee are satisfied that you understand the study and the written informed consent form, you will be permitted to sign it.

No subject may participate without a signed consent. By signing the informed consent you signify that the study has been explained to you with regard to its risks and requirements and you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to Americans, civilian and military, who may travel to these areas. For this reason, especially, your participation must be voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent at any time without prejudice.

SUBJECT AGREEMENT

CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled, Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document entitled, "EXPLANATION: AMDP EXPERIMENT NUMBER 14: Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration," which I have signed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examinations, if in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____	_____
Date	Witness - Human Use Comm. Cert.
_____	_____
Signature	Investigator Certification
_____	_____
Address	Witness

REAFFIRMATION OF CONSENT:

_____	_____
Date	Witness
_____	
Signature	

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FINAL REPORT

ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 14

PART II

TITLE:	PHARMACOKINETICS OF WR 180,409·H_3PO_4: (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PRINCIPAL INVESTIGATOR:	JOHN A. JOHNSON, M.D.
CLINICAL DIRECTOR:	KEVIN G. BARRY, M.D.
CONSULTING AND INSTITUTIONAL REVIEW BOARD MEMBERS:	JAMES A. CURTIN, M.D. STUART H. DANOVITCH, M.D.

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FINAL REPORT

EXPERIMENT NUMBER 14

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

PART II

TABLE OF CONTENTS

SUBJECT	PAGE
ABSTRACT	41
INTRODUCTION	42
METHODS AND MATERIALS	43
RESULTS	48
CONCLUSIONS AND RECOMMENDATIONS	49
Table III - Symptoms	50-53
Table IV - Laboratory Abnormalities Table	54-57
Individual Subject Final Summary Sheets	58-72
APPENDIX: a. Explanation for Potential Subjects b. Consent Form	

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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.

BIO - MED, Inc.

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FINAL REPORT

EXPERIMENT NUMBER 14

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

PART II

INTRODUCTION

WR 180,409·H_3PO_4, a substituted pyridinemethanol, is the first compound of this chemical class to be tested in the U.S. Army Antimalarial Program. It represents a potential new class of antimalarial drug. In animal test systems the compound was exceptionally well tolerated and had excellent antimalarial activity. The acute oral LD_{50} was 900 mg/kg in mice. In rats, the acute LD_{50} was 500 mg/kg. Clinical and pathological examination of rats 72 hours after a single oral dose of 100 mg/kg detected no adverse effect; a single oral dose of 300 mg/kg caused some decrease in weight; and 900 mg/kg caused weight loss, bleeding around the eyes, depression of lymphoid tissue and degenerative changes in the liver. When administered to beagle dogs, doses of 37 mg/kg or higher frequently caused vomiting. The drug was curative against the choloroquine-resistant Vietnam Smith strain of Plasmodium falciparum in the Aotus monkey when administered orally at a dose of 2.5 mg/kg/day for 7 days, at a dose of 12 mg/kg/day for 3 days, and as a single oral dose of 35 mg/kg.

A clinical Phase I safety and tolerance study with WR 180,409 H_3PO_4 was recently completed. Single doses of 5 to 1500 mg were administered to a total of 22 subjects in a double-blind rising dose study. Intolerance to the drug was manifested by nausea, vomiting, dizziness, and "mental fuzziness". One or more of these symptoms occurred in 3 of 4 subjects taking 1250 mg. Two subjects administered 1500 mg of WR 180,409·H_3PO_4 as a single dose experienced similar symptoms. Onset of symptoms was generally within 8 hours of drug administration, though 1 individual who took 1500 mg vomited 24 hours later. In all cases, the symptoms had subsided by 32 hours after dosing. There were no physical abnormalities or laboratory abnormalities attributed to the drug.

WR 180,409·H_3PO_4 was administered as a single oral dose of 750 mg to four subjects in an initial pilot study as Part I of Experiment Number 14. Two subjects received a capsule formulation (Lafayette E-556) and two received 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 Part II.

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 neurological 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 was considered possibly drug related.

METHODS AND MATERIALS:

Subject Qualification:

Twelve healthy male subjects, aged 21-38, weighing from 60-90 kg and within 10% of their ideal body weight, were employed for the study. They were recruited from the Washington, D. C. metropolitan area. Subjects were hired by BIO-MED, Inc. as temporary employees for study purposes.

Candidates for employment were presented with a complete explanation of the background and procedures to be used in the study, and of all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually in the presence of an investigator and a member of the Human Use Committee. Each participant was given the opportunity to ask questions. Following this, the subject information sheet was read and initialed by those wishing to participate, and the formal consent form was signed in the presence of a witness, investigator, and a member of the Human Use Committee.

Candidates were screened to obtain the subjects for this study. The qualifying medical evaluation included a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, and G6PD.

Subject acceptability criteria were based upon the precept that the risks of participation should be slight and comparable for all subjects. Following this guideline, certain candidates were rejected routinely: for example, candidates with organic heart murmurs, splenomegaly, or active lesions on chest x-ray.

The presence of conditions which did not increase risk or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes were not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean were cause for rejection. Deviations between 2 and 3 standard deviations from the mean were generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum sodium of 153 mEq/L of itself would not have caused rejection, whereas a serum calcium of 11.2 mg/dl would.

In addition to the above qualifications, no candidate having received the drug, WR 180,409·H_3PO_4 previously was permitted to participate in any phase of this pharmacokinetic protocol.

When doubt existed concerning eligibility of a candidate, a decision was made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates were given full consideration and the integrity and ethics of the Research Team protected.

Procedures:

Subjects were admitted in groups of 4 for each drug administration and housed for a period of 4 days, beginning 1 day prior to each drug administration, in a controlled environment in Nursing Unit 5W of the Washington Hospital Center. Two of the subjects in the group were given the tablet formulation (D-522) and 2 were given the capsule formulation (E-556).

Physical examinations, interviews, vital sign measurements, laboratory tests, and drug assay samplings were conducted according to the Schematic Study Plan (Table I) and the Assay Specimen Collection Schedule (Table II). On study day 4, the subjects were released from the controlled environment, returning for the various evaluations and blood samplings as indicated through study day 21, the last day of observation for their first drug administration.

Seven days after study day 21*, each of the subjects was given the opposite formulation of that which they had received previously. The same evaluations and blood samplings conducted following the first drug administration were repeated at the same time intervals for another period of 21 days.

This procedure was followed for 3 groups of 4 subjects each, representing a total of 12 subjects and 24 drug administrations. However, 2 subjects withdrew before their second drug administration.

On the last study day for each subject final physical and laboratory evaluations were conducted. All abnormal findings caused follow-up until normalcy, stabilization, or proper medical disposition was secured.

Drug Administration:

WR 180,409·H_3PO_4 was supplied as 250 mg tablets (INTERx D-522)and 250 mg capsules (Lafayette E-556). Subject code numbers for drug formulation assignment was by lottery. On the day of drug administration, the subjects fasted between midnight and 6 a.m. when they were given 360 ml of Sustacal (Mead Johnson product) containing a total of 360 calories. Subjects ingested a single oral 750 mg dose of WR 180,409·H_3PO_4 in either capsule or tablet form at approximately 0800, varying slightly with each group, in the presence of a staff nurse. They were then restricted to water for 6 hrs., followed by a light lunch. Nine hours after dosing, they resumed a regular diet which they selected from the hospital menu.

* 28 days after their first drug administration, an interval sufficient to allow the amount of drug present to be less than 10% of its peak level.

TABLE I

SCHEMATIC STUDY PLAN FOR PART II
COMPARATIVE BIOAVAILABILITY

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	14 Mon	21+ Mon
Dose		X						
Physical Exam	X		X					X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Laboratory Tests++	X		X					X
Blood for Drug Assay+++		X	----------	----------	----------	----------	----------	X

* Controlled Environment

\+ The entire sequence was then repeated 7 days later with each subject taking the same dose of the opposite formulation of WR 180,409·H_3PO_4.

++ Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Final blood profiles were conducted on Study Day 28 instead of Day 21 for the first drug administration.

+++ Drug Assay: The schedule of blood sampling was determined by information obtained from Part I of the study, and is shown in Table II, Assay Specimen Collection Schedule, page 6.

Drug Assay Specimen Collection and Time Schedule:

In order to analyze the pharmacokinetics and bioavailability of WR 180,409·H_3PO_4, blood specimens for drug assay were collected over a period of 21 days following each drug administration. This schedule was determined by the information obtained from Part I of this experiment. Ten ml of venous blood were drawn by a staff nurse for each drug assay. Six ml of the blood were transferred to a heparin-rinsed teflon capped glass tube and stored at -20 C pending transportation to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. The drug was assayed as a parent compound by high pressure liquid chromotography. Four ml of the blood were centrifuged and the serum separated. The serum was transported to the Department of Pharmacology, WRAIR, for bioassay of antimalarial activity.

TABLE II

Assay Specimen Collection Schedule

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME	SPECIMEN VOLUME (ml)
Day 1 Tuesday	1	-15 min	10
	2	1 hr	10
	3	2 hrs	10
	4	4 hrs	10
	5	6 hrs	10
	6	8 hrs	10
	7	12 hrs	10
	8	16 hrs	10
Day 2 Wednesday	9	22 hrs	10
	10	28 hrs	10
	11	34 hrs	10
	12	40 hrs	10
Day 3 Thursday	13	48 hrs	10
	14	56 hrs	10
	15	64 hrs	10
Day 4 Friday	16	72 hrs	10
Day 5 Saturday	17	96 hr	10
Day 7 Monday	18	144 hr	10
Day 9 Wednesday	19	192 hr	10
Day 11 Friday	20	240 hr	10
Day 14 Monday	21	312 hr	10
Day 17 Thursday	22	384 hr	10
Day 21 Monday	23	480 hr	10
		TOTAL	230 ml

Laboratory Test Specimen Collection:

During the first drug administration interval, 27 ml of venous blood were taken for hemotologic and biochemical profiles on study days 0, 2, and 28. During the second drug administration interval, the same profiles were conducted on days 0, 2, and 21. For these profiles, the blood was obtained before breakfast. Seven ml of the blood were used for determination of white blood cells and differential count, red blood cell count, hematocrit, hemoglobin, MCH, MCV, MCHC, and platelet count. Twenty ml of the venous blood were centrifuged and the serum separated into 2 samples. One sample was used on the day obtained to determine the values for serum glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin. The other sample was stored in the refrigerator as a "back-up" until the biochemical lab report was received.

Urinalysis was conducted for each subject on these same days, consisting of pH, glucose, protein, specific gravity, white blood cell count, red blood cell count, and presence of amorphous sediment.

Laboratory results are discussed under Results.

RESULTS

Symptoms:

Symptoms experienced by the subjects are summarized in Table III. Details of symptomatology are recorded in the individual subject summaries.

There were twelve subjects each with two treatment intervals, E-556 and D-522. Two subjects (353, 354) withdrew from the study after the first treatment interval. In each instance, E-556 was omitted from the crossover. Thus there were 12 treatments with D-522, and 10 with E-556.

Three subjects (350, 352, 355) were entirely asymptomatic throughout both treatment intervals. Two subjects (349, 356) were symptomatic (nausea, vomiting) with E-556 but not with D-522. One subject (358) had vague abdominal discomfort for 1.5 hours after ingestion of E-556, and had a headache of 6 hours duration 3 hours after ingesting D-522. Subject (357) had light-headedness after E-556 and nausea after D-522.

Symptoms in the remaining subjects (351, 359, 360) included emesis after both formulations (351); emesis after E-556 and diarrhea after D-522 (359); diarrhea and abdominal cramps after D-522 and abdominal discomfort after E-556, (360).

In summary, of the 10 subjects completing the crossover, 3 were totally asymptomatic, 3 had symptoms of gastrointestinal intolerance to both drugs, 2 showed gastrointestinal intolerance to E-556 but not to D-522, and 2 had equivocal symptoms to both drugs.

LABORATORY ABNORMALITIES:

In Table IV for each subject all values are displayed for each laboratory test wherein at least one abnormal value was detected.

The abnormal values were examined for possible association with the formulation administered and the order of the administration of the formulations. No such association could be demonstrated.

CONCLUSIONS AND RECOMMENDATIONS:

This crossover study to compare the intolerance of two formulations showed significant gastrointestinal intolerance to each formulation at a dose of 750 mg. In a few instances, vomiting occurred, an unacceptable side-effect of an oral medication.

Aside from elevation of the SGOT and SGPT in one subject on day 21, no significant biochemical deviations occurred.

These observations suggest that the intolerance seen here is the result of local gastrointestinal irritation, and that smaller, multiple doses may be better tolerated.

However, at this time the pharmacokinetic data have not been analyzed. That analysis should be taken into account before further studies of WR 180,409·H_3PO_4 are designed.

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE III: Symptoms

Group	CODE NUMBER	FORMULATION	Nausea		Emesis		Loose Stool		Other	
			Onset *	Duration+	Onset	Duration	Onset	Duration	Onset	Duration
I	349	E-556	.25	1.0					24.0 slightly	bloated
		D-522	No symptoms							
I	350	D-522	No symptoms							
		E-556	No symptoms							
I	351	E-556	2.25	6.0	3.5 3 episodes	<0.1			2.25 headache - mild accompanied nausea	6.0
		D-522	7.75	16.0	15.9 190cc food and mucus	<0.1			7.75 headache 8.75 lightheaded 7.75 little appetite	16.0 16.0 34.0
I	352	D-522	No symptoms							
		E-556	No symptoms							

* Onset hrs. after dosing + Duration hrs. after onset

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE III: Symptoms

Group	CODE NUMBER	FORMULATION	Nausea		Emesis		Loose Stool		Other	
			Onset *	Duration+	Onset	Duration	Onset	Duration	Onset	Duration
II	353	D-522	3.75 "queasy" feeling began after 2nd episode of emesis	1.25	1.6 3.75 30cc clear colorless fluid with relief of "tightness"	<0.1 <0.1	1.0 soft, well-formed stool		0.5 Abdominal	1.0 "tightness"
			Dropped from study - not dosed 2nd interval							
II	354	D-522	0.75 ended with normal stools	3.0						
			Dropped from study - not dosed 2nd interval							
II	355	E-556	No symptoms							
		D-522	No symptoms							
II	356	E-556	0.25 with epigastric discomfort, nausea subsided gradually	4.75	0.8 sustacal, questionable capsule content with retching 3-4x	<0.1			.25 "itching sensation" in ears, associated with epigastric discomfort	1.0
		D-522							6.5 Transient episodes of "dizziness"	5.5

* Onset hrs. after dosing + Duration hrs. after onset

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE III: Symptoms

Group	CODE NUMBER	FORMULATION	Nausea		Emesis		Loose Stool		Other	
			Onset *	Duration+	Onset	Duration	Onset	Duration	Onset	Duration
III	357	E-556							.25 transient episodes of light-headedness 2.0 sinus congestion	15.75 .5
		D-522	.50	13.5						
III	358	E-556							PTD "queasy"upon insertion of catheter .5 vague abd. sensation	<0.1 1.5
		D-522							3.0 mild frontal headache	6.0
III	359	D-522	1.8				1.8 2 liquid stools 2.1 liquid 3.33 liquid 3.5 liquid 8.5 small soft stool	0.2 <0.1 <0.1 <0.1 <0.1	1.8 "pressure lower abd. like when you know your're going to have diarrhea" 3.5 headache and abd. cramps "due to extreme hunger"	1.5 4.5

* Onset hrs. after dosing + Duration hrs. after onset

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE III: Symptoms

Group	CODE NUMBER	FORMULATION	Nausea		Emesis		Loose Stool		Other	
			Onset *	Duration+	Onset	Duration	Onset	Duration	Onset	Duration
III	359	E-556			0.6 vomited-400cc mostly clear vomitus with lge. amt. mucus 1.0 vomited-120cc appeared same	<0.1 <0.1			.2 hyperventilation 4.0 mild pectoralis aching	1.25 26.0
III	360	D-522					4.0 liquid stool 4.75 liquid stool	<0.1 <0.1	0.75 mild abdominal cramps	8.0
		E-556							1.0 vague abdominal discomfort	7.0

* Onset hrs. after dosing + Duration hrs. after onset

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE IV: Laboratory Abnormalities Table

Group & Code Number	Formulation		Tests	First Dose			Second Dose			Normals
				Study Day			Study Day			
	1st Dose	2nd Dose		Scr	0	2	0	2	21	
I 349	E-556	D-522	Sodium	137	136L	139	136L	139	138	137 - 151 mEq/L
			Globulin	2.5	2.2	2.10	1.7L	2.30	2.40	1.8 - 3.4 g/dl
			Triglyceride	162	60	77	215H	103	166	0 - 207 mg/dl
			SGPT	26	11	27	49H	15	9	0 - 47 U/L
			WBC	11.9H	9.4	10.8H	11.7H	8.6	8.1	3.1 - 9.5 thous/cu mm
I 350	D-522	E-556	Sodium	138	137	139	136L	138	138	137 - 151 mEq/L
			Uric Acid	6.3	7.5	5.3	8.2H	5.0	5.5	4 - 8 mg/dl
			Triglyceride	171	289H	262H	294H	304H	329H	0 - 207 mg/dl
			Eosin	4	6H	6H	9H	8H	6H	0 - 5 %
			Mono	10	12H	9	10	11H	11H	0 - 10 %
I 351	E-556	D-522	Glucose	78	78	81	118H	88	91	66 - 114 mg/dl
			LDH	149	158	267H	169	197	136	73 - 233 U/L
			Hematocrit	50.7H	49.3	52.3H	45.5	48.2	46.2	40 - 50 Vol.%
			Hemoglobin	16.6	16.7	17.8H	15.1	16.7	15.7	13.3 - 16.7 GMS%
			RBC	5.60	5.58	5.98H	5.33	5.77H	5.39	4.3 - 5.7 millon/cu
			Mono	14H	9	9	10	10	11H	0 - 10 %
I 352	D-522	E-556	BUN	15	21	28H	12	24H	12	9 - 21 mg/dl
			Potassium	4.5	4.5	5.0	5.3H	5.0	4.3	3.6 - 5.2 mEq/L
			Uric Acid	5.8	7.0	6.1	8.4H	5.9	9.3H	4 - 8 mg/dl
			Globulin	2.4	2.2	2.3	1.7L	2.0	2.3	1.8 - 3.4 g/dl
			Phosphate	3.3	3.5	4.0	2.7	4.7H	2.8	2.5 - 4.5 mg/dl
			Alka Phos	98H	98H	80	88	74	78	26 - 94 U/L

L = low H = high ND = not done

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE IV: Laboratory Abnormalities Table

Group & Code Number	Formulation		Tests	First Dose			Second Dose			Normals
				Study Day			Study Day			
	1st Dose	2nd Dose		Scr	0	2	0	2	21	
I 352 (cont)	D-522	E-556	LDH	182	181	372H	151	174	139	73 - 233 U/L
			Eosin	4	6H	5	5	4	2	0 - 5 %
			MCV	84	84	83	85	82	81L	82 - 98 cu microns
II 353	D-522		Eosin	ND	5	8H	ND	ND	ND	0 - 5 %
			Mono	ND	12H	2	ND	ND	ND	0 - 10 %
II 354	D-522		Glucose	130H	115H	93	ND	ND	ND	66 - 114 mg/dl
			Creatinine	1.0	1.5H	1.0	ND	ND	ND	0.8 - 1.4 mg/dl
			Phosphate	2.4L	2.4L	3.4	ND	ND	ND	2.5 - 4.5 mg/dl
			LDH	394H	279H	233	ND	ND	ND	73 - 233 U/L
			Lymph	16L	26	68H	ND	ND	ND	19 - 59 %
			SEG	78	65	24L	ND	ND	ND	36 - 80 %
			Eosin	2	4	6H	ND	ND	ND	0 - 5 %
II 355	E-556	D-522	Glucose	69	82	90	124H	96	140H	66 - 114 mg/dl
			Total Protein	6.6	6.4	6.7	6.2L	6.6	6.3L	6.4 - 8.0 g/dl
			Globulin	2.0	1.9	2.1	1.7L	1.9	1.9	1.8 - 3.4 g/dl
			SGPT	28	45	49H	35	21	42	0 - 47 U/L
II 356	E-556	D-522	Carbon Dioxide	26	31	32H	31	31	29	23 - 31 mEq/L
			Globulin	2.8	1.70L	2.0	1.8	1.70L	2.1	1.8 - 3.4 g/dl
			Phosphate	2.7	2.4L	3.3	3.1	4.1	3.6	2.5 - 4.5 mg/dl
			SGOT	26	22	7	15	19	88H	0 - 47 U/L
			SGPT	13	22	12	16	16	61H	0 - 47 U/L

L = low H = high ND = not done

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE IV: Laboratory Abnormalities Table

Group & Code Number	Formulation 1st Dose	Formulation 2nd Dose	Tests	First Dose Study Day Scr	First Dose Study Day 0	First Dose Study Day 2	Second Dose Study Day 0	Second Dose Study Day 2	Second Dose Study Day 21	Normals
III 357	E-556	D-522	Calcium	9.0	8.9L	9.3	8.3L	9.4	8.9L	9.0 - 10.9 mg/dl
			Phosphate	2.7	2.3L	3.8	3.1	3.8	3.5	2.5 - 4.5 mg/dl
			SGPT	18	21	13	50H	47	11	0 - 47 U/L
			Hematocrit	43.5	41.5	45.5	39.5L	44.2	45.0	40 - 50 Vol%
			Hemoglobin	13.9	13.7	14.7	13.0L	14.9	14.4	13.3 - 16.7 GMS%
III 358	E-556	D-522	Glucose	70	65L	78	85	79	82	66 - 114 mg/dl
			Total Protein	6.9	6.4	6.8	6.3L	6.0L	6.7	6.4 - 8.0 g/dl
			Calcium	9.5	9.2	9.2	8.9L	8.8L	9.3	9.0 - 10.9 mg/dl
			Mono	5	12H	8	6	9	10	0 - 10 %
III 359	D-522	E-556	BUN	8L	6L	4L	6L	6L	4L	9 - 21 mg/dl
			Sodium	137	136L	135L	136L	137	139	137 - 151 mEq/L
			Uric Acid	4.6	3.9L	3.8L	4.6	3.8L	5.2	4 - 8 mg/dl
			Total Protein	7.2	6.2L	7.3	7.1	6.8	6.8	6.4 - 8.0 g/dl
			Phosphate	2.6	2.5	3.2	2.2L	3.1	2.3L	2.5 - 4.5 mg/dl
			Alka Phos	125H	115H	133H	119H	113H	108H	26 - 94 U/L
			Hematocrit	36.9L	40.0	41.2	40.2	40.2	37.9L	40 - 50 Vol%
			Hemoglobin	12.5L	13.5	14.1	13.9	13.7	12.6L	13.3 - 16.7 GMS%
			WBC	15.8H	11.8H	9.5	11.4H	11.1H	11.3H	3.1 - 9.5 thous/cu mm
			RBC	4.12L	4.52	4.63	4.71	4.67	4.26L	4.3 - 5.7 million/cu

L = low H = high ND = not done

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION

PART II TABLE IV: Laboratory Abnormalities Table

Group & Code Number	Formulation 1st Dose	Formulation 2nd Dose	Tests	First Dose Study Day Scr	First Dose Study Day 0	First Dose Study Day 2	Second Dose Study Day 0	Second Dose Study Day 2	Second Dose Study Day 21	Normals
III 360	D-522	E-556	Glucose	86	79	82	101	81	136H	66 - 114 mg/dl
			Sodium	140	137	136L	139	139	138	137 - 151 mEq/L
			Potassium	4.2	4.4	5.5H	4.8	4.4	4.6	3.6 - 5.2 mEq/L
			Uric Acid	8.4H	7.6	7.4	8.6H	6.9	8.9H	4 - 8 mg/dl
			Total Protein	6.8	6.3L	6.3L	6.0L	6.6	6.3L	6.4 - 8.0 g/dl
			Globulin	2.1	1.8	2.1	1.7L	1.8	2.0	1.8 - 3.4 g/dl
			Triglycerides	71	210H	100	118	97	70	0 - 207 mg/dl
			LDH	233	198	374H	194	169	134	73 - 233 U/L
			Hematocrit	48.4	50.2H	48.9	47.3	46.7	47.5	40 - 50 Vol%
			Hemoglobin	16.3	17.1H	16.3	15.8	15.9	16.5	13.3 - 16.7 GMS%
			Mono	11H	11H	9	0	13H	10	0 - 10 %

L = low H = high ND = not done

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 349
DOSING DATE:	8/21/79	9/18/79	GROUP: I
TIME DOSED:	0800	0800	AGE: 22
DOSE(mg/kg):	12.4788	12.4788	HEIGHT: 168.91 (cm)
			WEIGHT: 60.1016 (kg)

ABNORMALITIES

DATE: 1979	8/6	8/20	8/21	8/22	9/10	9/17	9/18	9/19	10/8
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X						X
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry		X				X			
6. CBC	X			X		X			
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Sodium	137	136L	139	136L	139	138	137 - 151 mEq/L
Globulin	2.50	2.20	2.10	1.70L	2.30	2.40	1.8-3.4 g/dl
Triglyceride	162	60	77	215H	103	166	0-207 mg/dl
SGPT	26	11	27	49H	15	9	0-47 U/L
WBC	11.9H	9.4	10.8H	11.7H	8.6	8.1	3.1-9.5 thous/cu mm

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: Beginning fifteen minutes after ingestion of Formulation E-556 the subject experienced nausea which was recurrent for one hour. On Day 2, the subject reported feeling slightly "bloated" but did not experience any further nausea. Thereafter, the subject remained asymptomatic and the physical examination was unchanged.

Formulation D-522: On Day 21 the subject reported cold symptoms beginning on Day 14 with symptoms of nasal congestion and a slight cough persisting for seven days. The subject was afebrile on Day 21. The subject was otherwise asymptomatic and the physical examination remained unchanged.

Abnormalities Comment: The laboratory abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusions: Nausea beginning fifteen minutes after ingestion of Formulation E-556 and recurring for one hour possibly related to ingestion of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	E-556	CODE: 350
DOSING DATE:	8/21/79	9/18/79	GROUP: I
TIME DOSED:	0800	0800	AGE: 31
DOSE(mg/kg):	9.4482	9.4482	HEIGHT: 180.34 (cm)
			WEIGHT: 79.3794(kg)

ABNORMALITIES

DATE: 1979	8/17	8/20	8/21	8/22	9/10	9/17	9/18	9/19	10/8
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry		X		X		X		X	X
6. CBC		X		X		X		X	X
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Sodium	138	137	139	136L	138	138	137 - 151 mEq/L
Uric Acid	6.3	7.5	5.3	8.2H	5.0	5.5	4-8 mg/ld
Triglyceride	171	289H	262H	294H	304H	328H	0-207 mg/dl
Eosin	4	6H	6H	9H	8H	6H	0-5 %
Mono	10	12H	9	10	11H	11H	0-10 %

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: The subject was asymptomatic throughout the study interval and the physical examination remained unchanged.

Formulation D-522: The subject was asymptomatic throughout the study interval and the physical examination remained unchanged.

Abnormalities Comment: The subject demonstrated a consistent elevation of serum triglyceride and of per cent eosinophils both before and after drug administration of both formulations and were not considered study related. Other abnormalities were minimal or inconsistent and not considered of clinical significance.

Conclusions: No adverse effects from ingestion of either formulation of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 351
DOSING DATE:	8/21/79	9/18/79	GROUP: I
TIME DOSED:	0800	0800	AGE: 32
DOSE(mg/kg):	10.8423	10.8423	HEIGHT: 175.26 (cm)
			WEIGHT: 69.1735 (kg)

ABNORMALITIES

DATE: 1979	8/17	8/20	8/21	8/22	9/10	9/17	9/18	9/19	10/8
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X				X		
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry				X		X			
6. CBC	X			X				X	X
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Glucose	78	78	81	118H	88	91	66-114 mg/dl
LDH	149	158	267H	169	197	136	73-233 U/L
Hematocrit	50.7H	49.3	52.3H	45.5	48.2	46.2	40-50 Vol%
Hemoglobin	16.6	16.7	17.8H	15.1	16.7	15.7	13.3-16.7 GMS%
RBC	5.60	5.58	5.98H	5.33	5.77H	5.39	4.3-5.7 mill/cu
Mono	14H	9	9	10	10	11H	0-10 %

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: Two hours and fifteen minutes after ingestion of 750 mg Formulation E-556 the subject experienced nausea and a mild headache which was followed by 3 episodes of emesis between 3 hours 30 minutes and 3 hours 35 minutes post dosing. The subject reported no appetite for the meal 6 hours post dose, with a return to normal appetite at 9 hours post dose. The headache dissipated 6 hours after onset. Thereafter the subject remained asymptomatic and the physical examination remained unchanged.

Formulation D-522: Seven hours forty-five minutes after ingestion of Formulation D-522 the subject reported the onset of a frontal headache - "like a band - mild" with the simultaneous onset of nausea. The symptoms peaked between 8 and 10 hours post dose with severe nausea and orthostatic dizziness. At 16 hours post dose, upon getting up for an assay specimen, the subject vomited 190 cc of partially digested food and mucus with much relief. On Day 2, 24 hours after dosing, the subject had little appetite and reported feeling like he had a "sour stomach". Thereafter, the subject remained asymptomatic and the physical examination was unchanged.

Code: 351 (cont'd)

Abnormalities Comment: The subject demonstrated an elevation in hematocrit of 52.8 Vol %, a hemoglobin of 17.8 GMS %, and a RBC of 5.98 million/cu mm on Day 2 of the first study interval. Other abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusion: Three episodes of emesis 3 hours 30 minutes after ingestion of Formulation E-556 and an episode of emesis 7 hours 45 minutes with accompanying headache after ingestion of Formulation D-522 considered related to ingestion of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	E-556	CODE: 352
DOSING DATE:	8/21/79	9/18/79	GROUP: I
TIME DOSED:	0800	0800	AGE: 26
DOSE(mg/kg):	12.2477	12.2477	HEIGHT: 171.45 (cm)
			WEIGHT: 61.2355 (kg)

ABNORMALITIES

DATE: 1979	8/17	8/20	8/21	8/22	9/10	9/17	9/18	9/19	10/8
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X	X		X		X		X	X
6. CBC		X							X
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
BUN	15	21	28H	12	24H	12	9-21 mg/dl
Potassium	4.5	4.5	5.0	5.3H	5.0	4.3	3.6-5.2 mEq/L
Uric Acid	5.8	7.0	6.1	8.4H	5.9	9.3H	4-8 mg/dl
Globulin	2.4	2.2	2.3	1.7L	2.0	2.3	1.8-3.4 g/dl
Phosphate	3.3	3.5	4.0	2.7	4.7H	2.8	2.5-4.5 mg/dl
Alka Phos	98H	98H	80	80	74	78	26-94 U/L
LDH	182	181	372H	151	174	139	73-233 U/L
Eosin	4	6H	5	5	4	2	0-5 %
MCV	84	84	83	85	82	81L	82-98 cu microns

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: The subject was asymptomatic throughout the entire study interval and the physical examination remained unchanged.

Formulation D-522: The subject was asymptomatic throughout the entire study interval and the physical examination remained unchanged.

Abnormalities Comment: The subject demonstrated an elevated BUN of 28 mg/dl on Day 2 of the first study interval, and an elevation of 24 mg/dl on Day 2 of the second study interval. He also demonstrated an isolated elevation of serum LDH to 372 U/L on Day 2 of the second study interval. Other abnormalities were minimal and inconsistent and were not considered to be of clinical significance.

Conclusions: Elevation of serum BUN on Day 2 of both study intervals possibly but not probably related to ingestion of both formulations of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	Dropped from	CODE: 353
DOSING DATE:	8/28/79	study	GROUP: II
TIME DOSED:	0800		AGE: 26
DOSE(mg/kg):	10.204		HEIGHT: 185.42 (cm)
			WEIGHT: 73.4827 (kg)

ABNORMALITIES

DATE: 1979	8/17	8/27	8/28	8/29	9/10				
STUDY DAY:	Scr	0*	1*	2*	21	0	1+	2+	21+
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X								
6. CBC		X		X					
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Chloride	88L	98	101				98-110 mEq/L
Phosphate	2.3L	2.9	3.4				2.5-4.5 mg/dl
Eosin	ND	5.0	8.0H				0-5 %
Mono	ND	12H	2.0				0-10 %

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: The subject did not return for dosing of this formulation. Dropped from study.

Formulation D-522: Thirty minutes after ingestion of 750 mg of Formulation D-522 the subject experienced abdominal "tightness". One hour post dosing passed 1 soft but well formed stool, with relief of tightness. One hour and 35 minutes and 3 hours and 45 minutes after dosing experienced emesis and felt "queasy" afterward. Tolerated light lunch. No other symptoms noted. The physical examination was unchanged.

Abnormalities Comment: The laboratory abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusions: Abdominal "tightness" and soft stool were possibly due to ingestion of the drug. The repeated emesis subject experienced was probably due to ingestion of the drug.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	Dropped from	CODE: 354
DOSING DATE:	8/28/79	study	GROUP: II
TIME DOSED:	0800		AGE: 27
DOSE(mg/kg):	10.6674		HEIGHT: 172.72 (cm)
			WEIGHT: 70.3075 (kg)

ABNORMALITIES

DATE: 1979	8/27	8/27	8/28	8/29	9/10				
STUDY DAY:	Scr	0*	1*	2*	21	0	1+	2+	21+
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X	X							
6. CBC	X			X					
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Glucose	130H	115H	93				66-114 mg/dl
Creatinine	1.0	1.5H	1.0				0.8-1.4 mg/dl
Phosphate	2.4L	2.4L	3.4				2.5-4.5 mg/dl
LDH	394H	279H	233				73-233 U/L
Lymph	16L	26	68H				19-59 %

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: The subject did not return for dosing of this formulation. Subject dropped from study.

Formulation D-522: Forty-five minutes after ingesting 750 mg of Formulation D-522 subject experienced mild nausea without emesis. This persisted until 1200. Subject remained asymptomatic throughout remainder of study and physical examination was unchanged.

Abnormalities Comment: The laboratory abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusion: Feelings of nausea forty-five minutes after ingesting Formulation D-522 was considered related to ingestion of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 355
DOSING DATE:	8/28/79	9/25/79	GROUP: II
TIME DOSED:	0800	0800	AGE: 27
DOSE(mg/kg):	10.5651	10.5651	HEIGHT: 174.62 (cm)
			WEIGHT: 70.9879 (kg)

ABNORMALITIES

DATE: 1979	8/10	8/27	8/28	8/29		9/24	9/25	9/26	10/15
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry				X		X			X
6. CBC									
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Glucose	69	82	90	124H	96	140H	66-114 mg/dl
Total Protein	6.6	6.4	6.7	6.2L	6.6	6.3L	6.4-8.0 g/dl
Globulin	2.0	1.9	2.1	1.7L	1.9	1.9	1.8-3.4 g/dl
SGPT	28	45	49H	35	21	42	0-47 U/L

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: After ingesting Formulation E-556 subject remained asymptomatic throughout the study interval and the physical examination remained unchanged.

Formulation D-522: The subject was asymptomatic throughout the study interval and the physical examination remained unchanged.

Abnormalities Comment: The laboratory abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusion: No adverse effects from ingestion of either formulation E-556 or D-522, WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 356
DOSING DATE:	8/28/79	9/25/79	GROUP: II
TIME DOSED:	0800	0800	AGE: 27
DOSE(mg/kg):	10.4648	10.4648	HEIGHT: 176.53 (cm)
			WEIGHT: 71 (kg)

ABNORMALITIES

DATE: 1979	7/23	8/27	8/28	8/29		9/24	9/25	9/26	10/15
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry		X		X					X
6. CBC									
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Carbon Dioxide	26	31	32H	31	31	29	23-34 mg/dl
Globulin	2.8	1.7L	2.0	1.8	1.7L	2.1	1.8-3.4 g/dl
Phosphate	2.7	2.4L	3.3	3.1	4.1	3.6	2.5-4.5 mg/dl
SGOT	26	22	7	15	19	88H	0-47 U/L
SGPT	13	22	12	16	16	61H	0-47 U/L

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation E-556: Fifteen minutes after subject ingested 750 mg Formulation E-556 he experienced an epigastric discomfort which spread slowly upward to his throat; this persisted and subject experienced emesis times 4 fifty minutes post dosing, after which discomfort and nausea diminished. This stopped 5 hours post dosing. Physical examination remained unchanged.

Formulation D-522: Six and one half hours after dosing the subject complained of transient episodes of dizziness which lasted 5.5 hours. Subject remained asymptomatic throughout the rest of the study except for some cold symptoms that that had been present since 9/14/79. Subject stated that his mother was experiencing a strep throat and cold at the time. Throat cultures done. Physical examination remained unchanged.

Abnormalities Comment: The laboratory abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusions: The four episodes of emesis fifteen minutes post dosing of Formulation E-556 are considered related to ingestion of WR 180,409·H_3PO_4.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 357
DOSING DATE:	9/5/79	10/1/79	GROUP: III
TIME DOSED:	0900	0900	AGE: 26
DOSE(mg/kg):	11.4823	11.4823	HEIGHT: 172.72 (cm)
			WEIGHT: 63.3179 (kg)

ABNORMALITIES

DATE: 1979	9/4	9/4	9/5	9/6	9/24	10/1	10/2	10/3	10/22
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X				X		
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry		X				X			X
6. CBC						X			
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen†	0	2	0+	2+	21+	Normal Range
Calcium		8.9L	9.3	8.8L	9.4	8.9L	9.1-10.9 mg/dl
Phosphate		2.3L	3.8	3.1	3.8	3.5	2.5-4.5 mg/dl
SGPT		21	13	50H	47	11	0-47 U/L
Hematocrit		41.5	45.5	39.5L	44.2	45.0	40-50 Vol %
Hemoglobin		13.7	14.7	13.0L	14.9	14.4	13.3-16.7 GMS %

L = low H = high ND = not done † Screened on day 0

Symptoms and Physical Findings:

Formulation E-556: Fifteen minutes after ingesting 750 mg of Formulation E-556, the subject complained that he "felt as though I had been drugged - woozy" which he said lasted about an hour. Thereafter until 16 hours post dose he had orthostatic light-headedness, which was mild and not incapacitating. At two hours after ingestion he complained of congestion "like fluid in my nasal passages" of about 20 minutes duration. Thereafter the subject remained asymptomatic and the physical examination remained unchanged.

Formulation D-522: Thirty minutes after ingesting Formulation D-522 the subject reported mild nausea which lasted until he retired about 14 hours after dosing. He remained asymptomatic and physical examination unchanged for the rest of the study interval.

Abnormalities Comment: Laboratory abnormalites were minimal and inconsistent and not considered of clinical significance.

Conclusion: Light-headedness was possibly but not probably due to ingestion of the drug. The nausea he experienced probably was drug related.

BMI-ME8

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-556	D-522	CODE: 358
DOSING DATE:	9/5/79	10/2/79	GROUP: III
TIME DOSED:	0900	0900	AGE: 34
DOSE(mg/kg):	10.6674	10.6674	HEIGHT: 186.69 (cm)
			WEIGHT: 70.3075 (kg)

ABNORMALITIES

DATE: 1979	9/4	9/4	9/5	9/6	9/24	10/1	10/2	10/3	10/22
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X				X		
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry		X				X		X	
6. CBC		X							
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)

+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen†	0	2	0+	2+	21+	Normal Range
Glucose		65L	78	85	79	82	66-114 mg/dl
Total Protein		6.4	6.8	6.3L	6.0L	6.7	6.4-8.0 g/dl
Calcium		9.2	9.2	8.9L	8.8L	9.3	9.0-10.9 mg/dl
Mono		12H	8	6	9	10	0-10 %

L = low H = high ND = not done † Screened on day 0

Symptoms and Physical Findings:

Formulation E-556: The subject reported feeling "queasy" for less than 5 minutes upon insertion of the I.V. catheter prior to dosing. One half hour after ingestion of Formulation E-556, the subject experienced vague abdominal sensation which he was not able to categorize, and which lasted 1.5 hours. He also reported feeling "headachy" since the morning of Day 1 which the subject attributed to the closed environment. The subject was otherwise asymptomatic and the physical examination remained unchanged.

Formulation D-522: The subject reported a mild frontal headache from 3 hours after ingestion of Formulation D-522 for 6 hours which the subject attributed to reading and not eating.

Abnormalities Comment: Laboratory deviations were minimal or inconsistent and not considered significant.

Conclusions: Vague abdominal and neurological symptoms possibly due to ingestion of drug.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	E-556	CODE: 359
DOSING DATE:	9/5/79	10/2/79	GROUP: III
TIME DOSED:	0900	0900	AGE: 37
DOSE(mg/kg):	10.3340	10.3340	HEIGHT: 181.61 (cm)
			WEIGHT: 72.5755 (kg)

ABNORMALITIES

DATE: 1979	8/27	9/4	9/5	9/6	9/24	10/1	10/2	10/3	10/22
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X				X		
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X	X		X		X		X	X
6. CBC	X	X				X		X	X
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
BUN	8L	6L	4L	6L	6L	4L	9-21 mg/dl
Sodium	137	136L	135L	136L	137	139	137-151 mEq/L
Uric Acid	4.6	3.9L	3.8L	4.6	3.8L	5.2	4-8 mg/dl
Total Protein	7.2	6.2L	7.3	7.1	6.8	6.8	6.4-8.0 g/dl
Phosphate	2.6	2.5	3.2	2.2L	3.1	2.3L	2.5-4.5 mg/dl
Alka Phos	125H	115H	133H	119H	113H	108H	26-94 U/L
Hematocrit	36.9L	40	41.2	40.2	40.2	37.9L	40-50 Vol %
Hemoglobin	12.5L	13.5	14.1	13.9	13.7	12.6L	13.3-16.7 GMS %
WBC	15.8H	11.8H	9.5	11.4H	11.1H	11.3H	3.1-9.5 thous/cu mm
RBC	4.12L	4.52	4.63	4.71	4.67	4.26L	4.3-5.7 million/cu

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation D-522: Starting 1 hour and 50 minutes and ending 3 hours and 30 minutes after drug ingestion, subject had 5 liquid, small volume stools with mild lower quadrant pressure sensation. He had a normal bowel movement 8 hours and 30 minutes after dosing. The subject complained of a moderate frontal pressure headache starting 4 hours after dosing, decreasing from 6 and ending 8 hours after drug ingestion. Also complained of associated "hunger pains" which were relieved by eating dinner. Physical examination remained unchanged.

Formulation E-556: One half hour after dosing subject felt like something was caught in his throat, drank water and vomited. He related taking deep breaths, swallowing air "real hard" and having bilateral, severe, pectoralis pain with marked perspiration. At 1 hour after dosing he also vomited. He complained of right pectoralis aching 4 hours after dosing until 26 hours after dosing. Physical examination remained unchanged.

Code: 359 (cont'd)

Abnormalities Comment: Moderately elevated alkaline phosphatase seems to be usual for this subject. Other laboratory deviations were minimal or inconsistent and not considered of clinical significance.

Conclusions: Gastrointestinal symptoms probably due to drug ingestion. Neurological symptoms possibly due to drug ingestion. Sequence after taking formulation E-556 probably due to nausea from medication followed by air swallowing and hyperventilation finally with pectoralis fatigue and spasm.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 14: PHARMACOKINETICS OF WR 180,409·H_3PO_4
(A PYRIDINEMETHANOL) FOLLOWING ORAL ADMINISTRATION
PART II - 750 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	D-522	E-556	CODE: 360
DOSING DATE:	9/5/79	10/2/79	GROUP: III
TIME DOSED:	0900	0900	AGE: 29
DOSE(mg/kg):	8.4792	8.4792	HEIGHT: 189.23 (cm)
			WEIGHT: 88.4514 (kg)

ABNORMALITIES

DATE: 1979	8/28	9/4	9/5	9/6	9/24	10/1	10/2	10/3	10/22
STUDY DAY:	Scr	0*	1*	2*	21	0+*	1+*	2+*	21+
1. Symptoms			X				X		
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry	X	X		X		X			X
6. CBC	X	X						X	
7. Platelets									

KEY: X=abnormal *=controlled environment (Nursing Unit 5W, WHC)
+=2nd study interval, 28 days after dosing 1st study interval

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	0+	2+	21+	Normal Range
Glucose	86	79	82	101	81	136H	66-114 mg/dl
Sodium	140	137	136L	139	139	138	137-151 mEq/L
Potassium	4.2	4.4	5.5H	4.8	4.4	4.6	3.6-5.2 mEq/L
Uric Acid	8.4H	7.6	7.4	8.6H	6.9	8.9H	4-8 mg/dl
Total Protein	6.8	6.3L	6.3L	6.0L	6.6	6.3L	6.4-8.0 g/dl
Globulin	2.10	1.80	2.10	1.70L	1.80	2.0	1.8-3.4 g/dl
Triglyceride	71	210H	100	118	97	70	0-207 U/L
LDH	233	198	374H	194	169	134	73-233 U/L
Hematocrit	48.4	50.2H	48.9	47.3	46.7	47.5	40-50 Vol. %
Hemoglobin	16.3	17.1H	16.3	15.8	15.9	16.5	13.3-16.7 GMS %
Mono	11H	11H	9	0	13H	10	0-10 %

L = low H = high ND = not done

Symptoms and Physical Findings:

Formulation D-522: Forty-five minutes after ingestion of Formulation D-522, the subject reported mild abdominal cramps. After 2 hours, the cramps diminished but still persisted to some degree until 8 hours post dose when dinner was served. At 4 hours and at 4 hours and 45 minutes post dose, the subject passed liquid stools, each time feeling some relief of the abdominal cramps. Thereafter, the subject was asymptomatic and the physical examination remained unchanged.

Formulation E-556: Beginning 1 hour after dosing with Formulation E-556 and continuing until 8 hours post dose, the subject experienced vague abdominal discomfort, without nausea or diarrhea. Beginning on Day 11 the subject experienced recurrent, sharp, acute pain between the base of the second and third metacarpals of the right hand, each episode lasting from 30 minutes to 2 hours. Physical examination for ganglion and other abnormalities at that time was negative, and it was concluded that the symptoms were neuromuscular and not study related. The subject was otherwise asymptomatic and the physical examination remained unchanged.

Code: 360 (cont'd)

Abnormalities Comment: The subject demonstrated an elevated uric acid on 3 occasions ranging from 8.4 to 8.9 mg/dl both before and after dosing. He showed an isolated elevation of serum LDH of 374 U/L on Day 2 of the first study interval. He demonstrated a persistent depression of serum total protein both before and after dosing. His monocytes were also elevated on 3 occasions both before and after dosing, including a monocyte of 13 per cent on Day 2 of the second study interval. Other abnormalities were minimal and inconsistent and not considered to be study related.

Conclusions: Mild abdominal cramps and 2 liquid stools following ingestion of Formulation D-522, and vague abdominal discomfort beginning 1 hour after ingestion of Formulation E-556 considered probably related to ingestion of WR 180,409·H_3PO_4·

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EXPLANATION
ANTIMALARIAL DRUG PROJECT
EXPERIMENT NUMBER 14
Pharmacokinetics of WR 180,409·H_3PO_4
(A Pyridinemethanol) Following Oral Administration

GENTLEMEN:

This document explains the nature of the study, its purpose, procedures, risks, and benefits. You will be given the opportunity after reading it to ask additional questions. The present study will be conducted in three parts. If you choose to participate as a research subject, you may select only one of the three parts of the study.

The study for which you have applied involves taking by mouth the antimalarial drug WR 180,409·H_3PO_4, (A Pyridinemethanol). WR 180,409·H_3PO_4, a substituted pyridinemethanol, is the first compound of this chemical class to be tested in the U.S. Army Antimalarial Program. It represents a potential new class of antimalarial drug. In animal test systems, the compound was exceptionally well tolerated and had excellent antimalarial activity.

A Clinical Phase I safety and tolerance study with WR 180,409·H_3PO_4 was recently completed. Single doses of 5 to 1500 mg were administered to a total of 22 subjects in a double-blind rising dose study. Intolerance to the drug occurred at the 1000 mg dose level. One or more symptoms occurred including nausea, vomiting, dizziness and "mental fuzziness". Onset of symptoms was generally within 8 hours of drug administration, though one individual who took 1500 mg vomited 24 hours later. In all cases, the symptoms had subsided by 32 hours after dosing. There were no physical abnormalities or laboratory abnormalities attributed to the drug.

There are no data from human studies concerning the absorption and elimination pattern of this drug. In order to design further Phase I and Phase II studies with WR 180,409·H_3PO_4 additional information is needed to accurately determine the pattern in which the drug is absorbed and excreted. Therefore, the present study will be conducted in three parts.

Part I.

An initial pilot study will be conducted in which 750 mg of the drug will be administered orally to four subjects. Two will be given the drug in the form of a 250 mg capsule formulation and two will be given the drug in the form of a 250 mg tablet formulation. Ten ml of blood will be drawn at the times specified in Table I-A, page 13, to measure the drug serum concentrations to determine rates of absorption and elimination.

The schedule for Part I of the study is presented in the following schematic.

TABLE I

SCHEMATIC STUDY PLAN FOR PART I - PILOT STUDY

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	14 Mon	21 Mon
Dose		X						
Physical Exam	X		X					X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Laboratory Tests[+]	X		X					X
Blood for Drug Assay[++]		X	X	X	X	X———	X	X
Immunologic Studies[‡]	X		X					

*Controlled Environment

[+]Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

[++]Drug Assay: Each subject immediately prior to drug administration, and after dosing at 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 30, 36, 40, 44, 48, 60, 72 hours; and on study days 5, 7, 8, 14, and 21. (See Table I-A, page 13)

[‡]In addition to the blood samples listed in the protocol, 10 ml of clotted blood and 20 ml of heparinized blood will be drawn on Day 0 (prior to drug administration) and again on Day 2 (1 day after drug administration). The 20 ml sample will be drawn through a 19 gauge needle into a heparin rinsed syringe containing < 0.5 ml heparin. It will be stored and transported in the syringe at room temperature. These specimens will be used to measure serum IgG, IgM, and IgA, and to determine the proportion of circulating T-lymphocytes (E-rosettes) and B-lymphocytes (EAC-rosettes).

TABLE I-A: WR 180,409·H_3PO_4 (A Pyridinemethanol)
Specimen Collection Schedule for Drug Assay
PART I

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME		BLOOD VOLUME (ml)
Day 1	1	0	Prior to Dosing	10
	2	1 hr	9:00 AM	10
	3	2 hr	10:00 AM	10
	4	4 hr	NOON	10
	5	6 hr	2:00 PM	10
	6	8 hr	4:00 PM	10
	7	12 hr	8:00 PM	10
	8	16 hr	MIDNIGHT	10
	9	20 hr	4:00 AM	10
Day 2	10	24 hr	8:00 AM	10
	11	28 hr	NOON	10
	12	30 hr	2:00 PM	10
	13	36 hr	8:00 PM	10
	14	40 hr	MIDNIGHT	10
	15	44 hr	4:00 AM	10
Day 3	16	48 hr	8:00 AM	10
	17	60 hr	8:00 PM	10
Day 4	18	72 hr	8:00 AM	10
HOME				
Day 5	19	96-98 hr	8:00-10:00 AM	10
Day 7	20	144-146 hr	8:00-10:00 AM	10
Day 8	21	168-170 hr	8:00-10:00 AM	10
Day 14	22	312-314 hr	8:00-10:00 AM	10
Day 21	23	480-482 hr	8:00-10:00 AM	10
			TOTAL	230 ml

Part II.

This study will employ 3 groups of 4 subjects for a simple two-way cross-over administration. Four (4) subjects will be admitted to the unit as a group. Two subjects will be given the tablet formulation and two will be given the capsule formulation at the initiation of the study. You will receive one dose of each of the drug formulations designated according to the sequence shown in the table below.

PART II
SEQUENCE OF DRUG ADMINISTRATION

GROUP	SUBJECT	1st DOSING	2nd DOSING
A	1	E-556*	D-522
A	2	E-556	D-522
A	3	D-522+	E-556
A	4	D-522	E-556
B	5	E-556	D-522
B	6	E-556	D-522
B	7	D-522	E-556
B	8	D-522	E-556
C	9	E-556	D-522
C	10	E-556	D-522
C	11	D-522	E-556
C	12	D-522	E-556

*Lafayette Pharmacal, Inc. - 250 mg capsules

+INTERx - 250 mg tablets

The schedule for Part II of the study is presented in the schematic on page 16.

TABLE II

SCHEMATIC STUDY PLAN FOR PART II
COMPARATIVE BIOAVAILABILITY

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri*	7 Mon	~3-7 x $T_{\frac{1}{2}}$+ Mon
Dose		X					
Physical Exam	X		X				X
Interview	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Laboratory Tests++	X		X				X
Blood for Drug Assay+++							

*Controlled Environment

+The entire sequence will then be repeated after an interval of ~3-7 times the elimination half-life determined in Part I, with each subject taking the same dose of the opposite formulation of WR 180,409·H_3PO_4 the second time.

++Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

+++Drug Assay: The schedule of blood sampling will be determined by information obtained from Part I of the study. A total of approximately 36 samples of 10 ml each will be drawn over a period to include 3-7 times the elimination half-life of the drug.

Blood (10 ml) will be drawn at specific times after you take the drug to measure the amount of drug present. In addition, we will collect all of your urine during the first four days you are on the unit.

TABLE IIA: Schematic Drug Administration and Assay Specimen Collection Schedule

Dose: 750 mg WR 180,409·H_3PO_4
sequence as per explanation pg.15

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME		SPECIMEN VOLUME (ml)
Day 1 Tuesday	1	0	Prior to Dosing	10
	2	1 hr	9:00 AM	10
	3	2 hr	10:00 AM	10
	4	4 hr	NOON	10
	5	6 hr	2:00 PM	10
	6	8 hr	4:00 PM	10
	7	12 hr	8:00 PM	10
	8	16 hr	MIDNIGHT	10
Day 2 Wednesday	9	22 hr	6:00 AM	10
	10	28 hr	NOON	10
	11	34 hr	6:00 PM	10
	12	40 hr	MIDNIGHT	10
Day 3 Thursday	13	48 hr	8:00 AM	10
	14	56 hr	4:00 PM	10
	15	64 hr	MIDNIGHT	10
Day 4 Friday	16	72 hr	8:00 AM	10
HOME				
Day 5 Saturday	17	96 hr	8:00 AM	10
Day 7 Monday	18	144 hr	8:00 AM	10
Day 9 Wednesday	19	192 hr	8:00 AM	10
Day 11 Friday	20	240 hr	8:00 AM	10
Day 14 Monday	21	312 hr	8:00 AM	10
Day 17 Thursday	22	384 hr	8:00 AM	10
Day 21* Monday	23	480 hr	8:00 AM	10
			TOTAL	230 ml

*Day 0 for study interval 2nd drug administration

Part III. *

An additional four subjects will be needed to complete part three of the study. The information obtained from Parts I and II of the study will determine which formulation will be used in Part III. You will be given single doses of the drug on three separate occasions. Three different doses will be administered to each individual. It is anticipated that these doses will be 250 mg, 500 mg, and 750 mg pending results of Part II of the study. Two of you will receive the three doses in increasing order (250, 500, 750 mg), and two of you will receive the drug in decreasing order (750, 500, 250 mg). The specifics for Part III of the study are presented in the schematic below:

TABLE III

SCHEMATIC STUDY PLAN FOR PART III

Day of Study Day of Week	0 Mon*	1 Tue*	2 Wed*	3 Thu*	4 Fri	7 Mon	~3-7 x $T_{\frac{1}{2}}$+ Mon
Dose		X					
Physical Exam	X		X				X
Interview	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Laboratory Tests++	X		X				X
Blood for Drug Assay+++							

*Controlled Environment

+The entire sequence will be repeated twice beginning each time after an interval of ~3-7 times the elimination half-life of the drug as determined in previous studies. The subject will receive a total of 3 different single oral doses either in increasing or decreasing order.

++Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alk. Phos., SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies will be done as clinically indicated.

* Part III of Experiment #14 was cancelled.

+++Drug Assay: The schedule of blood sampling will be determined by information obtained from previous parts of the study. A total of approximately 20 samples of 10 ml each will be drawn over a period to include 3-7 times the elimination half-life of the drug.

You have already had many of the examinations listed in the Schematic Study Plans as part of your qualification examination.

No matter which part of the study you select to participate in, you will be admitted to the research unit for the first 4 days. You will be seen on brief visits thereafter for a period of time specific to your portion of the study. On the last day of your part of the study you will have a complete physical examination.

During the interval in the research unit the entire group will remain together with a member of the Unit Staff and will function according to their direction. Facilities provided while participating in the study include room and board with a study-lounge area.

On the day the drug is to be administered, you will have a liquid breakfast (Sustacal) at 6:00 a.m. and lunch will be withheld. You will be given the drug at 8:00 a.m.. You may have water as you wish until 2:00 p.m., at which time you may have a light lunch. Beginning at 5:00 p.m. you may resume the normal diet you select from the hospital menu until you are discharged from the unit.

At your discretion, 15 minutes before drug administration, a small teflon catheter can be placed in 1 of your arm veins. This will be used to obtain blood samples during the day you are dosed. In this way, repeated venipunctures may not be necessary on that day.

Ten ml of venous blood will be drawn by a staff nurse for each drug assay. Six ml of the blood will be transferred to a heparin-rinsed teflon capped glass tube and stored at -20°C pending transportation to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. The drug will be assayed as a parent compound by high pressure liquid chromatography. This method has previously been employed for drug assay in animal blood samples and spiked human samples and is working well. Four ml of the blood will be centrifuged and the serum separated. The serum will be transported to the Department of Pharmacology, WRAIR, for bioassay for antimalarial activity.

It is important that the blood be obtained as nearly as possible to the times specified in your part of the study. On the days you come in for blood drawing, it is important that you eat a light breakfast (i.e., cereal, milk, juice, coffee, bread -- no eggs or bacon). It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs, and lack of proper sleep may affect the level of drug in your blood on any given day.

The Human Use Committee is also looking after your safety. They insure that you are not subjected to undue risk and discomfort. A member of this committee will be available to speak with you at the Washington Hospital Center. After members of the investigating team and the Human Use Committee are satisfied that you understand the study and the written informed consent form, you will be permitted to sign it.

No subject may participate without a signed consent. By signing the informed consent you signify that the study has been explained to you with regard to its risks and requirements and you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to Americans, civilian and military, who may travel to these areas. For this reason, especially, your participation must be voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent at any time without prejudice.

SUBJECT AGREEMENT

CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled, Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document entitled, "EXPLANATION: AMDP EXPERIMENT NUMBER 14: Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration," which I have signed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examinations, if in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____	_____
Date	Witness - Human Use Comm. Cert.
_____	_____
Signature	Investigator Certification
_____	_____
Address	Witness

REAFFIRMATION OF CONSENT:

_____	_____
Date	Witness
_____	
Signature	

BMI-C2

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FINAL REPORT

EXPERIMENT NUMBER 15

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

TABLE OF CONTENTS

SUBJECT	PAGE
ABSTRACT	85
INTRODUCTION	86
METHODS AND MATERIALS	87
RESULTS	92
DISCUSSION	94
CONCLUSION AND RECOMMENDATIONS	94
TABLE VI - Laboratory Abnormalities	95-104
TABLE VII - Distribution of Laboratory Abnormalities by Laboratory Test and Study Day (WR 171,669)	105
TABLE VIII - Distribution of Laboratory Abnormalities by Laboratory Test and Study Day (Placebo)	106
TABLE IX - Phototoxicity Tests Results	107
Individual Subject Final Summary Sheets	108-135
Participant Summary	136
APPENDIX: a. Explanation for Potential Subjects b. Consent Form	

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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 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.

INTRODUCTION:

In previous Phase I and Phase II studies, WR 171,669 appeared to be an important new therapeutic agent against chloroquine-resistant Plasmodium falciparum. Six human volunteers experimentally infected with a multi-drug resistant strain of P. falciparum were cured with a dose of 250 mg administered orally every 6 hours for three days. When given to normal non-infected volunteers at a dose of 250 mg every six hours for five days, or 430 mg every eight hours for two or three days, most complained of mild nausea and abdominal discomfort. There was no vomiting or diarrhea. A 2 x 2, double-blind, rising single dose tolerance study was in progress at the University of Missouri when that contract was terminated in 1975. Single oral doses of 500 mg (2 individuals) and 750 mg (2 individuals) had been administered, and without adverse effect. Phototoxicity testing was included in all of the previous Phase I studies and was negative.

In preclinical testing, when administered at doses of 15mg/kg/day or higher for 28 days to beagle dogs, the drug caused weight loss, vomiting, diarrhea, low white blood cell counts and elevations of SGPT and BUN. Organic toxicity at higher doses occurred in lymphoid tissue, kidney, gastrointestinal tract, skeletal muscle and bone marrow. Doses in excess of 2000 to 3000 mg/kg were required to kill mice and rats. Recent phototoxicity testing in mice has indicated that there is definite toxicity at 80 mg/kg and equivocal toxicity at 40 mg/kg. In some instances the phototoxic response was delayed several days, implying that a metabolite may have been responsible.

The study reported here was undertaken to establish a maximum tolerated single dose and to study the pharmacokinetics of the drug.

METHODS AND MATERIALS:

1. Subject Qualification:

Twenty-eight healthy male subjects, age 18 to 42, weighing 60-90 kg and within 10% of ideal body weight, were employed for the study. They were recruited from the Washington, D.C. metropolitan area, and hired as temporary employees of BIO-MED, Inc.

Candidates were presented with a complete explanation of the background and procedures to be used in the study and of all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually in the presence of an investigator and a member of the Institutional Review Board. Each participant was given the opportunity to ask questions. The consent form was then read and those wishing to participate signed it in the presence of a witness, investigator, and member of the Institutional Review Board.

Candidates were screened to obtain subjects for study. The medical evaluation included a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin and G6PD.

Subject acceptability criteria were based upon the precept that the risks of participation should be slight and comparable for all subjects. Following this guideline, certain subjects were rejected routinely: for example, subjects with organic heart murmurs, splenomegaly, or active lesions on chest x-ray. The presence of conditions which did not increase risk or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes were not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean were cause for rejection. Deviations between 2 and 3 standard deviations from the mean were generally cause for rejection, dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would have caused rejection, whereas a serum sodium of 153 mEq/L of itself would not.

When doubt existed concerning entry acceptance of a subject for any reason, a decision was made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner questionable candidates were given full consideration and the integrity and ethics of the Research Team protected.

Each subject was then admitted to the controlled environment of the Clinical Facility in College Park for 3 days.

2. Dosing Design:

Subjects were admitted to the study in groups of 4 at each of 7 dosing levels as follows:

LEVEL	SUBJECTS	
	WR 171,669	Placebo
750 mg	2	2
750 mg	2	2
1000 mg	2	2
1250 mg	2	2
1500 mg	2	2
1750 mg	2	2
2000 mg	2	2

The drug and placebo bottles were coded at the Walter Reed Army Institute of Research to maintain the double-blind design. A sealed copy of the code was provided for the investigator to be used in the event of an emergency.

An interval of 1 week was required between each dosing level.

3. Drug Administration and Subject Evaluation:

The experiment design was a simple 2 x 2 double-blind, single rising dose design. Subjects were admitted to the unit in groups of 4 with 2 intended to receive the drug at the designated dose level and the other 2 to be given placebo. The drug WR 171,669, Lot #E454, was administered in the form of 250 mg hard gelatin capsules with matching placebos, Lot #388. All drug administration was done in the presence of a member of the investigative staff.

At 0600 on the day of dosing, the subjects drank 360 ml of Sustacal (Mead Johnson product) containing a total of 360 calories. The drug was administered at approximately 0800, varying slightly with each group. Measured amounts of water were taken ad lib until four hours after dosing, at which time the subjects were permitted to return to their regular diet, provided they had remained free of symptoms.

Interviews, physical examinations, phototoxicity testing and laboratory tests were conducted as outlined in the study schedule schematic below:

TABLE I
STUDY SCHEDULE SCHEMATIC

WR 171,669: Safety and Tolerance
and Preliminary Pharmacokinetics

Day of Study Day of Week	0* Mon	1* Tue	2* Wed	3 Thu	4 Fri	7 Mon	8 Tue	14 Mon	15 Tue
Dose		X							
Physical Exam	X		X					X	
Interview	X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X		X	
Laboratory Tests+	X		X	X		X		X	
Phototoxicity Test++	X		X			X		X	
Blood for Drug Assay†		X	X	X	X	X		X	
Immunologic Studies††	X		X						

*Controlled Environment

+Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Twenty-seven ml of venous blood were drawn on each scheduled laboratory test day. An additional lab test was done on two subjects who received drug in Group III on study day 21 between 1200 and 1400 hours.

++Phototoxicity testing involved a 5 to 10 minute exposure to a UV-B100 A Black Ray Lamp of a small target spot on the back. The energy of exposure used was approximately 8.3 joules for white skinned subjects and approximately 16.5 joules for dark skinned subjects. This procedure has been demonstrated to be effective using methylpsoralen as a positive control. On study days 8 and 15 subjects reported for reading of phototoxicity tests.

†Drug Assay: 10 ml of venous blood were taken from each subject for each of 20 samples drawn over the experiment interval. See Drug Assay Specimen Collection and Time Schedule.

††In addition to the blood samples listed in the protocol, 10 ml of clotted blood and 20 ml of heparinized blood were drawn on Day 0 (prior to drug administration) and again on Day 2 (1 day after drug administration). The 20 ml sample was drawn through a 19 gauge needle into a heparin-rinsed syringe containing less than 0.5 ml heparin. It was stored in the syringe at room temperature and transported to the Department of Gastroenterology, Walter Reed Army Institute of Research. The heparinized samples were used to determine the proportion of circulating T-lymphocytes (E-rosettes) and B-lymphocytes (EAC-rosettes). Arrangements for these immunoassays and the results were the responsibility of the Contracting Officer Technical Representative.

4. Drug Assay Specimen Collection and Time Schedule:

Ten ml of venous blood were obtained for assay of WR 171,669 immediately prior to drug administration and following dosing at 15, 30, 90, 120, 150, 180, 210, 240, 270, 300 and 360 minutes, 8, 12, 24, 36, 48 and 72 hours and on study days 7 and 14.[1] A total of 200 ml of blood were collected over a period of two weeks. Since this is a double-blind design, samples were also taken from the subjects given the placebo. An indwelling venous catheter was used whenever possible to avoid repeated venipunctures.

The blood for each drug assay was drawn by a staff nurse. Six ml of the blood were transferred to a heparin-rinsed teflon capped glass tube and stored at -20° C pending transportation to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. As of Nov. 26, 1980, the specimens from Groups I, II and III had been sent to WRAIR; specimens from Groups IV through VII remain at BIO-MED, Inc. The drug is to be assayed as a parent compound by high pressure liquid chromatography. This method has previously been employed for drug assay in animal blood samples and spiked human samples and has worked well.

Four ml of the blood were centrifuged and the serum separated. The serum from Groups I and II has been sent to the Department of Pharmacology, WRAIR, for bioassay of antimalarial activity. The serum from Groups III through VII remains at BIO-MED, Inc.

[1] Note: An additional assay was done on the 2 subjects who received drug in Group III on study day 21 between 1200 and 1400 hours.

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TABLE II: DRUG ASSAY COLLECTION

DAY OF THE STUDY	SPECIMEN	BLOOD SPECIMEN TIME	BLOOD VOLUME (ml)
1	1	Prior to dosing	10
	2	15 min	10
	3	30 min	10
	4	90 min	10
	5	120 min	10
	6	150 min	10
	7	180 min	10
	8	210 min	10
	9	240 min	10
	10	270 min	10
	11	300 min	10
	12	360 min	10
	13	8 hr	10
	14	12 hr	10
2	15	24 hr	10
	16	36 hr	10
3	17	48 hr	10
4	18	72 hr	10
7	19	144-146 hr	10
14	20	312-314 hr	10
		TOTAL	200 (ml)

TABLE III: TOTAL AMOUNT OF BLOOD WITHDRAWN FOR EACH STUDY SUBJECT FOLLOWING DRUG ADMINISTRATION

	HEMATOLOGY	CHEMISTTRY	IMMUNOLOGIC STUDIES	BLOOD ASSAY	TOTAL (ml)
DAY 0	7	20	30	-	57
1	-	-	-	140	140
2	7	20	30	20	77
3	7	20	-	10	37
4	-	-	-	10	10
7	7	20	-	10	37
14	7	20	-	10	37
			TOTAL		395 (ml)

RESULTS:

Twenty-eight subjects were enrolled in the study. All subjects completed the study. There were no significant departures from the study protocol. No emergent or adverse events occurred requiring special care or disposition.

Symptoms:

Symptoms were mild and not well-defined. In the majority of instances where symptoms occurred, the symptoms were not clearly related to the time of drug administration nor to the amount of drug:

TABLE IV: Symptoms in Drug Group

Subject#	Dose in mg	Symptom	Comment
400	750	None	
403	750	"gas pains" 9.5 hrs. PD x 2.5 hrs.	Vague symptoms, neg. P.E.
404	750	None	
406	750	1 hr. of nausea, day 4	Occurred after leaving facility
408	1000	None	
411	1000	3 formed small stools, 2 hrs. P.D.	No recurrence, no related symptoms
412	1250	None	
414	1250	"light-headedness", slight malaise, Day 2	Vague symptoms, neg. P.E.
416	1500	None	
417	1500	None	
420	1750	Mild abdominal pain 4 hrs. PD x 5 hrs.	Could well be drug effect
423	1750	Muscular "twitching", day 2	Mild, incidental
424	2000	Muscle cramp, day 4	Mild, incidental
426	2000	Slight anorexia, day 2	Slight, equivocal

In the placebo group, subject 419 for 1 hour complained of "cramps" in the upper abdomen 4 hours after receiving the capsules. Remarkably, there were no other symptoms in the placebo group.

Physical Findings:

No significant abnormalities were detected in the subjects during the course of the study.

Phototoxicity:

No phototoxicity was observed. See Table IX, page 22.

Laboratory Results:

Laboratory abnormalities are tabulated in Table VI, page 10.

The occurrence of each abnormality is displayed by day and type of test for the drug and placebo group in Tables VII and VIII.

There was no notable difference in frequency or degree of abnormality between the two groups.

There were, however, some abnormalities that are noteworthy: the SGPT and the SGOT. These are tabulated as follows:

TABLE V: SGOT AND SGOT ABNORMALITIES

Subject#	Dose	SGOT Day of Study 0	2	3	7	14	SGPT Day of Study 0	2	3	7	14
401	Placebo	24	26	28	50	25	42	39	44	44	49
410	Placebo						18	22	37	31	64
411	1000	19	16	14	48	27	15	15	19	80	139
416	1500						17	19	38	51	44
417	1500						46	60	85	66	37
422	Placebo						47	45	50	50	49
424	2000	19	31	84	18	14	25	44	142	46	14
425	Placebo						23	43	48	58	31

With casual inspection, the frequency of SGPT elevation (with corroborating SGOT elevation in a few instances) would seem to be equal in the drug and placebo groups. However, if one poses the possibility that SGPT elevations after discharge from the facility (days 7 and 14) are likely due to ethanol ingestion, then one is left with two subjects receiving relatively high doses of the drug who developed significant SGPT elevations on days 2 or 3. The possibility of minor, transient hepatic toxicity cannot be dismissed in 2 of the 14 subjects receiving the drug. There were no attendant symptoms in either instance.

DISCUSSION:

This was a smooth and - aside from the abnormality of hepatic enzymes - an uneventful study. No symptoms developed which could be clearly labelled as those connoting "intolerance".

Nevertheless, it must be noted that 8 of 14 subjects receiving drug had physical complaints of some sort - however mild or vague. Only 1 of 14 receiving placebo had a complaint.

Overall, the observer is left with the impression that although specific symptoms of intolerance were not seen, the group receiving drug was "less well" than the placebo group. That impression is based on the observations recorded in Table IV, which were made under the conditions of the double-blind design.

The possible association of transient SGPT elevation with drug administration in 2 of the subjects is troublesome. Should there be a true cause-and-effect relationship, the relationship is not dose-dependent for all subjects. One is therefore left with the possibility of seeking the prevalence of "hepatic intolerance" to this drug in the general population - an experimental endeavor of staggering proportions.

CONCLUSIONS AND RECOMMENDATIONS:

In terms of symptoms produced, the drug WR 171,669 was well tolerated up to and including single oral doses of 2000 mg. Transient SGPT elevation may have occurred as a consequence of taking the drug in 2 of 14 subjects.

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7 *	14	Normals
I 750 mg	400	Drug	Glucose	74	88	99	90	132H	93	66-114 mg/dl
			BUN	18	16	21	17	25H	21	9-21 mg/dl
			Creatinine	1.1	1.3	1.2	1.1	1.1	1.6H	0.8-1.4 mg/dl
			Potassium	4.1	4.0	4.1	3.9	3.5L	4.3	3.6-5.2 mEq/L
			Carbon Dioxide	28	30	30	28	28	22L	23-31 mEq/L
			Total Protein	6.4	6.9	6.5	6.2L	6.0L	6.8	6.4-8.0 g/dl
			Calcium	8.9L	9.3	8.9L	9.0	8.7L	9.4	9.0-10.9 mg/dl
			Hematocrit	43.8	45.6	43.3	42.4	39.7L	42.2	40-50 Vol %
			Mono	11H	11H	9	9	9	8	0-10 %
I	401	Placebo	Glucose	86	124H	94	85	100	101	66-114 mg/dl
			Sodium	138	136L	140	138	140	139	137-151 mEq/L
			Potassium	3.5L	3.7	3.5L	3.5L	3.5L	3.7	3.6-5.2 mEq/L
			Carbon Dioxide	28	29	32H	31	30	29	23-31 mEq/L
			SGOT	23	24	26	28	50H	25	0-47 U/L
			SGPT	47	42	39	44	44	49H	0-47 U/L
			Hematocrit	41.8	41.0	44.4	44.0	40.7	38.4L	40-50 Vol %
			Hemoglobin	13.9	13.9	14.7	14.9	13.6	13.2L	13.3-16.7 GMS %
			RBC	4.67	4.59	4.87	4.86	4.52	4.28L	4.3-5.7 mill/cu mm
			IgG	ND	1480	1800H	ND	ND	ND	816-1654 mg/dl

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

* Code # 400 values done on study day 8.

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
I 750 mg	402	Placebo	BUN	17	22H	18	17	19	15	9-21 mg/dl
			Total Protein	6.9	6.5	6.9	6.2L	7.0	7.1	6.4-8.0 g/dl
			Triglyceride	166	137	177	209H	192	184	0-207 mg/dl
I	403	Drug	Carbon Dioxide	34H	31	32H	33H	33H	31	23-31 mEq/L
			IgG	ND	1070	1700H	ND	ND	ND	635-1400 mg/dl
			IgA	ND	325H	245	ND	ND	ND	60-297 mg/dl
			Eosin	2	3	4	6H	4	3 **	0-5 %
II 750 mg	404	Drug	Carbon Dioxide	29	31	31	30	31	32H	23-31 mEq/L
			Total Protein	7.1	6.8	6.1L	5.9L	6.4	6.9	6.4-8.0 g/dl
			Phosphate	2.2L	2.9	3.6	3.7	2.5	2.3L	2.5-4.5 mg/dl
			Iron	134	162H	124	87	139	144	40-150 MCG/dl
			Lymph	34	41	18L	35	32	35	19-59 %
			Eosin	6H	5	1	5	14H	8H	0-5 %
II	405	Placebo	BUN	10	16	14	14	24H	13	9-21 mg/dl
			Total Protein	7.4	7.1	6.9	6.3L	6.8	7.2	6.4-8.0 g/dl
			Phosphate	2.6	2.7	2.8	2.8	2.3L	2.3L	2.5-4.5 mg/dl
			WBC	5.5	4.7	6.4	5.8	11.2H	6.5	3.1-9.5 thou/cu mm
			Eosin	3	3	3	4	3	8H	0-5 %

** Eosin value for study day 17

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
II 750 mg	406	Drug	Creatinine	1.4	1.5H	1.2	1.4	1.5H	1.4	0.8-1.4 mg/dl
			Carbon Dioxide	30	28	29	32H	28	28	23-31 mEq/L
			LDH	295H	201	163	167	193	252H	73-233 U/L
II	407	Placebo	BUN	8L	10	10	8L	7L	6L	9-21 mg/dl
			Potassium	4.3	4.3	3.9	4.0	3.5L	3.5L	3.6-5.2 mEq/L
			Uric Acid	3.5L	3.5L	2.7L	3.0L	3.1L	3.2L	4-8 mg/dl
			Total Protein	6.8	7.1	6.0L	6.1L	6.6	6.5	6.4-8.0 g/dl
			Calcium	9.5	10.0	8.9L	9.2	9.3	9.2	9.0-10.9 mg/dl
			Phosphate	2.5	3.1	4.3	3.3	2.7	2.4L	2.5-4.5 mg/dl
			Iron	79	102	83	160H	68	56	40-150 MCG/dl
			Lymph	22	20	26	19	18L	22	19-59 %
			Mono	9	11H	11H	11H	8	6	0-10 %
III 1000 mg	409	Placebo	BUN	16	23H	19	19	23H	22H	9-21 mg/dl
			Sodium	144	140	135L	141	140	140	137-151 mEq/L
			Uric Acid	7.7	7.8	5.9	6.3	7.9	8.9H	4-8 mg/dl
			Total Protein	7.2	7.1	6.1L	6.9	7.0	7.0	6.4-8.0 g/dl
			Iron	84	70	40	55	383H	49	40-150 MCG/dl
			Hematocrit	42.3	41.1	38.6L	39.3L	40.8	42.1	40-50 Vol %
			Hemoglobin	13.6	13.9	12.8L	13.1L	13.2L	13.7	13.3-16.7 GMS %
			MCV	83	81L	82	82	83	83	82-98 cu microns
			MCH	26.4L	27.5	27.3	27.4	26.9L	27.3	27-33 micromicroGM
			IgM	ND	45	40L	ND	ND	ND	41-248 mg/dl

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	21	Normals
III 1000mg	408	Drug	Glucose	127H	93	62L	80	87	47L	81	66-114 mg/dl
			Potassium	5.0	4.3	5.3H	4.6	4.1	4.9	4.6	3.6-5.2 mEq/L
			Carbon Dioxide	29	29	30	29	31	32H	28	23-31 mEq/L
			Total Protein	6.3L	6.3L	6.3L	6.6	7.4	6.8	7.1	6.4-8.0 g/dl
			Alka Phos	83	77	78	74	86	87	99H	26-94 U/L
			Iron	128	104	90	131	145	66	241H	40-150 MCG/dl
			IgG	ND	560L	600L	ND	ND	ND	ND	635-1400 mg/dl
			IgA	ND	310H	350H	ND	ND	ND	ND	60-297 mg/dl
III	411	Drug	Calcium	9.5	9.4	9.1	9.3	9.5	8.8L	9.4	9.0-10.9 mg/dl
			SGOT	20	19	16	14	48H	27	16	0-47 U/L
			SGPT	24	15	15	19	80H	139H	30	0-47 U/L
			Hemoglobin	16.2	17.0H	16.2	15.5	14.8	15.5	16.0	13.1-16.7 GMS %
			Eosin	2	4	5	3	4	7H	2	0-5 %
			UA - ph	6	6	6	5	7	7	8H	5-7
			UA - WBC	N	2	N	3	8H w/ clumps	occ	5 w/ clumps	0-5
			IgG	ND	1550H	1260	ND	ND	ND	ND	635-1400 mg/dl

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
III 1000 mg	410	Placebo	Carbon Dioxide	26	30	31	32H	27	28	23-31 mEq/L
			Total Protein	7.4	6.7	6.7	7.3	6.8	6.2L	6.4-8.0 g/dl
			Calcium	9.4	8.9L	9.1	9.5	9.1	8.6L	9.0-10.9 mg/dl
			Phosphate	3.8	2.4L	3.2	3.0	2.5	3.0	2.5-4.5 mg/dl
			Triglyceride	266H	147	134	151	250H	83	0-207 mg/dl
			SGPT	73H	18	22	37	31	64H	0-47 U/L
			Iron	98	83	97	153H	98	66	40-150 MCG/dl
			UA - protein	N	N	N	N	N	Trace H	N
IV 1250 mg	412	Drug	BUN	10	12	10	8L	8L	14	9-21 mg/dl
			Creatinine	1.5H	1.4	1.4	1.5H	1.5H	1.5H	0.8-1.4 mg/dl
			Uric Acid	8.2H	7.9	7.2	6.9	8.5H	9.5H	4-8 mg/dl
			Total Protein	7.1	7.5	6.4	6.3L	6.8	7.0	6.4-8.0 g/dl
			Albumin	4.4	4.5	4.0L	3.9L	4.2	4.3	4.1-5.1 g/dl
			Alka Phos	100H	99H	86	87	86	84	26-94 U/L
			Iron	144	107	108	160H	156H	109	40-150 MCG/dl
			RBC	5.83H	5.86H	5.46	5.38	5.30	5.34	4.3-5.7 mill/cu mm
			Eosin	5	7H	7H	8H	3	8H	0-5 %
			MCV	82	82	83	81L	82	80L	82-98 cu microns
			MCH	27.4	27.0	27.2	27.1	26.9L	26.7L	27-33 micromicroGM
			UA - protein	N	N	N	N	Trace H	N	N
			UA - WBC	TNTC H	TNTC H	TNTC H	10H	TNTC H	N	0-5

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
IV 1250 mg	413	Placebo	Total Protein	6.8	7.2	6.8	6.7	6.5	6.3L	6.4-8.0 g/dl
			Phosphate	2.7	2.3L	2.3L	2.4L	2.6	2.7	2.5-4.5 mg/dl
			Eosin	6H	7H	5	5	1	4	0-5 %
			UA - RBC	N	N	N	8H	N	N	0-3
IV	414	Drug	Glucose	77	86	83	81	50L	77	66-114 mg/dl
			Potassium	4.1	3.9	4.2	4.6	3.4L	3.6	3.6-5.2 mEq/L
			Eosin	5	4	4	4	4	6H	0-5 %
			UA - protein	N	N	N	N	N	Trace H	N
			IgA	ND	315H	260	ND	ND	ND	60-297 mg/dl
IV	415	Placebo	Iron	170H	136	98	186H	137	86	40-150 MCG/dl
			Eosin	6H	7H	7H	6H	6H	9H	0-5 %
			MCH	32.9	32.5	32.4	33.1H	32.6	32.6	27-33 micromicroGM
			IgM	ND	40L	26L	ND	ND	ND	41-248 mg/dl

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
V 1500 mg	416	Drug	BUN	13	14	9	7L	13	9	9-21 mg/dl
			Total Protein	7.2	6.9	6.1L	6.3L	6.2L	6.1L	6.4-8.0 g/dl
			Phosphate	3.2	3.9	4.6H	4.0	3.8	3.4	2.4-4.5 mg/dl
			Triglyceride	146	228H	422H	253H	165	167	0-207 mg/dl
			Alka Phos	154H	137H	152H	139H	130H	117H	29-94 U/L
			SGPT	20	17	19	38	51H	44	0-47 U/L
			Hematocrit	44.6	43.7	41.7	39.8L	38.7L	41.0	40-50 Vol %
			RBC	4.81	4.70	4.58	4.35	4.23L	4.44	4.3-5.7 mill/cu mm
			IgG	ND	720	622L	ND	ND	ND	635-1400 mg/dl
V	417	Drug	Potassium	3.9	3.8	3.7	3.8	3.5L	3.8	3.6-5.2 mEq/L
			Triglyceride	70	195	167	237H	263H	126	0-207 mg/dl
			Alka Phos	86	86	93	103H	105H	95H	26-94 U/L
			SGPT	30	46	60H	85H	66H	37	0-47 U/L
			Iron	133	92	94	144	232H	145	40-150 MCG/dl
			UA - protein	N	N	N	N	Trace H	Trace H	N
V	418	Placebo	Carbon Dioxide	32H	30	30	34H	32H	31	23-31 mEq/L
			Albumin	5.0	5.2H	4.8	4.7	4.6	4.8	4.1-5.1 g/dl
			Iron	79	104	73	131	191H	100	40-150 MCG/dl
			Hematocrit	45.8	45.1	41.8	42.6	50.6H	43.2	40-50 Vol %
			Hemoglobin	15.5	15.2	14.2	14.4	16.8H	14.9	13.3-16.7 GMS %
			UA - protein	N	N	N	N	1+ H	Trace H	N

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
V 1500 mg	419	Placebo	BUN	14	11	10	9	8L	11	9-21 mg/dl
			Creatinine	1.4	1.5H	1.4	1.4	1.4	1.5H	0.8-1.4 mg/dl
			Carbon Dioxide	32H	30	31	34H	29	30	23-31 mEq/L
			Total Protein	7.0	6.3L	5.7L	6.5	6.2L	6.4	6.4-8.0 g/dl
			Albumin	4.5	4.3	3.9L	4.1	4.1	4.2	4.1-5.1 g/dl
			Iron	49	123	34L	30L	83	50	40-150 MCG/dl
			IgG	ND	1000	800L	ND	ND	ND	816-1654 mg/dl
			IgM	ND	36L	68	ND	ND	ND	47-275 mg/dl
VI 1750 mg	420	Drug	Creatinine	1.4	1.5H	1.3	1.3	1.3	1.4	0.8-1.4 mg/dl
			Carbon Dioxide	32H	29	31	31	32H	31	23-31 mEq/L
			Uric Acid	8.1H	7.5	6.1	5.8	8.2H	7.4	4-8 mg/dl
			Iron	106	66	55	156H	113	101	40-150 MCG/dl
			UA - protein	Trace H	N	N	N	N	Trace H	N
VI	421	Placebo	BUN	9	9	10	8L	9	9	9-21 mg/dl
			Carbon Dioxide	32H	29	30	32H	30	30	23-31 mEq/L
			Iron	148	149	88	64	171H	50	40-150 MCG/dl
			UA - protein	Trace H	N	N	N	N	Trace H	N

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
VI 1750 mg	422	Placebo	Triglyceride	94	120	175	270H	116	203	0-207 mg/dl
			Alka Phos	95H	93	83	92	107H	92	26-94 U/L
			SGPT	45	47	45	50H	50H	49H	0-47 U/L
			Iron	79	89	66	99	377H	71	40-150 MCG/dl
			UA - protein	N	N	N	N	Trace H	N	N
VI	423	Drug	Carbon Dioxide	32H	29	32H	34H	31	30	23-31 mEq/L
			Alka Phos	111H	113H	113H	120H	107H	113H	26-94 U/L
			UA - protein	N	Trace H	N	N	N	N	N
VII 2000 mg	424	Drug	Total Protein	6.7	6.6	6.5	7.3	6.2L	6.8	6.4-8.0 g/dl
			Triglyceride	125	157	173	119	240H	106	0-207 mg/dl
			SGOT	17	19	31	84H	18	14	0-47 U/L
			SGPT	19	25	44	142H	46	14	0-47 U/L
			Hematocrit	46.4	45.5	44.2	48.3	39.4L	42.6	40-50 Vol %
			Retic Count	ND	ND	ND	ND	ND	1.8H	0.5-1.5 %

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

EXPERIMENT NO. 15: CONINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS

TABLE VI: Laboratory Abnormalities Table

Group	Code Number	Drug/ Placebo	Test	Study Days SCR	0	2	3	7	14	Normals
VII 2000 mg	425	Placebo	Potassium	4.3	3.5L	5.0	4.1	4.5	5.4H	3.6-5.2 mEq/L
			Phosphate	3.5	4.4	3.9	5.1H	3.6	3.8	2.5-4.5 mg/dl
			SGPT	25	23	43	48H	58H	31	0-47 U/L
			Eosin	9H	7H	ND	8H	10H	9H	0-5 %
			MCV	95	100H	ND	98	98	98	82-98 cu microns
			MCH	32.6	33.6H	ND	33.0	32.5	32.8	27-33 micromicroGM
			IgM	ND	40L	36L	ND	ND	ND	41-248 mg/dl
			Retic Count	ND	ND	ND	ND	ND	2.4H	0.5-1.5 %
VII	426	Drug	Triglyceride	81	112	257H	351H	106	105	0-207 mg/dl
			Hematocrit	42.7	43.2	41.8	44.1	39.3L	41.3	40-50 Vol %
			Eosin	5	5	4	6H	6H	4	0-5 %
			IgG	ND	1900H	1400	ND	ND	ND	635-1400 mg/dl
VII	427	Placebo	Carbon Dioxide	31	32H	32H	32H	31	29	23-31 mEq/L
			Albumin	4.8	5.2H	4.4	4.9	4.7	5.0	4.1-5.1 g/dl
			Hematocrit	43.2	47.8	40.6	45.3	41.6	39.9L	40-50 Vol %
			Lymph	36	25	35	29	34	17L	19-59 %
			UA - protein	Trace H	Trace H	Trace H	N	Trace H	Trace H	N

KEY: H - high L - low ND - not done N - negative w/ - with occ - occasional TNTC - too numerous to count

TABLE VII - EXPERIMENT NO. 15

DISTRIBUTION OF LABORATORY ABNORMALITIES BY LABORATORY TEST AND STUDY DAY

TREATMENT: WR 171,669 * Subject tested study day 8

LABORATORY TEST	STUDY DAY 0	2	3	7	14	21	
BLOOD CHEMISTRIES							
Glucose		L		H*L	L		
BUN			LL	H*L			
Creatinine	HH		H	HH	HH		
Sodium							
Potassium		H		L*LL			
Chloride							
Carbon Dioxide		HH	HHH	HH	HHL		
Uric Acid				HH	H		
Total Protein	L	LLL	LLLL	LLL	L		
Albumin		L	L				
Globulin							
Calcium		L		L*	L		
Phosphate		H			L		
Cholesterol							
Triglycerides	H	HH	HH	HH			
Alka Phos	HHH	HH	HH	HHH	HHH	H	
SGOT			H	H			
SGPT		H	HH	HHH	H		
LDH					H		
Total Bilirubin							
Retic Count					H		
HEMATOLOGY							
Hematocrit			H	L*LLL			
Hemoglobin	H						
RBC	H			L			
WBC							
Lymph		L					
Seg							
Mono	H						
Eosin	H	H	HHH	HH	HHHH		
% ATL							
MCV			L		L		
MCH				L	L		
MCHC							
Platelets							
Iron	H		HH	HH		H	
URINE							
pH							
Spec Gravity							
Protein	H			HH	HHH		
Glucose							
Microscopic							
Casts							
WBC	H	H	H	H	H	H	
RBC							
IgG	LHH	LHL					
IgA	LHH	L					
TOTAL NUMBER OF ABNORMALITIES	20	22	26	39	26	3	136

TABLE VIII - EXPERIMENT NO. 15

DISTRIBUTION OF LABORATORY ABNORMALITIES BY LABORATORY TEST AND STUDY DAY

TREATMENT: PLACEBO

* Subject tested study day 8

LABORATORY TEST	STUDY DAY 0	2	3	7	14	21	
BLOOD CHEMISTRIES							
Glucose	HH		L	L	L		
BUN	H		L	HHL	H		
Creatinine	H			H			
Sodium	L	L	L	L			
Potassium	L	L		L	LH		
Chloride		H					
Carbon Dioxide	H	H	HHHHH	H			
Uric Acid	L	L	L	L	HL		
Total Protein	L	LLL	LLL	L	LL		
Albumin	H	LH					
Globulin							
Calcium		L			L		
Phosphate	LL	L	HL	L	LL		
Cholesterol							
Triglycerides			HH	H			
Alka Phos				H			
SGOT				H			
SGPT			HH	HH	HHH		
LDH							
Total Bilirubin							
Retic Count					H		
HEMATOLOGY							
Hematocrit		L	L	H	LL		
Hemoglobin		L	L	LH	L		
RBC					L		
WBC				H			
Lymph				L	L		
Seg							
Mono	H	H	H				
Eosin	HHH	H	HH	HH	HHH		
% ATL							
MCV	LH						
MCH	H		H	L			
MCHC							
Platelets							
Iron		L	HHHL	HHHH			
URINE							
pH							
Spec Gravity							
Protein	H	H		HHH	HHH		
Glucose							
Microscopic							
Casts							
WBC							
RBC			H				
IgG		HL					
IgM	LLL	LLL					
TOTAL NUMBER OF ABNORMALITIES	23	23	29	31	26	00	132

TABLE IX - EXPERIMENT NO. 15

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

PHOTOTOXICITY TESTS RESULTS

Group Number	Dose Level	Subject Code	Placebo-P Drug-D	PTD* Effect	PD* Effect
I	750mg	#400	D	None	None
		#401	P	None	None
		#402	P	None	None
		#403	D	None	None
II	750mg	#404	D	None	None
		#405	P	None	None
		#406	D	None	None
		#407	P	None	None
III	1000mg	#408	D	None	None
		#409	P	None	None
		#410	P	None	None
		#411	D	None	None
IV	1250mg	#412	D	None	None
		#413	P	None	None
		#414	D	None	None
		#415	P	None	None
V	1500mg	#416	D	None	None
		#417	D	None	None
		#418	P	None	None
		#419	P	None	None
VI	1750mg	#420	D	None	None
		#421	P	None	None
		#422	P	None	None
		#423	D	None	None
VII	2000mg	#424	D	None	None
		#425	P	None	None
		#426	D	None	None
		#427	P	None	None

PTD-Prior to Dosing
PD-Post Dosing

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 750 mg DOSING DATE: 4/1/80 CODE: 400 AGE: 26
DOSE PER Kg: 11.96 mg/kg TIME DOSED: 0800 GROUP: I
DRUG HEIGHT: 162.56 cm WEIGHT: 62.73 kg

ABNORMALITIES:

DATE: 1980	3/11	3/31	4/1	4/2	4/3	4/4	4/7	4/8	4/14	4/15
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X			X	X			X	X	
6. CBC	X	X						X		
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	8	14	Normal Range
Glucose	74	88	99	90	132H	93	66-114 mg/dl
BUN	18	16	21	17	25H	21	9-21 mg/dl
Creatinine	1.1	1.3	1.2	1.1	1.1	1.6H	0.8-1.4 mg/dl
Potassium	4.1	4.0	4.1	3.9	3.5L	4.3	3.6-5.2 mEq/L
Carbon Dioxide	28	30	30	28	28	22L	23-31 mEq/L
Total Protein	6.4	6.9	6.5	6.2L	6.0L	6.8	6.4-8.0 g/dl
Calcium	8.9L	9.3	8.9L	9.0	8.7L	9.4	9.0-10.9 mg/dl
Hematocrit	43.8	45.6	43.3	4.24	39.7L	42.2	40-50 Vol %
Mono	11H	11H	9	9	9	8	0-10 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic during the study interval. The physical exam was normal and remained normal throughout the study interval.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal and inconsistent and not considered study related.

CONCLUSION: No adverse effect from drug.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 4/1/80 CODE: 401 AGE: 32
DOSE PER Kg: 0 mg/kg TIME DOSED: 0800 GROUP: I
PLACEBO HEIGHT: 198.12 cm WEIGHT: 90.68 kg

ABNORMALITIES:

DATE: 1980	3/11	3/31	4/1	4/2	4/3	4/4	4/7	4/8	4/14	4/15
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X		X	X		X		X	
6. CBC									X	
7. Platelets										
8. Immunoglobulins				X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Glucose	86	124H	94	85	100	101	66-114 mg/dl
Sodium	138	136L	140	138	140	139	137-151 mEq/L
Potassium	3.5L	3.7	3.5L	3.5L	3.5L	3.7	3.6-5.2 mEq/L
Carbon Dioxide	28	29	32H	31	30	29	23-31 mEq/L
SGOT	23	24	26	28	50H	25	0-47 U/L
SGPT	47	42	39	44	44	49H	0-47 U/L
Hematocrit	41.8	41.0	44.4	44.0	40.7	38.4L	40-50 Vol%
Hemoglobin	13.9	13.9	14.7	14.9	13.6	13.2L	13.3-16.7 GMS%
RBC	4.67	4.59	4.87	4.86	4.52	4.28L	4.3-5.7mil/cum
IgG	ND	1480	1800H	ND	ND	ND	816-1654 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject remained asymptomatic throughout the study interval. The physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Potassium was decreased slightly most of study interval. SGOT rose to 49 on study day 14. SGPT was elevated to 49 on Day 7, increased to 78 during the month following his participation. He was unable to come in for repeat testing until 3 months later, when value was within normal range. Other deviations were minimal or inconsistent and not considered to be drug related.

CONCLUSION: Transient SGOT, SGPT elevation, cause unknown.

BMI-MEB

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 4/1/80 CODE: 402 AGE: 21
DOSE PER Kg: 0 mg/kg TIME DOSED: 0800 GROUP: I
PLACEBO HEIGHT: 170.18 cm WEIGHT: 72.27 kg

ABNORMALITIES:

DATE: 1980	3/11	3/31	4/1	4/2	4/3	4/4	4/7	4/8	4/14	4/15
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry		X			X					
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	17	22H	18	17	19	15	9-21 mg/dl
Total Protein	6.9	6.5	6.9	6.2L	7.0	7.1	6.4-8.0 g/dl
Triglyceride	166	137	177	209H	192	184	0-207 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic and had an unchanged normal physical examination throughout the study interval.

ABNORMALITIES COMMENT: Abnormalities considered minimal and inconsistent and not of significance.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 750 mg DOSING DATE: 4/1/80 CODE: 403 AGE: 18
DOSE PER Kg: 8.97 mg/kg TIME DOSED: 0805 GROUP: I
DRUG HEIGHT: 180.97 cm WEIGHT: 83.64 kg

ABNORMALITIES:

DATE: 1980	3/24	3/31	4/1	4/2	4/3	4/4	4/7	4/8	4/14	4/15
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms			X							
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X			X	X		X			
6. CBC					X					
7. Platelets										
8. Immunoglobulins		X		X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	34H	31	32H	33H	33H	31	23-31 mEq/L
IgG	ND	1070	1700H	ND	ND	ND	635-1400 mg/dl
IgA	ND	325H	245	ND	ND	ND	60-297 mg/dl
Eosin	2	3	4	6H	4	3*	0-5 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 1 the subject complained of mild "gas pains" which started 9.5 hours after dosing and lasted for about 2.5 hours. He had an unchanged normal physical examination throughout the study interval.

ABNORMALITIES COMMENT: Carbon dioxide elevated 32 to 33 for most of the study interval. Other deviations were minimal or inconsistent and not considered of significance.

CONCLUSION: "Gas pains" possibly drug related.

*Eosin value for study day 17.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 750 mg
DOSE PER Kg: 10.31 mg/kg
DOSING DATE: 4/8/80
TIME DOSED: 0800
HEIGHT: 172.72 cm
CODE: 404 AGE: 26
GROUP: II
WEIGHT: 72.73 kg

ABNORMALITIES:

DATE: 1980	3/17	4/7	4/8	4/9	4/10	4/11	4/14	4/15	4/21	4/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X		X	X				X	
6. CBC	X			X			X		X	
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	29	31	31	30	31	32H	23-31 mEq/L
Total Protein	7.1	6.8	6.1L	5.9L	6.4	6.9	6.4-8.0 g/dl
Phosphate	2.2L	2.9	3.6	3.7	2.5	2.3L	2.5-4.5 mg/dl
Iron	134	162H	124	87	139	144	40-150 MCG/dl
Lymph	34	41	18L	35	32	35	19-59 %
Eosin	6H	5	1	5	14H	8H	0-5 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic and had an unchanged normal physical examination throughout the study interval.

ABNORMALITIES COMMENT: Abnormalities minimal and inconsistent and not considered significant.

CONCLUSION: No adverse effect from drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 4/8/80 CODE: 405 AGE: 23
DOSE PER Kg: 0 mg/kg TIME DOSED: 0800 GROUP: II
PLACEBO HEIGHT: 183.52 cm WEIGHT: 72.27 kg

ABNORMALITIES:

DATE: 1980	3/17	4/7	4/8	4/9	4/10	4/11	4/14	4/15	4/21	4/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry					X		X		X	
6. CBC							X		X	
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	10	16	14	14	24H	13	9-21 mg/dl
Total Protein	7.4	7.1	6.9	6.3L	6.8	7.2	6.4-8.0 g/dl
Phosphate	2.6	2.7	2.8	2.8	2.3L	2.3L	2.5-4.5 mg/dl
WBC	5.5	4.7	6.4	5.8	11.2H	6.5	3.1-9.5th/cumm
Eosin	3	3	3	4	3	8H	0-5 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic and had an unchanged normal physical examination throughout the study interval.

ABNORMALITIES COMMENT: Deviations were minimal or inconsistent and considered not significant.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE:	750 mg	DOSING DATE:	4/8/80	CODE: 406	AGE: 20
DOSE PER Kg:	10.70 mg/kg	TIME DOSED:	0800	GROUP:	II
DRUG		HEIGHT:	170.82 cm	WEIGHT:	70.11 kg

ABNORMALITIES:

DATE: 1980	3/24	4/7	4/8	4/9	4/10	4/11	4/14	4/15	4/21	4/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms						X				
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X			X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Creatinine	1.4	1.5H	1.2	1.4	1.5H	1.4	0.8-1.4 mg/dl
Carbon Dioxide	30	28	29	32H	28	28	23-31 mEq/L
LDH	295H	201	163	167	193	252H	73-233 U/L

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 4 became nauseated after leaving unit. Nausea lasted about 1 hour. Asymptomatic for the remainder of the study and physical exam remained normal.

ABNORMALITIES COMMENT: LDH was elevated on Screening and again on day 14 of study but had returned to normal when he returned for it to be repeated one week later. Other deviations were minimal or inconsistent and not considered significant.

CONCLUSION: No adverse reaction to drug.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg | DOSING DATE: 4/7/80 | CODE: 407 | AGE: 30
DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: II
PLACEBO | HEIGHT: 182.88 cm | WEIGHT: 78.64 kg

ABNORMALITIES:

DATE: 1980	3/17	4/7	4/8	4/9	4/10	4/11	4/14	4/15	4/21	4/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms									X	
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X		X	X		X		X	
6. CBC		X		X	X		X			
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	8L	10	10	8L	7L	6L	9-21 mg/dl
Potassium	4.3	4.3	3.9	4.0	3.5L	3.5L	3.6-5.2 mEq/L
Uric Acid	3.5L	3.5L	2.7L	3.0L	3.1L	3.2L	4-8 mg/dl
Total Protein	6.8	7.1	6.0L	6.1L	6.6	6.5	6.4-8.0 g/dl
Calcium	9.5	10.0	8.9L	9.2	9.3	9.2	9.0-10.9 mg/dl
Phosphate	2.5	3.1	4.3	3.3	2.7	2.4L	2.5-4.5 mg/dl
Iron	79	102	83	160H	68	56	40-150 MCG/dl
Lymph	22	20	26	19	18L	22	19-59 %
Mono	9	11H	11H	11H	8	6	0-10 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject was asymptomatic until day 14 when he complained of having "stomach cramps" for about 3 hours. Physical examination remained normal.

ABNORMALITIES COMMENT: Uric acid remained decreased throughout study interval. Other deviations were minimal or inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

BMI-MFB

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1000 mg
DOSE PER Kg: 14.10 mg/kg
DRUG

DOSING DATE: 4/15/80
TIME DOSED: 0805
HEIGHT: 180.34 cm

CODE: 408 AGE: 30
GROUP: III
WEIGHT: 70.91 kg

ABNORMALITIES:

DATE: 1980	3/11	4/14	4/15	4/16	4/17	4/18	4/21	4/22	4/28	4/29	5/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15	21
1. Symptoms											
2. Physical Exam											
3. Phototoxicity											
4. Urinalysis											
5. Biochemistry	X	X		X					X		X
6. CBC											
7. Platelets											
8. Immunoglobulins		X		X							

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	21	Normal Range
Glucose	127H	93	62L	80	87	47L	81	66-114 mg/dl
Potassium	5.0	4.3	5.3H	4.6	4.1	4.9	4.6	3.6-5.2 mEq/L
CarbonDioxide	29	29	30	29	31	32H	28	23-31 mEq/L
Total Protein	6.3L	6.3L	6.3L	6.6	7.4	6.8	7.1	6.4-8.0 g/dl
Alka Phos	83	77	78	74	86	87	99H	26-94 U/L
Iron	128	104	90	131	145	66	241H	40-150 MCG/dl
IgG	ND	560L	600L	ND	ND	ND	ND	635-1400 g/dl
IgA	ND	310H	350H	ND	ND	ND	ND	60-297 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: Total Protein values low during screening and day 0 and 2 and then normal thereafter. Alkaline phosphatase was 99 on day 21 and returned to normal on repeat testing. IgG values low on days 0 and 2 and IgA values high on days 0 and 2. Other laboratory abnormalities were minimal or inconsistent and not considered significant.

CONCLUSION: No adverse reaction to drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 4/15/80 CODE: 409 AGE: 27
DOSE PER Kg: 0 mg/kg TIME DOSED: 0805 GROUP: III
PLACEBO HEIGHT: 173.36 cm WEIGHT: 61.82 kg

ABNORMALITIES:

DATE: 1980	3/17	4/14	4/15	4/16	4/17	4/18	4/21	4/22	4/28	4/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry		X		X			X		X	
6. CBC	X	X		X	X		X			
7. Platelets										
8. Immunoglobulins				X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	16	23H	19	19	23H	22H	9-21 mg/dl
Sodium	144	140	135L	141	140	140	137-151 mEq/L
Uric Acid	7.7	7.8	5.9	6.3	7.9	8.9H	4-8 mg/dl
Total Protein	7.2	7.1	6.1L	6.9	7.0	7.0	6.4-8.0 g/dl
Iron	84	70	40	55	383H	49	40-150 MCG/dl
Hematocrit	42.3	41.1	38.6L	39.3L	40.8	42.1	40-50 Vol %
Hemoglobin	13.6	13.9	12.8L	13.1L	13.2L	13.7	13.3-16.7 GMS %
MCV	83	81L	82	82	83	83	82-98 cu micron
MCH	26.4L	27.5	27.3	27.4	26.9L	27.3	27-33micrmicrGM
IgM	ND	45	40L	ND	ND	ND	41-248 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: BUN slightly elevated on days 0, 7 and 14 then returned to normal on repeat testing. Hematocrit values were low on days 2 and 3 then returned to normal on day 7. Hemoglobin values were low on days 2, 3 and 7 then returned to normal on day 14.

CONCLUSION: No adverse effect from placebo admininstration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg | DOSING DATE: 4/15/80 | CODE: 410 | AGE: 41
DOSE PER Kg: 0 mg/kg | TIME DOSED: 0805 | GROUP: III
PLACEBO | HEIGHT: 180.34 cm | WEIGHT: 84.09 kg

ABNORMALITIES:

DATE: 1980	3/11	4/14	4/15	4/16	4/17	4/18	4/21	4/22	4/28	4/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis									X	
5. Biochemistry	X	X			X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	26	30	31	32H	27	28	23-31 mEq/L
Total Protein	7.4	6.7	6.7	7.3	6.8	6.2L	6.4-8.0 g/dl
Calcium	9.4	8.9L	9.1	9.5	9.1	8.6L	9.0-10.9 mg/dl
Phosphate	3.8	2.4L	3.2	3.0	2.5	3.0	2.5-4.5 mg/dl
Triglyceride	266H	147	134	151	250H	83	0-207 mg/dl
SGPT	73H	18	22	37	31	64H	0-47 U/L
Iron	98	83	97	153H	98	66	40-150 MCG/dl
UA - protein	N	N	N	N	N	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: SGPT elevated on screening day and day 14. Value was normal when subject returned for repeat testing.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1000 mg | DOSING DATE: 4/15/80 | CODE: 411 | AGE: 18
DOSE PER Kg: 12.94 mg/kg | TIME DOSED: 0805 | GROUP: III
DRUG | HEIGHT: 177.8 cm | WEIGHT: 77.27 kg

ABNORMALITIES:

DATE: 1980	3/24	4/14	4/15	4/16	4/17	4/18	4/21	4/22	4/24	4/25	5/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15	21
1. Symptoms		X	X								
2. Physical Exam											
3. Phototoxicity											
4. Urinalysis							X				X
5. Biochemistry							X		X		
6. CBC		X							X		
7. Platelets											
8. Immunoglobulins		X									

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	21	Normal Range
Calcium	9.5	9.4	9.1	9.3	9.5	8.8L	9.4	9.0-10.9 mg/dl
SGOT	20	19	16	14	48H	27	16	0-47 U/L
SGPT	24	15	15	19	80H	139H	30	0-47 U/L
Hemoglobin	16.2	17.0H	16.2	15.5	14.8	15.5	16.0	13.3-16.7 GMS %
Eosin	2	4	5	3	4	7H	2	0-5 %
UA - ph	6	6	6	5	7	7	8H	5-7
UA - WBC	N	2	N	3	8H	occ	N	0-5
IgG	ND	1550H	1260	ND	ND	ND	ND	635-1400 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 0 of study, subject felt "light-headed" with pre-frontal headache for 4 hours after blood-letting. On day 1, subject had 3 small, formed stools within 2 hours after dosing.

ABNORMALITIES COMMENT: SGOT slightly elevated on day 7, then returned to normal on day 14. SGPT elevated to 80 on day 7 and to 139 on day 14, then returned to normal on day 21. WBC count in urine elevated on days 7 and 21.

CONCLUSION: SGOT and SGPT elevations considered possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1250 mg | DOSING DATE: 7/8/80 | CODE: 412 | AGE: 18
DOSE PER Kg: 16.98 mg/kg | TIME DOSED: 0754 | GROUP: IV
DRUG | HEIGHT: 184.15 cm | WEIGHT: 73.64 kg

ABNORMALITIES:

DATE: 1980	7/2	7/7	7/8	7/9	7/10	7/11	7/14	7/15	7/21	7/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis	X	X		X	X		X			
5. Biochemistry	X	X		X	X		X		X	
6. CBC	X	X		X	X		X		X	
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	10	12	10	8L	8L	14	9-21 mg/dl
Creatinine	1.5H	1.4	1.4	1.5H	1.5H	1.5H	0.8-1.4 mg/dl
Uric Acid	8.2H	7.9	7.2	6.9	8.5H	9.5H	4-8 mg/dl
Total Protein	7.1	7.5	6.4	6.3L	6.8	7.0	6.4-8.0 g/dl
Albumin	4.4	4.5	4.0L	3.9L	4.2	4.3	4.1-5.1 g/dl
Alka Phos	100H	99H	86	87	86	84	26-94 U/L
Iron	144	107	108	160H	156H	109	40-150 MCG/dl
RBC	5.83H	5.86H	5.46	5.38	5.30	5.34	4.3-5.7mil/cumm
Eosin	5	7H	7H	8H	3	8H	0-5 %
MCV	82	82	83	81L	82	80L	82-98 cu micron
MCH	27.4	27.0	27.2	27.1	26.9L	26.7L	27-33micrmicrGM
UA - protein	N	N	N	N	TraceH	N	N
UA - WBC	TNTC H	TNTC H	TNTC H	10H	TNTC H	N	0-5

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: Uric acid elevated on days screening, 7 and 14. Alka Phos elevated on screening day and day 0 and returned to normal on day 2. RBC's elevated on screening and day 0 and returned to normal on day 2. Eosin level elevated on days 0-3 and 14. WBC's found in urine on all days of study except for day 14. Other deviations minimal and inconsistent and considered not significant.

CONCLUSIONS: No adverse effect from drug administration.
BMI-MDS

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 7/8/80 CODE: 413 AGE: 29
DOSE PER Kg: 0 mg/kg TIME DOSED: 0755 GROUP: IV
PLACEBO HEIGHT: 181.61 cm WEIGHT: 75.45 kg

ABNORMALITIES:

DATE: 1980	7/2	7/7	7/8	7/9	7/10	7/11	7/14	7/15	7/21	7/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam		X		X						
3. Phototoxicity										
4. Urinalysis					X					
5. Biochemistry		X		X	X				X	
6. CBC	X	X								
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Total Protein	6.8	7.2	6.8	6.7	6.5	6.3L	6.4-8.0 g/dl
Phosphate	2.7	2.3L	2.3L	2.4L	2.6	2.7	2.5-4.5 mg/dl
Eosin	6H	7H	5	5	1	4	0-5 %
UA - RBC	N	N	N	8H	N	N	0-3

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 0, left submandibular node 2x2x1 cm., non-tender. On day 2, lymph nodes were slightly swollen. Otherwise, subject asymptomatic and physical exam unchanged during study.

ABNORMALITIES COMMENT: Phosphate levels slightly decreased on days 0-3, then returned to normal on day 7. Eight RBC's found in urine on day 3 and returned to normal on day 7. Other deviations minimal, inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1250 mg | DOSING DATE: 7/8/80 | CODE: 414 | AGE: 19
DOSE PER Kg: 17.80 mg/kg | TIME DOSED: 0756 | GROUP: IV
DRUG | HEIGHT: 180.34 cm | WEIGHT: 70.23 kg

ABNORMALITIES:

DATE: 1980	7/2	7/7	7/8	7/9	7/10	7/11	7/14	7/15	7/21	7/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms				X						
2. Physical Exam		X								
3. Phototoxicity										
4. Urinalysis									X	
5. Biochemistry							X			
6. CBC									X	
7. Platelets										
8. Immunoglobulins		X								

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Glucose	77	86	83	81	50L	77	66-114 mg/dl
Potassium	4.1	3.9	4.2	4.6	3.4L	3.6	3.6-5.2 mEq/L
Eosin	5	4	4	4	4	6H	0-5 %
UA - protein	N	N	N	N	N	Trace H	N
IgA	ND	315H	260	ND	ND	ND	60-297 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 0, small, non-tender lymph nodes at angle of each jaw. On day 2 of study, subject felt "light-headed" with slight malaise and slight decrease in appetite. Subject asymptomatic for remainder of study and physical exam normal and unchanged for rest of study.

ABNORMALITIES COMMENT: Laboratory deviations minimal or inconsistent and not considered significant.

CONCLUSION: "Light-headedness", slight malaise and slight decrease in appetite considered possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 7/8/80 CODE: 415 AGE: 20
DOSE PER Kg: 0 mg/kg TIME DOSED: 0757 GROUP: IV
PLACEBO HEIGHT: 175.26 cm WEIGHT: 72.05 kg

ABNORMALITIES:

DATE: 1980	7/2	7/7	7/8	7/9	7/10	7/11	7/14	7/15	7/21	7/22
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam									X	
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X				X					
6. CBC	X	X		X	X		X		X	
7. Platelets										
8. Immunoglobulins		X		X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Iron	170H	136	98	186H	137	86	40-150 MCG/dl
Eosin	6H	7H	7H	6H	6H	9H	0-5 %
MCH	32.9	32.5	32.4	33.1H	32.6	32.6	27-33micmicrGM
IgM	ND	40L	26L	ND	ND	ND	41-248 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic for entire study. On study day 14 during physical exam it was noted that subject had conjunctivitis in left eye due to being hit in eye while playing basketball.

ABNORMALITIES COMMENT: Eosin values consistently elevated during study.

CONCLUSION: Mild eosinophilia, not relatel to study. No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1500 mg | DOSING DATE: 7/15/80 | CODE: 416 AGE: 19
DOSE PER Kg: 22.60 mg/kg | TIME DOSED: 0800 | GROUP: V
DRUG | HEIGHT: 167.64 cm | WEIGHT: 66.36 kg

ABNORMALITIES:

DATE: 1980	7/2	7/14	7/15	7/16	7/17	7/18	7/21	7/22	7/28	7/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X		X	X		X		X	
6. CBC					X		X			
7. Platelets										
8. Immunoglobulins				X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	13	14	9	7L	13	9	9-21 mg/dl
Total Protein	7.2	6.9	6.1L	6.3L	6.2L	6.1L	6.4-8.0 g/dl
Phosphate	3.2	3.9	4.6H	4.3	3.8	3.4	2.5-4.5 mg/dl
Triglyceride	146	228H	422H	253H	165	167	0-207 mg/dl
Alka Phos	154H	137H	152H	139H	130H	117H	26-94 U/L
SGPT	20	17	19	38	51H	44	0-47 U/L
Hematocrit	44.6	43.7	41.7	39.8L	38.7L	41.0	40-50 Vol %
RBC	4.81	4.70	4.58	4.35	4.23L	4.44	4.3-5.7mil/cumm
IgG	ND	720	622L	ND	ND	ND	635-1400 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: Total protein values decreased on days 2, 3, 7 and 14. Alkaline Phosphatase elevated during entire study. SGPT elevated to 51 on day 7 then returned to normal on day 14. Other deviations minimal, inconsistent and not considered significant.

CONCLUSION: Alkaline Phosphatase elevation considered normal for age. No adverse effects from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1500 mg | DOSING DATE: 7/15/80 | CODE: 417 | AGE: 23
DOSE PER Kg: 19.64 mg/kg | TIME DOSED: 0800 | GROUP: V
DRUG | HEIGHT: 175.26 cm | WEIGHT: 76.36 kg

ABNORMALITIES:

DATE: 1980	7/9	7/14	7/15	7/16	7/17	7/18	7/21	7/22	7/28	7/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis							X		X	
5. Biochemistry				X	X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Potassium	3.9	3.8	3.7	3.8	3.5L	3.8	3.6-5.2 mEq/L
Triglyceride	70	195	167	237H	263H	126	0-207 mg/dl
Alka Phos	86	86	93	103H	105H	95H	26-94 U/L
SGPT	30	46	60H	85H	66H	37	0-47 U/L
Iron	133	92	94	144	232H	145	40-150 MCG/dl
UA - protein	N	N	N	N	Trace H	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: Alkaline phosphatase levels elevated on days 3, 7 and 14. SGPT values elevated on days 2, 3 and 7, then returned to normal on day 14. Other deviations minimal or inconsistent and not considered significant.

CONCLUSION: Alkaline phosphatase and SGPT elevations considered possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 7/15/80 CODE: 418 AGE: 25
DOSE PER Kg: 0 mg/kg TIME DOSED: 0800 GROUP: V
PLACEBO HEIGHT: 186.06 cm WEIGHT: 73.64 kg

ABNORMALITIES:

DATE: 1980	7/9	7/14	7/15	7/16	7/17	7/18	7/21	7/22	7/28	7/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis							X		X	
5. Biochemistry	X	X			X		X			
6. CBC							X			
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	32H	30	30	34H	32H	31	23-31 mEq/L
Albumin	5.0	5.2H	4.8	4.7	4.6	4.8	4.1-5.1 g/dl
Iron	79	104	73	131	191H	100	40-150 MCG/dl
Hematocrit	45.8	45.1	41.8	42.6	50.6H	43.2	40-50 Vol %
Hemoglobin	15.5	15.2	14.2	14.4	16.8H	14.9	13.3-16.7 GMS%
UA - protein	N	N	N	N	1+ H	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject asymptomatic and physical exam normal and unchanged during entire study.

ABNORMALITIES COMMENT: Laboratory deviations minimal or inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

BMI-MFB

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg | DOSING DATE: 7/15/80 | CODE: 419 | AGE: 21
DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: V
PLACEBO | HEIGHT: 180.97 cm | WEIGHT: 79.55 kg

ABNORMALITIES:

DATE: 1980	7/9	7/14	7/15	7/16	7/17	7/18	7/21	7/22	7/28	7/29
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms			X							
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry	X	X		X	X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins		X		X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	14	11	10	9	8L	11	9-21 mg/dl
Creatinine	1.4	1.5H	1.4	1.4	1.4	1.5H	0.8-1.4 mg/dl
Carbon Dioxide	32H	30	31	34H	29	30	23-31 mEq/L
Total Protein	7.0	6.3L	5.7L	6.5	6.2L	6.4	6.4-8.0 g/dl
Albumin	4.5	4.3	3.9L	4.1	4.1	4.2	4.1-5.1 g/dl
Iron	49	123	34L	30L	83	50	40-150 MCG/dl
IgG	ND	1000	800L	ND	ND	ND	816-1654 mg/dl
IgM	ND	36L	68	ND	ND	ND	47-275 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 1, 4 hours and 15 minutes after dosing, subject experienced "cramps" in upper abdomen. Upper abdomen felt firm, full and slightly tender. Bowel sounds were hypoactive. At 5.5 hours after dosing, subject was asymptomatic. Physical examination normal remainder of study.

ABNORMALITIES COMMENT: Laboratory abnormalities minimal or inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1750 mg | DOSING DATE: 7/22/80 | CODE: 420 | AGE: 21
DOSE PER Kg: 21.24 mg/kg | TIME DOSED: 0800 | GROUP: VI
DRUG | HEIGHT: 186.06 cm | WEIGHT: 82.39 kg

ABNORMALITIES:

DATE: 1980	7/16	7/21	7/22	7/23	7/24	7/25	7/28	7/29	8/4	8/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms			X							
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis	X								X	
5. Biochemistry	X	X			X		X			
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Creatinine	1.4	1.5H	1.3	1.3	1.3	1.4	0.8-1.4 mg/dl
Carbon Dioxide	32H	29	31	31	32H	31	23-31 mEq/L
Uric Acid	8.1H	7.5	6.1	5.8	8.2H	7.4	4-8 mg/dl
Iron	106	66	55	156H	113	101	40-150 MCG/dl
UA - protein	Trace H	N	N	N	N	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 1 of study, 4 hours after dosing subject complained of vague lower abdominal pain, not cramping. Five hours later subject was still having some discomfort. Five and one-half hours after dosing subject was asymptomatic. Subject was asymptomatic for remainder of study and physical exam was normal and remained unchanged.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered significant.

CONCLUSION: Abdominal discomfort possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg | DOSING DATE: 7/22/80 | CODE: 421 | AGE: 20
DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: VI
PLACEBO | HEIGHT: 167.64 cm | WEIGHT: 64.09 kg

ABNORMALITIES:

DATE: 1980	7/16	7/21	7/22	7/23	7/24	7/25	7/28	7/29	8/4	8/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis	X								X	
5. Biochemistry	X				X		X			
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
BUN	9	9	10	8L	9	9	9-21 mg/dl
Carbon Dioxide	32H	29	30	32H	30	30	23-31 mEq/L
Iron	148	149	88	64	171H	50	40-150 MCG/dl
UA - protein	Trace H	N	N	N	N	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject remained asymptomatic during entire study. Physical exam normal and unchanged during study interval.

ABNORMALITIES COMMENT: Laboratory abnormalities were minimal or inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg | DOSING DATE: 7/22/80 | CODE: 422 | AGE: 22
DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: VI
PLACEBO | HEIGHT: 175.90 cm | WEIGHT: 67.84 kg

ABNORMALITIES:

DATE: 1980	7/9	7/21	7/22	7/23	7/24	7/25	7/28	7/29	8/4	8/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis							X			
5. Biochemistry	X				X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Triglyceride	94	120	175	270H	116	203	0-207 mg/dl
Alka Phos	95H	93	83	92	107H	92	26-94 U/L
SGPT	45	47	45	50H	50H	49H	0-47 U/L
Iron	79	89	66	99	377H	71	40-150 MCG/dl
UA - protein	N	N	N	N	Trace H	N	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: The subject was asymptomatic and had an unchanged physical examination throughout the study interval.

ABNORMALITIES COMMENT: Subject's SGPT elevated (66) day 4 of study, minimally elevated days 3 and 14, but was normal when he returned for repeat testing one month later. Other deviations minimal or inconsistent and not considered to be significant.

CONCLUSION: No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 1750 mg | DOSING DATE: 7/22/80 | CODE: 423 | AGE: 18
DOSE PER Kg: 24.40 mg/kg | TIME DOSED: 0800 | GROUP: VI
DRUG | HEIGHT: 189.23 cm | WEIGHT: 71.70 kg

ABNORMALITIES:

DATE: 1980	7/9	7/21	7/22	7/23	7/24	7/25	7/28	7/29	8/4	8/5
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms				X					X	
2. Physical Exam									X	
3. Phototoxicity										
4. Urinalysis		X								
5. Biochemistry	X	X		X	X		X		X	
6. CBC										
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	32H	29	32H	34H	31	30	23-31 mEq/L
Alka Phos	111H	113H	113H	120H	107H	113H	26-94 U/L
UA - protein	N	Trace H	N	N	N	N	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject experienced slight muscle twitching in left shoulder on day 2 of study. On 14th day of study, subject complained of earache for past week. Physical exam revealed inflamed right ear canal.

ABNORMALITIES COMMENT: Carbon dioxide levels elevated on screening day, 2 and 3 and then returned to normal on day 7. Alkaline phosphatase consistently high during entire study. Other deviations minimal, inconsistent and not considered significant.

CONCLUSION: Alkaline phosphatase elevation considered normal for age and no adverse effects of drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE:	2000 mg	DOSING DATE:	8/5/80	CODE: 424	AGE: 23
DOSE PER Kg:	29.33 mg/kg	TIME DOSED:	0835	GROUP:	VII
DRUG		HEIGHT:	170.18 cm	WEIGHT:	68.18 kg

ABNORMALITIES:

DATE: 1980	7/30	8/4	8/5	8/6	8/7	8/8	8/11	8/12	8/18	8/19
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms						X				
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry					X		X			
6. CBC							X		X	
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Total Protein	6.7	6.6	6.5	7.3	6.2L	6.8	6.4-8.0 g/dl
Triglyceride	125	157	173	119	240H	106	0-207 mg/dl
SGOT	17	19	31	84H	18	14	0-47 U/L
SGPT	19	25	44	142H	46	14	0-47 U/L
Hematocrit	46.4	45.5	44.2	48.3	39.4L	42.6	40-50 Vol %
Retic Count	ND	ND	ND	ND	ND	1.8H	0.5-1.5 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 4 of study, subject complained of muscle cramps which he attributed to the hot weather. Physical exam was normal and remained unchanged throughout the study interval.

ABNORMALITIES COMMENT: SGOT on day 3 of study was elevated two times normal and returned to normal on day 7. SGPT on day 3 was elevated three times normal and returned to normal on day 7. Other laboratory abnormalities were minimal and inconsistent and not considered related to study participation.

CONCLUSION: SGOT and SGPT elevations considered possibly drug related. No adverse effects from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE:	0 mg	DOSING DATE:	8/5/80	CODE: 425	AGE: 20
DOSE PER Kg:	0 mg/kg	TIME DOSED:	0835	GROUP:	VII
PLACEBO		HEIGHT:	175.26 cm	WEIGHT:	72.04 kg

ABNORMALITIES:

DATE: 1980	7/21	8/4	8/5	8/6	8/7	8/8	8/11	8/12	8/18	8/19
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms										
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry		X			X		X		X	
6. CBC	X	X			X		X		X	
7. Platelets										
8. Immunoglobulins		X		X						

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Potassium	4.3	3.5L	5.0	4.1	4.5	5.4H	3.6-5.2 mEq/L
Phosphate	3.5	4.4	3.9	5.1H	3.6	3.8	2.5-4.5 mg/dl
SGPT	25	23	43	48H	58H	31	0-47 U/L
Eosin	9H	7H	ND	8H	10H	9H	0-5 %
MCV	95	100H	ND	98	98	98	82-98 cu micron
MCH	32.6	33.6H	ND	33.0	32.5	32.8	27-33micmicrGM
IgM	ND	40L	36L	ND	ND	ND	41-248 mg/dl
Retic Count	ND	ND	ND	ND	ND	2.4H	0.5-1.5 %

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: Subject remained asymptomatic and physical exam unchanged during entire study.

ABNORMALITIES COMMENT: Eosin level remained elevated during entire study. Other deviations minimal, inconsistent and not considered significant.

CONCLUSION: Mild eosinophilia not considered drug related. No adverse effect from placebo administration.

BMI-MEB

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE:	2000 mg	DOSING DATE:	8/5/80	CODE: 426	AGE: 21
DOSE PER Kg:	31.31 mg/kg	TIME DOSED:	0835	GROUP:	VII
DRUG		HEIGHT:	170.18 cm	WEIGHT:	63.86 kg

ABNORMALITIES:

DATE: 1980	7/30	8/4	8/5	8/6	8/7	8/8	8/11	8/12	8/18	8/19
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms				X						
2. Physical Exam										
3. Phototoxicity										
4. Urinalysis										
5. Biochemistry				X	X					
6. CBC					X		X			
7. Platelets										
8. Immunoglobulins		X								

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Triglyceride	81	112	257H	351H	106	105	0-207 mg/dl
Hematocrit	42.7	43.2	41.8	44.1	39.3L	41.3	40-50 Vol %
Eosin	5	5	4	6H	6H	4	0-5 %
IgG	ND	1900H	1400	ND	ND	ND	635-1400 mg/dl

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 2 of study, subject having slight decrease in appetite. Subject remained asymptomatic and physical exam unchanged during rest of study.

ABNORMALITIES COMMENT: Laboratory deviations were minor and inconsistent and not considered significant.

CONCLUSION: No adverse effect from drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TOTAL DOSE: 0 mg DOSING DATE: 8/5/80 CODE: 427 AGE: 25
DOSE PER Kg: 0 mg/kg TIME DOSED: 0835 GROUP: VII
PLACEBO HEIGHT: 186.05 cm WEIGHT: 73.63 kg

ABNORMALITIES:

DATE: 1980	7/28	8/4	8/5	8/6	8/7	8/8	8/11	8/12	8/18	8/19
STUDY DAY:	Scr	0*	1*	2*	3	4	7	8	14	15
1. Symptoms				X						
2. Physical Exam				X						
3. Phototoxicity										
4. Urinalysis	X	X		X			X		X	
5. Biochemistry		X		X	X					
6. CBC									X	
7. Platelets										
8. Immunoglobulins										

KEY: X=abnormal *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

Study Day:	Scr	0	2	3	7	14	Normal Range
Carbon Dioxide	31	32H	32H	32H	31	29	23-31 mEq/L
Albumin	4.8	5.2H	4.4	4.9	4.7	5.0	4.1-5.1 g/dl
Hematocrit	43.2	47.8	40.6	45.3	41.6	39.9L	40-50 Vol %
Lymph	36	25	35	29	34	17L	19-59 %
UA - protein	Trace H	Trace H	Trace H	N	Trace H	Trace H	N

KEY: H - high L - low ND - not done N - negative occ - occasional
TNTC - too numerous to count

SYMPTOMS AND PHYSICAL FINDINGS: On day 2 of study, physical exam revealed liver edge sharp and nontender. Subject somewhat fatigued. Subject remained asymptomatic during rest of study.

ABNORMALITIES COMMENT: Carbon dioxide level elevated on days 0-3 and then returned to normal on day 7. Subject's urine consistently showed traces of protein. Other deviations minimal and inconsistent and not considered significant.

CONCLUSION: No adverse effect from placebo administration.

BMI-MEB

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

EXPERIMENT NUMBER 15

PARTICIPANT SUMMARY

Group Number	Code Number	Dose Level	Subject's Name	Drug/Placebo
I	#400	750 mg	Deleted *	Drug
	#401			Placebo
	#402			Placebo
	#403			Drug
II	#404	750 mg	Deleted *	Drug
	#405			Placebo
	#406			Drug
	#407			Placebo
III	#408	1000 mg	Deleted *	Drug
	#409			Placebo
	#410			Placebo
	#411			Drug
IV	#412	1250 mg	Deleted *	Drug
	#413			Placebo
	#414			Drug
	#415			Placebo
V	#416	1500 mg	Deleted *	Drug
	#417			Drug
	#418			Placebo
	#419			Placebo
VI	#420	1750 mg	Deleted *	Drug
	#421			Placebo
	#422			Placebo
	#423			Drug
VII	#424	2000 mg	Deleted *	Drug
	#425			Placebo
	#426			Drug
	#427			Placebo

The drug was provided in individual vials for each subject by the Walter Reed Army Institute of Research, identified by drug name (WR 171,669), amount and group number. Code identifying drug or placebo were provided separately in a sealed envelope.

* Names on record, available for legitimate need.

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

BIO - MED, Inc.

EXPLANATION FOR POTENTIAL SUBJECTS
ANTIMALARIAL DRUG PROJECT
EXPERIMENT NUMBER 15
Continuation of Single Dose Rising Dose Level
Studies with Orally Administered WR 171,669:
Short Term Safety and Tolerance.
Preliminary Pharmacokinetics.

GENTLEMEN:

The study for which you have applied involves taking by mouth an investigational new drug, not approved by the Food and drug administration for general use. The drug is the antimalarial drug WR 171,669 or you may receive a placebo containing no active drug. WR 171,669 is a phenanthrene methanol which has demonstrated antimalarial activity in both animals and human subjects. Six men experimentally infected with a drug resistant strain of Plasmodium falciparum were cured using a dose of 250 mg administered every six hours for a total dose of 3000 mg. Normal non-infected human subjects have received from 3870 mg in 3 days to 5000 mg in 5 days. Most subjects experienced temporary mild nausea and abdominal discomfort without other evidence of intolerance.

The present study was initiated at another institution and the 750 mg dose level had been administered without causing intolerance. It should be noted that while no increase susceptibility to sunburn occurred in human subjects, it has occurred in mice at high dose levels. The study, sponsored by the U.S. Army and approved by the Food and Drug Administration will continue the tolerance testing in addition to providing information concerning the gastrointestinal absorption of the drug, distribution in the body, and elimination from the body.

The study method is called a two-by-two double-blind rising dose level design. At each dose level, four subjects are employed. Two receive drug and two receive placebo (no active drug). Neither the subjects nor the investigators know which subjects are receiving drug until the study for that dose level is completed. At that time, the code may be broken and you will be told if your received the drug. The amount of drug given is increased at each succeeding dose level. A new dose level is not started until the results of the previous dose level have been reported and evaluated. Specifications are presented in the schematic.

STUDY SCHEDULE SCHEMATIC

WR 171,669: Safety and Tolerance
and Preliminary Pharmacokinetics

Day of Study Day of Week	0* Mon	1* Tue	2* Wed	3 Thu	4 Fri	7 Mon	8 Tue	14 Mon	15 Tue
Dose		X							
Physical Exam	X		X					X	
Interview	X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X		X	
Laboratory Tests+	X		X	X		X		X	
Phototoxicity Test++	X		X			X		X	
Blood for Drug Assay‡		X	X	X	X	X		X	
Immunologic Studies##	X		X						

*Controlled Environment

+Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Twenty-seven ml of venous blood will be drawn on each scheduled laboratory test day.

++Phototoxicity testing involves a 5 to 10 minute exposure to a UV-B100 A Black Ray Lamp of a small target spot on the back. The energy of exposure used is approximately 8.3 joules for white skinned subjects and approximately 16.5 joules for dark skinned subjects. This procedure has been demonstrated to be effective using methylpsoralen as a positive control. On study days 8 and 15 subjects will report for reading of phototoxicity tests.

‡Drug Assay: Each subject immediately prior to drug administration, and after dosing at 15, 30, 90, 120, 150, 180, 210, 240, 270, 300, and 360 minutes, and 8, 12, 24, 36, 48, and 72 hours, and on study days 7 and 14. Note: These specific times apply only to the 750 mg dose level, as the sampling times may be altered following evaluation at that dose level.

#In addition to the blood samples listed in the protocol, 10 ml of clotted blood and 20 ml of heparinized blood will be drawn on Day 0 (prior to drug administration) and again on Day 2 (1 day after drug administration). The 20 ml sample will be drawn through a 19 gauge needle into a heparin rinsed syringe containing < 0.5 ml heparin. It will be stored and transported in the syringe at room temperature. These specimens will be used to measure serum IgG, IgM, and IgA, and to determine the proportion of circulating T-lymphocytes (E-rosettes) and B-lymphocytes (EAC-rosettes).

Additional Blood Specimens for Pharmacokinetic Evaluation:

Ten ml of venous blood will be obtained for assay of WR 171,669 immediately prior to drug administration and following dosing at 15, 20, 90, 120, 150, 180, 210, 240, 270, 300, and 360 minutes, 8, 12, 24, 36, 48, and 72 hours, and on study days 7 and 14. A total of 200 ml of blood will, therefore, be obtained over a period of 2 weeks. Following evaluation of the first 4 subjects given 750 mg of the drug, the precise timing of sampling may be altered, but the total volume obtained will not exceed 200 ml of 2 weeks. Since this is a double-blind design, samples will also be taken from subjects given the placebo. Samples from subjects receiving placebo not used for drug assay may be discarded. An indwelling venous catheter will be used as practical to avoid repeated venipunctures.

The blood for each drug assay will be drawn by a staff nurse. Six ml of the blood will be transferred to a heparin-rinsed teflon capped glass tube and stored at -20°C pending transportation to the Department of Pharmacology, Walter Reed Army Institute of Research, for drug assay. The drug will be assayed as a parent compound by high pressure liquid chromatography. This method has previously been employed for drug assay in animal blood samples and spiked human samples and is working well. Four ml of the blood will be centrifuged and the serum separated. The serum will be transported to the Department of Pharmacology, WRAIR, for bioassay for antimalarial activity.

You have already had many of the examinations listed on the schematic as part of your qualification examination. The phototoxicity test is a 5-10 minute exposure of small areas on your back to long-wave ultraviolet light. It is not uncomfortable and has not caused any reaction in subjects receiving other candidate antimalarials at this facility.

As previously noted WR 171,669 in multiple dose studies has caused temporary mild nausea and abdominal discomfort. No intolerance has occurred in the initial single dose studies, however, unexpected reactions might occur. The increased sensitivity to ultra-violet light noted in mice at extremely high dose levels has not yet been observed in human subjects.

During the interval in the research unit the entire group will remain together with a member of the Clincial Facility Staff and will function according to their direction. Facilities provided while participating in the study include room and board with a study-lounge area.

On the day the drug is to be administered, you will have a liquid breakfast (Sustacal) at 6:00 a.m.. You will be given the drug at 8:00 a.m.. You may have measured amounts of water until noon, at which time you may resume the normal diet if you remain symptom free.

At your discretion, 15 minutes before drug administration, a small teflon catheter can be placed in one of your arm veins. This will be used to obtain blood samples during the day you are dosed. In this way, repeated venipunctures may not be necessary on that day.

It is important that the blood be obtained as nearly as possible to the times previously specified. On the days you come in for blood drawing, it is important that you eat a light breakfast (i.e., cereal, milk, juice, coffee, bread -- no eggs or bacon). It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs, and lack of proper sleep may affect the level of drug in your blood on any given day.

The Institutional Review Board also is looking after your safety. They insure that you are not subjected to undue risk or discomfort. A member of this committee will be available to speak with you and to answer any questions you might have. A member may also visit you at the Clinical Facility in College Park. After members of the investigating team (and perhaps the Institutional Review Board), have interviewed you individually and are satisfied that you understand the study and written informed consent form, you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent, you signify that the study has been explained to you with regard to its risks and requirements, and you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to Americans, civilian and military, who may travel to these areas. For this reason, especially, your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent at any time without prejudice.

EXPERIMENT NO. 15: CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.

TABLE I: DRUG ASSAY COLLECTION

DAY OF THE STUDY	SPECIMEN NUMBER	BLOOD SPECIMEN TIME		BLOOD VOLUME (ml)
1	1	0	Prior to dosing	10
	2	15 min	8:15 AM	10
	3	30 min	8:30 AM	10
	4	90 min	9:30 AM	10
	5	120 min	10:00 AM	10
	6	150 min	10:30 AM	10
	7	180 min	11:00 AM	10
	8	210 min	11:30 AM	10
	9	240 min	NOON	10
	10	270 min	12:30 PM	10
	11	300 min	1:00 PM	10
	12	360 min	2:00 PM	10
	13	8 hr	4:00 PM	10
	14	12 hr	8:00 PM	10
2	15	24 hr	8:00 AM	10
	16	36 hr	8:00 PM	10
3	17	48 hr	8:00 AM	10
HOME				
4	18	72 hr	8:00 AM	10
7	19	144-146 hr	8:00-10:00 AM	10
14	20	312-314 hr	8:00-10:00 AM	10
			TOTAL	200 (ml)

TABLE II: TOTAL AMOUNT OF BLOOD WITHDRAWN FOR EACH STUDY SUBJECT FOLLOWING DRUG ADMINISTRATION

	HEMATOLOGY	CHEMISTRY	IMMUNOLOGIC STUDIES	BLOOD ASSAY	TOTAL (ml)
DAY 0	7	20	30	-	57
1	-	-	-	140	140
2	7	20	30	20	77
3	7	20	-	10	37
4	-	-	-	10	10
7	7	20	-	10	37
14	7	20	-	10	37
				TOTAL	395 (ml)

SUBJECT AGREEMENT

CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled WR 171,669: Short Term Safety and Tolerance: Continuation of Single Oral Dose Rising Dose Level Studies: Preliminary Pharmacokinetics.

The implications of my voluntary participation; the nature; duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Doctor _____, and are set forth in the document titled "EXPLANATION FOR POTENTIAL SUBJECTS, AMDP EXP. #15: WR 171,669: Short Term Safety and Tolerance: Continuation of Single Oral Dose Rising Dose Level Studies: Preliminary Pharmacokinetics, which I have signed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that workmen's compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at anytime; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____
Date

_____ _____
Signature Investigator Certification

_____ _____
Address Witness

REAFFIRMATION OF CONSENT:

_____ _____
Date Witness

_____
Signature

BMI-C2

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

BIO - MED, Inc.

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 16

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

EXPERIMENT NUMBER 16

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

TABLE OF CONTENTS

SUBJECT	PAGE
ABSTRACT	146
INTRODUCTION	147
METHODS AND MATERIALS	149
RESULTS	152
DISCUSSION	155
CONCLUSIONS AND RECOMMENDATIONS	156
- Individual Subject Final Summary Sheets	157-164
- Creatinine Excretion Tables	165-166
APPENDIX: a. Explanation for Potential Subjects	167-169
b. Consent Form	170

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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.

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FINAL CLINICAL REPORT

EXPERIMENT NUMBER 16

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

INTRODUCTION

Sodium stibogluconate was formulated for the treatment of Leishmaniasis. Leishmaniasis is an infectious parasitic disease occuring in humans mainly in equatorial and subequatorial areas of the Americas, Africa, the Middle East, and the Asian subcontinent. It is one of the most prevalent parasitic diseases of this planet. The disease occurs in two forms - the visceral, which untreated is largely fatal after years of morbidity, and cutaneous forms which can progress to deformity and disability.

Antimonials have long been known to have a favorable effect upon Leishmaniasis. However, the initial therapeutic studies used the trivalent form of antimony and this was found to be acutely toxic to man. Therapeutic development has been channeled toward finding formulations of antimonials which have therapeutic effect but have minimal acute toxic properties.

Sodium stibogluconate, a pentavalent antimonial, appears to have as high a therapeutic ratio as any of the antimonials developed so far. No controlled studies have been done which would allow a reliable estimate of the cure-rate of stibogluconate in Leishmaniasis but the evidence that the drug has beneficial therapeutic effect is overwhelming.

WR 229,870 (Sodium Stibogluconate Injection BP) seems to be among the least toxic of the commonly utilized pentavalent antimony compounds and the only one available in this country. Side effects of antimonials include gastrointestinal disturbances, jaundice, albuminuria, weakness, skin-rash, cough, pneumonia and changes in the electrocardiogram. These effects are more frequent in patients being treated for visceral Leishmaniasis with trivalent antimonials and are briefly detailed below:

Gastrointestinal Effects: Reports of gastrointestinal effects (abdominal pain, nausea, vomiting) have been noted in patients with the disease receiving multiple doses of the drug.

Hepatotoxicity: Jaundice has been reported in one of 1400 cases. (Sun, 1949).

Renal Toxicity: Transient albuminuria has been reported in 3 of 32 patients, and in 1 of 24 patients.

Cough: Cough appears to be immediate and transient following I.V. administration in about 25% of patients.

Pneumonia: 1400 cases were treated without pneumonia being observed, yet pneumonia, found at autopsy, has been reported in association with 2 fatal cases.

Skin Rash: Skin rash appears to be an unusual and mild complication.

Changes in Electrocardiogram: Minor changes in the T waves, which resolve after discontinuation of the drug, have been noted in patients after repeated doses of the drug.

The goal of this study was to determine the pharmacokinetics of sodium stibogluconate in humans so that an optimal treatment schedule may be developed, i.e. a schedule based on the best estimate of the dynamic distributions of the drug amongst body compartments. Preliminary results suggest a 3 compartment model with a mean T 1/2 for each of 3 phases of 0.3, 1.7, and 29.8 hours. Refinement of these estimates could have important implications regarding optimal amounts per dose and intervals of dose.

METHODS AND MATERIALS

1. Procurement of Subjects and Subject Acceptability Criteria:

Eight healthy male subjects, aged 18-35 years, were recruited from the Washington, D.C. metropolitan area. Candidates were hired as temporary employees of BIO-MED, Inc.

Candidates for employment were screened to obtain the subjects for study. The medical evaluation included a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatese, SGOT, SGPT, LDH, and total bilirubin.

Subject acceptability criteria were based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects were rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest X-ray. The presence of conditions which do not increase risk or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy," or scarred tympanic membranes are not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean are cause for rejection. Deviations between 2 and 3 standard deviations from the mean are generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example a serum sodium of 153 mEq/L of itself would not, whereas a serum calcium of 11.2 mg/dl would cause rejection. Subjects should weigh from 50-100 kg, and be within 10% of their ideal body weight.

When doubt existed concerning entry acceptance of a subject for any reason, a decision was made following consultation with fellow M.D. investigator and other specialists, as appropriate. In this manner questionable candidates were given full consideration and the integrity and ethics of the research team protected.

Qualified candidates were given a complete explanation of the background and procedures to be used in the study and all details of the protocol as it involved the individual subjects. They were interviewed in a group and individually by the investigator in the presence of a witness. Each participant was given the opportunity to ask questions. Following the individual interview, the consent form was read, and if the investigator believed the subject understood his participation adequately to give informed consent, the subject was given the opportunity to sign the consent form. "Information for Subjects" or the subject explanation form is at appendix "a". The consent form is at appendix "b".

2. Experimental Procedures:

The subjects were housed in a controlled environment at the BIO-MED Clinical Facility, College Park, Maryland. Four groups of 2 subjects each were used. The subjects were admitted to the Clinical Facility on Monday, the day prior to dosing. At that time a complete medical examination, interview, and screening laboratory tests were repeated.

On Tuesday, Day 1 of study, after a light breakfast, an intravenous infusion of 5% D/H_2O at 300 cc/hr was initiated in an upper extremity vein. When freeflow was confirmed the 50 cc solution containing drug was infused by volutrol at the same rate to deliver 600 mg sodium stibogluconate injection B.P., over a 10 minute period.

Prior to drug infusion, a catheter was placed in the opposite extremity for blood specimen collection. After the a.m. voiding, a 24-hour urine collection was intiated immediately after drug dosing.

Sodium stibogluconate was supplied as Pentostam® brand sodium stibogluconate injection B.P.- a sterile, stable solution containing the equivalent of 100 mg of pentavalent antimony per ml. Each subject was given 600 mg of Pentostam® by i.v. infusion over 10 minutes. The infusion was prepared by mixing 600 mg of Pentostam® and 5% dextrose and water qs to 50 cc.

Ten cc of blood was collected into heparinized vacutainers for antimony blood determinations at the following times: prior to drug administration, at 10 min., 20 min., 30 min., 45 min., 1 hr., 2 hr., 3 hr., 4 hr., 6 hr., 8 hr., 12 hr., 16 hr., 24 hr., 48 hr., 72 hr., 96 hr., and 144 hr. after dosing. The blood specimens were stored in a refrigerator at BIO-MED prior to transfer to Walter Reed for shipment to Environmental Sciences Associates for assay of antimony.

On the last study day for each subject, a final physical and repeat laboratory evaluation was done. Any subject with an abnormal finding was followed until normality, stabilization or proper medical disposition occurred.

The clinical and laboratory evaluation of the subjects is outlined below:

SCHEMATIC STUDY PLAN - SINGLE INTRAVENOUS DOSE ADMINISTRATION WR 229,870

Study Day	0*	1*	2*	3*	4*	5	7
Dose		X					
Physical Examination	X		X		X		X
Interview	X	X	X	X	X	X	X
Complete Vital Signs	X	X	X	X	X	X	X
Electrocardiogram (Lead II)	X	X	X				X
Laboratory Tests†	X		X				X
Drug Level Assay		X	X	X	X	X	X

*Controlled Environment - Clinical Facility, College Park, Maryland

†Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Uric Acid, Total Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, SGOT, SGPT, LDH, Total Bilirubin, CBC (differential and indices), Platelets, Reticulocyte Count, Urinalysis. Additional studies will be done as clinically indicated.

3. Emergencies: No medical emergencies occurred.

ANTIMONY ASSAY METHOD:

Blood and urine specimens for assay of antimony were to be sent to Environmental Sciences Associates, Bedford, Massachusetts. Antimony will be assayed by aniotic voltametry and results will be reported to Walter Reed Army Institute of Research (WRAIR).

RESULTS

All individual data was recorded daily and reviewed promptly by an investigator. Individual worksheets were maintained for each subject. The following were recorded on individual forms: blood pressure, pulse, weight, clinical labortatory results, subjective symptoms and physical examination. A cumulative master log was kept which included laboratory data and results of a non-directed symptomatology interview. In addition, a specimen schedule form was kept for each subject with the exact date and time of drug administration and specimen collections recorded (including total urine volume).

General Summary:

Eight subjects participated in the study. There were no emergent reactions to the procedures and there were no significant departures from the study protocol.

Detailed Clinical Summary:

Individual summaries of the observations made of each subject were prepared (Tab A). Critical elements of the individual summaries are listed below:

Symptoms:

At 12 hours after drug infusion, subject 386 experienced "stomach cramps" for 1 hours. Physical examination 15 hours later was unrevealing. This subject also developed induration at the site of the intracath placement. The induration subsequently resolved without intervention. No other subjects had significant symptoms.

Physical Findings:

No physical abnormalities were noted in any subject during the course of the study other than the induration at the intracath site noted in subject 386.

Electrocardiogram:

No abnormalities of the Lead II rhythm strips were found.

Biochemistry:

Blood samples for biochemistries were drawn from each subject on days 0, 2 and 7 (in one group of 2 subjects, scheduling demanded that biochemistries be drawn on day 8).

The occurence* of abnormal values (shown as H(High) or L(Low)) is summarized in the following table:

LABORATORY STUDY	STUDY DAY 0	2	7	8
Glucose				L
Urea Nitrogen		L,L,L	L	
Creatinine	H			H
Sodium				
Potassium	L	L		
Chloride				
CO_2				
Uric Acid		L		
T. Protein		L,L,L	H	
Albumin		L		
Globulin				
Calcium		L		
Phosphate				
Cholesterol				
Triglycerides	H			
Alka.Phos.	H,H	H	H	
SGOT			H	
SGPT	H	H	H,H,H	H
LDH			H	
T. Bilirubin				

* for each cell, N=8, except for Day 7(N=6) and Day 8(N=2)

A cluster of low blood urea nitrogens occurred on day two, and were judged to be of no clinical significance. A simular cluster of marginally low total serum proteins occurred on day two, and were judged to be of no clinical significance. Elevated alkaline phosphatase's were consistent with the individuals state of physical maturity and were of no clinical significance.

A cluster of elevated SGPT's was seen on day 7 and 8. In one subject, the SGOT was also elevated on day 7.

The SGPT patterns are recapitulated in detail:

Subject No.	MGM/KGM of Drug	STUDY DAY 0	2	7	8	Rpt.(+ days from last SGPT)	
389	8.80	13	11	15			
385	8.83	18	11	24			
386	9.91	25	21	69		20(+40 days)	
387	6.62	56	77	78		35(+90 days)	
388	8.54	10	9	21			
389	8.81	16	19	234		110(+4 days)	26(+37 days)
390	7.54	12	9		65	16(+20 days)	
391	8.34	8	7		24		

One subject (#387) had an SGPT elevation on study day 0. Inclusion of this subject (a result of inadequate reporting of laboratory values, since corrected) in the study is questionable. However, three other individuals with normal values for SGPT on days 0 and 2 had elevated SGPT's on day 7 or 8. All subject values subsequently reverted to normal.

It is, therefore, a distinct - although statistically unassessable - possibility that the elevated SGPT's were related to drug administration.

Other laboratory abnormalities were minimal or inconsistant, inviting no speculation or comment.

Hematology:

Two subjects had borderline low hematocrits on day 7. One subject had an increased percentage of monocytes on day 0 and day 2. Another had persistant eosiniphilia. There is no indication that these findings were of clinical significance or related to the study.

Creatinine Excretion:

Creatinine excretion for each collection interval is reported for each subject at Tab B. The importance of these values lies in their comparison with urinary excretion of antimony. Urinary antimony assays have not yet been accomplished.

DISCUSSION

This study of sodium stibogluconate was conducted primarily to determine the pharmacokinetics of the drug in humans. At the time this clinical report was prepared antimony assays of collected blood and urine samples have not been done. Therefore pharmacokinetics must be the subject of another report.

In this group of eight subjects, some interesting clinical finds can be reported.

There were a number of clinical events which were looked for and not observed. During infusion of the drug and for the first few hours after infusion, we looked for, and did not find:

1. cough
2. gastrointestinal complaints
3. complaints of "weakness"
4. skin rash
5. changes in the electrocardiogram (rhthym strips on days 1, 2 and 7)

Albuminura did not occur. Twelve hours after infusion of the drug, one subject complained of abdominal cramps.

The only indication of drug intolerance was an elevation of the SGPT in 3 subjects on day 7 or 8. In one of these three subjects, the SGOT was elevated at the same time.

The validity of this association cannot be specifically assessed.

There were no "control" subjects in this study. Even had there been matching controls, the number would have been too small to provide a reliable estimate of base rate frequency of elevated SGPT's in this population under these circumstances.

Intuitively, one judges that elevation of the SGPT within 7 or 8 days of drug administration in 3 of 8 subjects is something other than coincidence. Alternatively, one must consider that the elevations occurred after discharge from the clinical facility in young men suddenly in possession of financial resources with free time for recreation.

CONCLUSIONS AND RECOMMENDATIONS:

In this study, eight healthy males received 600 mg of Pentostam® intravenously in a period of 10 minutes. There were no acute untoward reactions. On the seventh day, two of these subjects developed an elevation of the SGPT. Another developed an elevation of the SGPT by the eighth day. In each subject, SGPT values subsequently returned to normal. Aside from this possible association between drug administration and transient SGPT elevation, the sudy was carried out without misadventure.

Blood samples and urine samples are at hand from each subject for Antimony Assay. Creatinine excretions for each subject are reported for each interval of urine collection as a general test of the reliability of urine collection.

The raw material for determination of the pharmacokinetics of Sodium Stibogluconate in man has been collected. Recommendations must await the analysis of the specimens provided.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 4/29/80 CODE: 384 AGE: 23
DOSE PER Kg: 8.80 mg/kg TIME INTERVAL DOSED: 0805-0815 GROUP: I
HEIGHT: 170.18 cm WEIGHT: 68.18 kg

==========

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	4/9	4/28	4/29	4/30	5/1	5/2	5/3	5/5
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
Triglyceride	118	441-H	196	160	0-207 mg/dl
Hct	46.9	44.5	51.2-H	44.2	40-50 Vol %
Hgb	15.9	15.3	17.6-H	14.9	13.3-16.7 GMS%

SYMPTOMS AND PHYSICAL FINDINGS

The subject was asymptomatic during the study interval. Slight injection of the oro-naso pharynx present on study admission was absent thereafter. The rest of the physical examination was normal and remained unchanged.

ABNORMALITIES COMMENT

Laboratory abnormalities were minimal or inconsistent and not considered study related.

CONCLUSION

No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 4/29/80 CODE: 385 AGE: 21
DOSE PER Kg: 8.83 mg/kg TIME INTERVAL DOSED: 0950-1000 GROUP: I
HEIGHT: 165.1 cm WEIGHT: 67.95 kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	4/23	4/28	4/29	4/30	5/1	5/2	5/3	5/5
STUDY DAY	Screen	0*	1*	2*	3	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
Alka Phos	96-H	99-H	92	89	26-94 U/L
LDH	236-H	198	192	245-H	73-233 U/L

SYMPTOMS AND PHYSICAL FINDINGS

The subject was asymptomatic and had an unchanged normal physical examination throughout the study interval.

ABNORMALITIES COMMENT

Minimal elevation of LDH on screening examination and on day 7 not considered significant. Subject was requested, but failed to report for repeat determination. Other abnormalities were minimal or inconsistent.

CONCLUSION

No adverse effect from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/6/80 CODE: 386 AGE: 19
DOSE PER Kg: 9.91 mg/kg TIME INTERVAL DOSED: 0801-0811 GROUP: II
HEIGHT: 170.18 cm WEIGHT: 60.57 kg

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SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	4/9	5/5	5/6	5/7	5/8	5/9	5/10	5/12
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
BUN	14	17	8-L	17	9-21 mg/dl
Uric Acid	4.9	4.7	3.6-L	5.4	4-8 mg/dl
T.Prot.	6.7	6.5	6.3-L	6.8	6.4-8.0 g/dl
SGPT	16	25	21	69-H	0-47 U/L
Monos	11-H	12-H	12-H	10	0-10 %

SYMPTOMS AND PHYSICAL FINDINGS

Approximately 12 hours after drug infusion the patient experienced "stomach cramps" of 1.5 hours duration in the right upper quadrant. Physical examination approximately 15 hours later remained within normal limits. On day 7 the subject was noted to have induration with discoloration at the site of the intracath placement. The subject noted some discomfort in the area beginning on day 5 and was advised to return if the symptom and the physical appearance did not continue to return to normal over the next few days.

ABNORMALITIES COMMENT

Laboratory abnormalities were minimal or inconsistent and not considered study related. An isolated elevation of SGPT of 69 U/L was present on day 7. This was normal when the subject returned for repeat testing.

CONCLUSION

SGPT elevation, possibly due to study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/6/80 CODE: 387 AGE: 32
DOSE PER Kg: 6.62 mg/kg TIME INTERVAL DOSED: 0900-0910 GROUP: II
HEIGHT: 198.12 cm WEIGHT: 90.68 kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	3/11	5/5	5/6	5/7	5/8	5/9	5/10	5/12
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
Potassium	3.5-L	3.5-L	3.2-L	4.0	3.6-5.2 mEq/l
SGPT	47	56-H	77-H	78-H	0-47 U/L
Hct	41.8	39.6-L	44.1	38.6-L	40-50 Vol %
Hgb	13.9	13.3	14.8	13.0-L	13.3-16.7 GMS%
UA-WBC	0	occ	0	7	0-5 HpF

SYMPTOMS AND PHYSICAL FINDINGS

The subject was asymptomatic, and physical examination remained normal throughout the study interval.

ABNORMALITIES COMMENT

SGPT was elevated to 56 U/L on day 0, 77 on day 2 and 78 on day 7. Minimal hypokalemia was present on day 0 and 2 and normal on day 7. Hematocrit decreased from 39.6 on study day 0 to 38.6 on study day 7 with 44 VOL.% on day 2. Similarly there was slight variations of the hemoglobin from 13.3 on day 0 to 13 GMS% on day 7. These were normal on repeat testing.

CONCLUSION

SGPT elevation, possibly caused by study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/13/80 CODE: 388 AGE: 18
DOSE PER Kg: 8.54 mg/kg TIME INTERVAL DOSED: 0800-0810 GROUP: III
HEIGHT: 171.45 cm WEIGHT: 70.23 kg

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SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	4/9	5/12	5/13	5/14	5/15	5/16	5/17	5/19
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
BUN	9	12	9	8-L	9-21 mg/dl
Alka.Phos.	120-H	112-H	125-H	120-H	137-151 mEq/l
Hct	42.3	40.8	41.1	39.8-L	40-50 Vol %
WBC	3.1	3.4	2.7-L	3.2	3.1-9.5 Thou/cu mm

SYMPTOMS AND PHYSICAL FINDINGS

The subject had edema over the third metacarpal of the right hand upon study entry secondary to previous trauma. This abnormality cleared by study day 4. Subject was asymptomatic throughout the study interval.

ABNORMALITIES COMMENT

The subject's alkaline phosphatase was persistently elevated from 1 month prior to study entry and during study itself. The values ranged from 112 U/L to 125 U/L with the upper limits of normal of 94. This finding is considered a normal variation on this subject and not of significance. Electrocardiogram performed during the infusion of WR 229,870 was unchanged from the normal tracing significance. Other laboratory abnormalities were minimal or inconsistent. Electrocardiogram performed during the infusion of WR 229,870 was unchanged from normal tracing preceding study entry. It should be noted that this cardiogram was done because, although not called for by protocol, the subject had EKG monitoring, and the scope suggested abnormalities not found when a tracing was done at a time when the scope "abnormalities" persisted.

CONCLUSION

No adverse effects from study participation.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/13/80 CODE: 389 AGE: 33
DOSE PER Kg: 8.81 mg/kg TIME INTERVAL DOSED: 0900-0910 GROUP: III
HEIGHT: 175.26 cm WEIGHT: 72.73 kg

==========

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	5/1	5/12	5/13	5/14	5/15	5/16	5/17	5/19
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	7
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
Calcium	9.4	9.4	8.9-L	9.0	9.0-10.9 mg/dl
SGOT	18	14	29	110-H	0-47 U/L
SGPT	16	16	19	234-H	0-47 U/L

SYMPTOMS AND PHYSICAL FINDINGS

The subject exhibited mild anxiety on day 0, but had no further symptoms during the course of the study including during the infusion of the drug. Physical examination remained normal and unchanged during the study interval.

ABNORMALITIES COMMENT

On study day 7 SGOT was elevated to 110 U/L and SGPT to 234 U/L. Other abnormalities were minimal and inconsistent. When the subject returned for repeat testing, these were within normal limits.

CONCLUSION

SGOT and SGPT elevation on day 7, possibly caused by drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/20/80 CODE: 390 AGE: 21
DOSE PER Kg: 7.54 mg/kg TIME INTERVAL DOSED: 0810-0820 GROUP: IV
HEIGHT: 180.97 cm WEIGHT: 79.55 kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	4/28	5/19	5/20	5/21	5/22	5/23	5/24	5/27
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	8
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	8	Normal Range
Glucose	88	81	79	64-L	66-114 mg/dl
BUN	12	11	7-L	15	9-21 mg/dl
Creatinine	1.4	1.5-H	1.4	1.5-H	0.8-1.4 mg/dl
T.Prot.	6.5	6.8	6.1-L	7.0	6.4-8.0 g/dl
Albumin	4.4	4.5	4.0-L	4.6	4.5-5.1 g/dl
SGPT	17	12	9	65-H	0-47 U/L
Hgb	15.8	17.0-H	16.2	15.8	13.3-16.7 GMS%

SYMPTOMS AND PHYSICAL FINDINGS

The subject was asymptomatic and normal physical examination unchanged throughout the study interval.

ABNORMALITIES COMMENT

Serum creatinine varied from 1.4 and 1.5 before drug administration to 1.4 and 1.5 on days 2 and 7 respectively. SGPT which varied from 9 to 17 U/L prior was elevated to 65 U/L on study day 8. Blood sugar was depressed to 64 ml% on that date. These were normal upon repeat testing.

CONCLUSION

SGPT elevation on study day 8, possibly related to drug administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 16: WR 229,870: (SODIUM STIBOGLUCONATE INJECTION BP): PHARMACOKINETICS FOLLOWING A SINGLE INTRAVENOUS DOSE.

TOTAL DOSE: 600 mg DOSING DATE: 5/20/80 CODE: 391 AGE: 22
DOSE PER Kg: 8.34 mg/kg TIME INTERVAL DOSED: 0900-0910 GROUP: IV
HEIGHT: 177.80 cm WEIGHT: 71.93 kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1980	5/7	5/19	5/20	5/21	5/22	5/23	5/24	5/27
STUDY DAY:	Screen	0*	1*	2*	3*	4	5	8
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Urinalysis								
5. Biochemistry								
6. CBC								
7. Platelets								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
BUN	10	10	6-L	9	9-21 mg/dl
T.Prot.	6.6	7.0	6.3-L	7.3	6.4-8.0 g/dl
RBC	5.54	5.74-H	5.47	5.56	4.3-5.7 mill/cu mm
Eosin	10-H	15-H	13-H	9-H	0-5 %
MCV	81-L	83	81-L	83	82-98 cu microns

SYMPTOMS AND PHYSICAL FINDINGS

Although not noted on physical examination until study day 2, the subject stated that the small vesicles at the angle of the left mandible were present prior to drug infusion and represent a recurring condition. Vesicles had disappeared by study day 4.

ABNORMALITIES COMMENT

The subject had eosinophilia varying from 9 to 15% both before and after dosing without significant change. Other abnormalities were minimal and inconsistent.

CONCLUSION

No adverse effect from study participation.

EXPERIMENT NUMBER 16

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

URINE CREATININE DETERMINATIONS

GROUP	CODE	SPEC NO.	STUDY DAY	COLLECTION INTERVAL	MIN. INT.	CREATININE MG/DL	TOTAL VOL.	MGM TOTAL	MGM/MIN
I	384	1	0	0615-0615	1440	69.8	3010	2100.98	1.459
		2	1	0615-1415	480	37.5	1335	500.63	1.042
		3	1	1415-2015	360	46.7	1500	700.50	1.945
		4	1	2015-0215	360	79.4	630	500.22	1.389
		5	1	0215-1345	690	165.0	665	1097.25	1.590
		6	2	1345-1730	225	108.0	370	399.60	1.776
		7	3	0815-1415	360	149.0	335	499.15	1.386
		8	4	0556-1156	360	192.0	260	499.20	1.386
		9	5	0700-1245	345	78.4	510	399.84	1.158
		10	7	0900-1445	345	138.0	290	400.20	1.160
	385	1	0	0615-0615	1440	33.6	3570	1199.52	0.833
		2	1	0615-1600	585	72.7	550	399.85	0.683
		3	1	1600-2200	360	65.2	1380	899.76	2.499
		4	1	2200-0400	360	160.0	250	400.00	1.111
		5	1	0400-1000	360	82.5	485	400.13	1.111
		6	2	1000-1640	400	106.0	660	699.60	1.749
		7	3	0630-1230	360	174.0	230	400.20	1.111
		8	4	0549-1145	356	138.0	290	400.20	1.124
		9	5	0530-1120	345	121.0	330	399.30	1.157
		10	7	0530-1130	360	200.0	200	400.00	1.111
II	386	1	0	0545-0545	1440	122.0	980	1195.60	0.830
		2	1	0545-1415	510	115.0	870	1000.50	1.961
		3	1	1415-2010	355	42.3	710	300.33	0.846
		4	1	2010-0215	365	100.0	500	500.00	1.369
		5	1	0215-0830	375	190.0	210	399.00	1.064
		6	2	0830-1420	350	94.0	530	498.20	1.423
		7	3	0600-1230	390	167.0	240	400.80	1.027
		8	4	0500-1100	360	208.0	240	499.20	1.386
		9	5	0500-1055	355	123.0	325	399.75	1.126
		10	7	0600-1130	330	118.0	370	436.60	1.323
	387	1	0	0610-0610	1440	129.0	2800	3612.00	2.508
		2	1	0610-1515	545	93.0	860	799.80	1.467
		3	1	1515-2108	353	159.0	440	699.60	1.981
		4	1	2108-0315	367	184.0	380	699.20	1.905
		5	1	0315-0915	360	439.0	65	285.35	0.792
		6	2	0915-1500	345	117.0	600	702.00	2.034
		7	3	0630-1230	360	102.0	590	601.80	1.671
		8	4	0500-1130	390	355.0	90	319.50	0.819
		9	5	0540-1140	360	343.0	130	445.90	1.238
		10	7	0545-1145	360	200.0	100	200.00	0.555

EXPERIMENT NUMBER 16

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

URINE CREATININE DETERMINATIONS

GROUP	CODE	SPEC NO.	STUDY DAY	COLLECTION INTERVAL	MIN. INT.	CREATININE MG/DL	TOTAL VOL.	MGM TOTAL	MGM/MIN
III	388	1	0	0430-0445	1455	183.0	1100	2013.00	1.383
		2	1	0445-1415	570	65.0	980	637.00	1.117
		3	1	1415-2015	360	83.0	650	539.50	1.498
		4	1	2015-0210	355	130.0	450	585.00	1.647
		5	1	0210-1015	485	74.0	160	118.40	0.244
		6	2	1015-1515	300	125.0	110	137.50	0.458
		7	3	0610-1440	510	123.0	490	602.70	1.181
		8	4	0505-1105	360	148.0	120	177.60	0.493
		9	5	0530-1130	360	481.0	100	481.00	1.336
		10	7	0400-1030	390	113.0	110	124.30	0.318
	389	1	0	0500-0500	1440	126.0	1300	1638.00	1.137
		2	1	0500-1530	630	95.0	910	864.50	1.372
		3	1	1530-2108	338	92.0	400	368.00	1.088
		4	1	2108-0330	382	68.0	800	544.00	1.424
		5	1	0330-0940	370	74.0	530	392.20	1.060
		6	2	0940-1540	360	108.0	115	124.20	0.345
		7	3	0610-1210	360	71.0	455	323.05	0.897
		8	4	0505-1105	360	83.0	480	398.40	1.106
		9	5	0600-1130	330	187.0	210	392.70	1.190
		10	7	0500-1100	360	209.0	200	418.00	1.161
IV	390	1	0	0615-0600	1425	195.0	1140	2223.00	1.560
		2	1	0600-1410	490	101.0	820	828.20	1.690
		3	1	1410-2020	380	101.0	730	737.30	1.940
		4	1	2020-0220	360	113.0	600	678.00	1.883
		5	1	0220-0900	400	238.0	260	618.80	1.547
		6	2	0900-1550	410	93.0	840	781.20	1.905
		7	3	0620-1220	360	229.0	270	618.30	1.717
		8	4	0610-1210	360	241.0	270	650.70	1.807
		9	5	0605-1305	420	262.0	290	759.80	1.809
		10	8	0600-1200	360	185.0	360	666.00	1.850
	391	1	0	0700-0600	1380	134.0	1570	2103.80	1.524
		2	1	0600-1510	550	87.0	980	852.60	1.550
		3	1	1510-2110	360	89.0	720	640.80	1.780
		4	1	2110-0310	360	99.0	580	574.20	1.595
		5	1	0310-0920	380	163.0	350	570.50	1.501
		6	2	0920-1550	390	72.0	870	626.40	1.606
		7	3	0625-1225	360	155.0	390	604.50	1.679
		8	4	0615-1215	360	115.0	500	575.00	1.597
		9	5	0600-1215	375	203.0	200	406.00	1.082
		10	8	0700-1230	330	183.0	330	603.90	1.830

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

BIO - MED, Inc.

EXPLANATION FOR POTENTIAL SUBJECTS

EXPERIMENT NUMBER

WR 229,870 (Sodium Stibogluconate Injection BP):
Pharmacokinetics Following a Single Intravenous Dose

GENTLEMEN:

The study in which you have volunteered to participate involves your receiving an intravenous injection of an investigational new drug called Pentostam®. Pentostam® is a drug used throughout the world for treatment of a parasitic disease called leishmaniasis. It is given intravenously to patients.

Pentostam® is the only drug which is currently recommended for the treatment of these diseases in the United States. It has been available since the late 1940's. The drug is quite effective in decreasing the severity of leishmaniasis. However, there is a possible 40% failure to cure the disease with the current recommendations of the manufacturer.

A recent study at Walter Reed suggests that conventional therapy can be improved. In order to achieve better blood levels of the drug, we need to know what happens to this drug in normal, healthy people.

Our knowledge of the undesirable side effects from the use of Pentostam® comes mostly from the treatment of patients receiving multiple doses of the drug. That experience suggests that side effects are uncommon and not severe. Jaundice, usually a symptom of liver damage, was reported. Some patients have had signs of kidney damage, with the signs later disappearing. Abdominal pain, nausea and vomiting may occur. Cough can occur immediately, and briefly, after the drug is given. There are reports of hives, fever, nose bleeds, sweating, headaches, and weakness in association with use of the drug. The electrical activity of the heart has changed briefly, manifested by minor transient changes in the electrocardiogram.

We expect that if you have symptoms, they will be mild and of a short duration. We expect no long-term adverse effect upon your health. However, an element of risk is involved for subjects in this study. However slight, it must be understood and acknowledged.

In this study, each volunteer subject will be given the standard, single dose of Pentostam® (600 mg) intravenously over a period of 10 minutes. Blood will be collected at intervals from the arm opposite from the injection. Urine specimens will be collected over 6 hours each day of the study. The study will cover 8 days. Subjects must be continually present in the research facility during the first 5 days.

The study plan is presented in outline below:

STUDY PLAN OUTLINE

DAY of STUDY	0	1	24 2	48 3	72 4	96 5	120 6	144 7
EVENTS								
Interview	X	X	X	X	X	X	X	X
Physical	X		X		X			X
Electrocardiogram	X	X	X					X
Urine Collection	X	X	X	X	X	X	X	X
Venipuncture	X	X	X	X	X	X	X	X
Drug administered		X						
DAYS in FACILITY	X	X	X	X	X			

The Institutional Review Board will also look after your safety. The Board will insure that you are not subject to undue risk or discomfort. A member of this committee will be available to speak with you and to answer any questions you might have. A member may also visit you at the Clinical Facility in College Park. After members of the investigating team (and perhaps the Institutional Review Board) have interviewed you individually and are satisfied that you understand the study and written informed consent, you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent, you signify that the study has been explained to you with regard to risks and requirements, and that you wish to participate. It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where leishmaniasis is a serious problem, and to Americans, civilian and military, who may travel to these areas. Your participation must be entirely voluntary, with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw from the study at any time and without penalty to yourself.

SCHEMATIC ASSAY SPECIMEN COLLECTION SCHEDULE

DAY OF THE STUDY	SPECIMEN NUMBER	SPECIMEN TIME		SPECIMEN VOLUME (ml)
Day 1 Tuesday	1	0	Prior to Dosing	5
	2	10 min	8:10 AM	5
	3	20 min	8:20 AM	5
	4	30 min	8:30 AM	5
	5	45 min	8:45 AM	5
	6	1 hr	9:00 AM	5
	7	2 hr	10:00 AM	5
	8	3 hr	11:00 AM	5
	9	4 hr	NOON	5
	10	6 hr	2:00 PM	5
	11	8 hr	4:00 PM	5
	12	12 hr	8:00 PM	5
	13	16 hr	MIDNIGHT	5
Day 2 Wednesday	14	24 hr	8:00 AM	5
Day 3 Thursday	15	48 hr	8:00 AM	5
Day 4 Friday	16	72 hr	8:00 AM	5
HOME				
Day 5 Saturday	17	96 hr	8:00 AM	5
Day 7 Monday	18	144 hr	8:00 AM	5
			TOTAL	90 ml

Urine specimens will be collected within blocks of 6 Hours, and the precise time of collection recorded.

SUBJECT AGREEMENT

CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled "WR 229,870 (Sodium Stibogluconate Injection BP): Pharmacokinetics Following a Single Intravenous Dose."

The implications of my voluntary participation; the nature; duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Doctor _____, and are set forth in the document titled "EXPLANATION FOR POTENTIAL SUBJECTS: WR 229,870 (Sodium Stibogluconate Injection BP): Pharmacokinetics Following a Single Intravenous Dose", which I have signed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks.The discomforts and potential risks of participation asa subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study.

I understand that as a temporary employee of BIO-MED, Inc. that workmen's compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____
Date

_____ _____
Signature Investigator Certification

_____ _____
Address Witness

REAFFIRMATION OF CONSENT:

_____ _____
Date Witness

_____
Signature

BIO - MED, Inc.

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PROGRESS REPORT

Addendum Number 2 to Experiment Number 13

WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels.

The subject protocol was implemented 6 October 1980. Four subjects were admitted to the clinical facility and received drug or placebo according to the 2 x 2 double-blind schedule.

During the administration of the study materials, it was noted that 2 of the 4 vials had a distinct odor. The COTR was consulted. He confirmed the investigator's observation and recommended that no further subjects be studied under this protocol until the nature of this "distinct odor" could be clarified.

On study day 2, the code was broken and it was ascertained that the distinct odor was associated with the vials that contained active drug. Both subjects receiving the drug developed neutrophilic leucocytosis and reverted to normal by the 4th day of study. There were no symptoms and no adverse physical findings associated with administration of the drug.

It is intended that this protocol will be re-implemented when questions about the drug formulation have been resolved.

BIO - MED, Inc.

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

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 13

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

PRINCIPAL INVESTIGATOR: JOHN A. JOHNSON, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

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JOHN A. JOHNSON, M.D.
PRINCIPAL INVESTIGATOR

TITLE: WR 172,435·CH_3SO_3H*: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels.

PURPOSE:

To determine the short term safety and tolerance of multiple oral doses of the antimalarial WR 172,435 including the effect on the leukocyte count.

RATIONALE:

WR 172,435, a pyridine methanol, is an effective blood schizonticide for drug resistant P. falciparum malaria. In the Aotus monkey, a total dose of 17.5-35 mg/kg was required for cure of resistant malaria.

In previous Phase I testing of WR 172,435, drug administration in a single oral dose was associated with transient, mild gastrointestinal symptoms in one of two subjects receiving 800 mg, and two of four subjects receiving 1000 mg. Leukocytosis without change in differential counts occurred in nine subjects, seven of whom received drug and two placebo. Three of the four subjects who received 1000 mg developed leukocytosis. To verify that administration of WR 172,435 was associated with leukocytosis, an addendum to the Phase I study was performed. In this study, the drug was administered orally in a single dose of 1000 mg. Six subjects were given the drug and six placebo in 2 x 2 double-blind design. Blood was obtained by venipuncture prior to administration of drug or placebo and at intervals following administration. Analysis of the results confirmed that administration of WR 172,435 is associated with transient leukocytosis. Total white blood cell counts of subjects receiving drug were significantly greater than those receiving placebo. The count rose to 2-3 times the baseline values 12 hours after dosing, except in one case where the count was 1.8 times the baseline. Differential white blood cell counts showed that the leukocytosis was secondary to an increased number of mature neutrophils. White blood cell counts returned to normal within 72 hours.

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* WR 172,435·CH_3SO_3H will be hereinafter designated as WR 172,435.

Since the top tolerated single oral dose in man was 1000 mg (about 14.5 mg/kg) in the previous study and 17.5-35 mg/kg was required to cure malaria in the Aotus monkey, the total top tolerated dose using multiple dose drug administration, and the effect on the white blood cell count will be determined.

METHODS:

Subject Acceptability Criteria

Subject acceptability criteria are based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects are rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest x-ray. The presence of conditions which do not increase risk for the subject or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes are not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean are cause for rejection. Deviations between 2 and 3 standard deviations from the mean are generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would cause rejection, whereas a serum sodium of 153 mEq/L of itself would not.

When doubt exists concerning acceptance of a subject for any reason a decision is made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates are given full consideration and the integrity and ethics of the Research Team protected.

Subject Selection:

Approximately 24 male subjects between the ages of 18 and 35 with body weight 50-100 kg will be recruited from the Washington, D.C. metropolitan area. Candidates will be hired as temporary employees of BIO-MED, Inc.

Candidates for employment will be medically evaluated to obtain the subjects for study. The medical evaluation will include a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential counts, red blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin.

Subjects must abstain from smoking during the study. Qualified candidates will be given a complete explanation of the background and procedures to be used in the study and all details of the protocol as it involves the individual subjects. They will be interviewed in a group and individually in the presence of an investigator. Each participant will be given the opportunity to ask questions. Following this, at the individual interview, the consent form will be read and if the investigator believes the subject understands his participation adequately to give informed consent, the subject will be permitted to sign the consent form. The subject will reaffirm his consent by signature on study day 1.

Study Plan:

1. A 2 x 2 rising dose level double-blind design will be used. Each group shall include 4 subjects. Two subjects will receive drug and two placebo. Drug will be administered every 12 hours for 3 doses.

WR 172,435 DRUG ADMINISTRATION SCHEDULE

	Dose 1	Dose 2	Dose 3
Group I	400 mg	400 mg	400 mg
Group II	600 mg	400 mg	400 mg
Group III	800 mg	400 mg	400 mg
Group IV	800 mg	600 mg	400 mg
Group V	800 mg	800 mg	600 mg
Group VI	800 mg	800 mg	800 mg

2. One group of 4 subjects will be tested during each study interval. Two subjects will receive active drug and two will be given placebo. The dose will be increased in the above sequential groups until intolerance occurs. Two additional groups will then be studied at the previous lower dose to confirm a tolerated dose. Additional groups may be studied at any of the dose levels presented if needed to obtain statistical significance of the data. As each group finishes its dosing schedule, the subjects will be observed through the 6th study day before the next group is initiated.

3. Assignment to the double-blind study shall be random through lottery with the code sealed and available only for emergencies to the investigator and his staff.

4. The test subtances will be supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research in the form of 200 mgm tablets labelled "WR 172,435·CH_3SO_3H.".

5. The tablet(s) will be ingested in the presence of a member of the investigating team.

6. On the last study day for each subject, final physical and laboratory evaluation will be done. All abnormal findings will cause follow-up until normalcy, stabilization or proper medical disposition is assured.

7. Emergencies: Immediate action will be taken to first care for the subject in emergent need including consultation and hospitalization if warranted and second, to notify the Army Clinical Monitor by telephone followed within 24 hours by written communication.

8. The clinical and laboratory evaluation of the subjects is outlined in the following schematic.

SCHEMATIC STUDY PLAN - MULTIPLE ORAL DOSE ADMINISTRATION OF WR 172,435

Study day	0*	1*	2*	3	4	7	14
Dose		X	--- X				
Physical Examination	X		X				X
Interview	X	X	X	X		X	X
Complete Vital Signs	X	X	X	X		X	X
Phototoxicity Test	X		X				
Electrocardiogram (Lead II)	X	X	X				
Laboratory Tests+	X		X	X		X	X
Hematologic Studies++	X	X	--- X	--- X	X	X	X

*controlled environment

+glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

++CBC (differential and indices), platelets and reticulocyte count. Seven ml blood for these studies will be obtained by venipuncture twice on day 0 at 1400 and 2000; twice on day 1 prior to dosing, at 0200 and 0755, at 6, 12 and 18 hours after each of the 3 doses; and then 24 and 48 hours, and 5 and 12 days after the last dose, according to the sampling schedule below.

DAY OF WEEK	STUDY DAY	SPEC NO.	DOSE TIME	SPEC.COLL.TIME FOR HEMATOLOGY	CUMULATIVE TIME
MON.	0	1		1400	-18:00
		2		2000	-12:00
TUE.	1	3		0200	- 6:00
		4	0800	0755	0:00
		5		1400	6:00
		6	2000	1955	11:55
WED.	2	7		0200	18:00
		8	0800	0755	23:55
		9		1400	30:00
		10		2000	36:00
THURS.	3	11		0200	42:00
		12		0800	48:00
FRI.	4	13		0800	72:00
MON.	7	14		0800	144:00
MON.	14	15		0800	312:00

HEMATOLOGY METHODS:

Blood specimens will be collected by venipuncture from the antecubital veins with care taken to minimize trauma and tourniquet time. Blood will be collected in vacutainer tubes for the hematology studies.

The determinations will be performed at National Health Laboratories. Tests will be done within 8 hours of venipuncture. Red blood cell counts, hemoglobin level, hematocrit level, red blood cell indices and white blood cell counts will be determined using a Coulter Counter, Model S.

Platelet counts will be determined on a Clay-Adams Uniflow-100. White blood cell differential counts will be performed using Technicon's Hemalog D/90 for a 10,000 cell sample. Peripheral blood smears will be made and retained at the BIO-MED Clinical Facility. Reticulocyte counts will be performed at National Health Laboratories using the standard methylene blue differential technique.

RESULTS AND REPORTING:

All data will be recorded daily for each subject. Any deviation from normal will be brought to the attention of the investigator. Individual work sheets will be maintained for each subject. The following will be recorded on standard forms: blood pressure, pulse, weight, clinical laboratory results, subjective symptoms and physical examination. A specimen schedule form will be kept for each subject and the exact time of drug administration and specimen collections recorded. A cumulative master log will also be kept, which will include laboratory data. This will provide for ongoing availability of data at all times to the Institutional Review Board, BIO-MED, Inc., and the Army Clincal Monitor.

Upon completion of the study, a report will be submitted detailing the results of the drug administration and all associated clinical and laboratory evaluations.

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EXPLANATION FOR POTENTIAL SUBJECTS
ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 13

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

GENTLEMEN:

The study for which you have applied involves taking by mouth the antimalarial drug WR 172,435 or a placebo containing no active drug. WR 172,435 has previously undergone safety and tolerance testing at this facility.

Animal studies suggest that WR 172,435 may be more effective against chloroquine-resistant falciparum malaria than drugs currently used in the prevention and treatment of this disease. The United States Army Medical Service, sponsors of this study, and the Food and Drug Administration have approved WR 172,435 for clinical testing in human subjects.

Clinical testing of WR 172,435 was initiated in a prior study. At each dose level 2 subjects received drug and 2 received placebo (no active drug). A single dose was administered without either the investigators or the subjects knowing which two were given the drug and which two were given the placebo. This was done to help ensure objectivity. 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 the drug and occurred in 1 of 2 subjects receiving 800 mg and 2 of 4 subjects receiving 1000 mg WR 172,435.

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* WR 172,435·CH_3SO_3H will be hereinafter designated WR 172,435.

Leukocytosis, an increase in the circulating white blood cells of the blood, without change in the ratio of the different kinds of white blood cells occurred in 9 study subjects. Seven of these received WR 172,435. Three of 4 subjects receiving 1000 mg had leukocytosis 24 hours after dosing which returned to normal within 48 hours: leukocytosis in these subjects was observed on day 2 with a return to normal leukocyte counts on day 3. The data suggested a dose effect, but the small number of observations was inadequate for definite conclusions. Therefore additional subjects were studied at the 1000 mg dose level.

The occurrence of leukocytosis following oral administration of WR 172,435 was confirmed by this study in the 6 of whom received the drug. White blood cell counts returned to normal within 72 hours of dosing.* Furthermore, all subjects who received the single 1000 mgm oral dose of WR 172,435 had transient, mild gastrointestinal symptoms including abdominal pain, nausea and diarrhea.

There are two purposes of the study for which you are being considered: 1) to see whether gastrointestinal symptoms are avoided by giving the drug in smaller, divided doses (three doses per individual) and 2) to see if multiple doses produce an increase in the circulating white blood cell count (leukocytosis).

The design of this study is called "a double-blind, rising dose level". Four subjects will be admitted to the research unit at a time for the study of each dosing level. By random assignment, two subjects will receive drug and two will receive placebo. Neither the subjects nor the research staff will know who received drug or placebo until the study is completed. Subjects will receive the tablets (drug or placebo) in three doses, each given every 12 hours. The lowest total dose will be 1200 mg and the highest will be 2400 mg.

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* There is no indication that a transient leukocytosis is harmful to a subject.

SCHEMATIC STUDY PLAN - MULTIPLE ORAL DOSE ADMINISTRATION OF WR 172,435

Study day	0*	1*	2*	3	4	7	14
Dose		X	--- X				
Physical Examination	X		X				X
Interview	X	X	X	X		X	X
Complete Vital Signs	X	X	X	X		X	X
Phototoxicity Test	X		X				
Electrocardiogram (Lead II)	X	X	X				
Laboratory Tests+	X		X	X		X	X
Hematologic Studies++	X	X	--- X	--- X	X	X	X

*controlled environment

+glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

++CBC (differential and indices), platelets and reticulocyte count. Seven ml blood for these studies will be obtained by venipuncture twice on day 0 at 1400 and 2000; twice on day 1 prior to dosing, at 0200 and 0755, at 6, 12 and 18 hours after each of the 3 doses; and then 24 and 48 hours, and 5 and 12 days after the last dose, according to the sampling schedule below.

DAY OF WEEK	STUDY DAY	SPEC NO.	DOSE TIME	SPEC.COLL.TIME FOR HEMATOLOGY	CUMULATIVE TIME
MON.	0	1		1400	-18:00
		2		2000	-12:00
TUE.	1	3		0200	- 6:00
		4	0800	0755	0:00
		5		1400	6:00
		6	2000	1955	11:55
WED.	2	7		0200	18:00
		8	0800	0755	23:55
		9		1400	30:00
		10		2000	36:00
THURS.	3	11		0200	42:00
		12		0800	48:00
FRI.	4	13		0800	72:00
MON.	7	14		0800	144:00
MON.	14	15		0800	312:00

You have already had many of the examinations listed on the schematic as part of your qualification examination. As mentioned previously, only mild temporary symptoms occurred with use of WR 172, 435 in our previous clinical testing. Although there can be no guarantee that unexpected reactions will not occur, past experience makes it likely that any effects of the drug will be minor and of short duration.

After members of the investigating team have interviewed you individually and are satisfied that you understand the study and the written informed consent form you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent, you signify that the study has been explained to you with regard to risks and requirements and that you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to individuals who may travel to these areas.Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent and your participation in the project at any time without prejudice to you, the subject.

_____

Initials

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____, hereby give my informed consent to participate as a study subject in the study entitled "WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document titled "Explanation for Potential Subjects, Addendum Number 2 to Experiment No. 13: WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Multiple Oral Doses, Rising Dose Levels," which I have initialed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____
Date

_____ _____
Signature Investigator Certification

_____ _____
Address Witness

REAFFIRMATION OF CONSENT:

_____ _____
Date Witness

_____
Signature

BMI-300

BIO - MED, Inc.

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EXPERIMENT NUMBER 17

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

PRINCIPAL INVESTIGATOR: JOHN A. JOHNSON, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

INSTITUTIONAL REVIEW BOARD MEMBERS:

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BIO - MED, Inc.

INSTITUTIONAL CERTIFICATION

The professional staff of BIO-MED, Inc. has reviewed the protocol entitled: WR 180,409·H_3PO_4: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.

This protocol is recommended for implementation at BIO-MED, Inc.

John A. Johnson, M.D., Principal Investigator

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

Leslie B. Altstatt, M.D., Assoc. Director

Concurrences:

Charles L. Pamplin, III, M.D.,
Maj., MC
Contracting Officer (COTR)
DAMD 17-75-C-5036

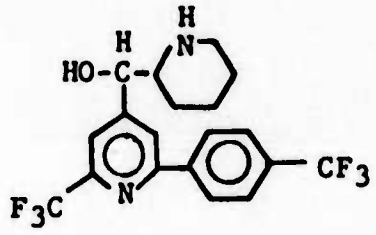
TITLE: WR 180,409·H_3PO_4*: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.

PURPOSE:

To establish a well-tolerated dose of WR 180,409 given in multiple doses over 24 hours.

RATIONALE OF STUDY:

WR 180,409 is a 4-pyridinemethanol with the following structure:



It is being studied for its potential for curing chloroquine resistant falciparum malaria in man using a short term (24 hr.) course of therapy.

Pre-clinical efficacy studies in mice showed that the drug cured malaria at 640 mg/kg. Studies in Aotus monkeys showed that 12 mg/kg per dose in 3 daily doses cured 5 of 5 animals infected with chloroquine resistant P. falciparum malaria (Vietnamese strain) and that doses of 5 mg/kg given daily for 7 days cured 8 of 8 Aotus monkeys similarly infected.

Pre-clinical toxicity studies showed that in mice and rats the acute LD_{50}'s were 900 mg/kg and 500 mg/kg respectively. However, single doses of 37 mg/kg frequently caused vomiting in beagle dogs. Thus, the curative dose for monkeys (about 35 mg/kg) was well below the LD_{50} dose for rodents (500-900 mg/kg), but close to the amount producing vomiting in dogs (37 mg/kg) when given in a single dose.

In man, in Phase I clinical studies, 13 of 16 subjects who received 750 mg in a single oral dose (8.5-12.5 mg/kg) developed nausea and/or vomiting. Although these subjects developed no abnormal physical findings or laboratory values, it is clearly impractical to attempt higher single doses of this formulation.

* WR 180,409·H_3PO_4 will be hereinafter designated as WR 180,409.

The next logical step is to determine whether multiple doses of the drug can be given over a 24 hour period, circumventing the undesirable gastro-intestinal effects while achieving a curative blood level of the drug.

In this study, subjects will be observed for tolerance to 3 doses of the drug, while at the same time, the pharmacokinetics of the multiple doses will be determined. Previous studies in humans showed that a single 750 mg dose produced a mean peak level of 362 ng/ml*, a mean time of peak level of 13.2 hours, and a mean half-life of 6.9 days.

METHODS:

Subject Acceptability Criteria

Subject acceptability criteria are based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects are rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest x-ray. The presence of conditions which do not increase risk for the subject or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes are not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean are cause for rejection. Deviations between 2 and 3 standard deviations from the mean are generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would cause rejection, whereas a serum sodium of 153 mEq/L of itself would not. Subjects shall be 50-100 kg body weight.

When doubt exists concerning acceptance of a subject for any reason, a decision is made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates are given full consideration and the integrity and ethics of the Research Team protected.

Subject Selection:

Approximately 32 male subjects between the ages of 18 and 35 will be recruited from the Washington, D.C. metropolitan area. Candidates will be hired as temporary employees of BIO-MED, Inc.

* With Vietnamese cholorquine resistant strains of *P. falciparum*, 48.5 ng/ml inhibits parasite growth *in vitro*.

Candidates for employment will be medically evaluated to obtain the subjects for study. The medical evaluation will include a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential counts, red blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin.

Qualified candidates will be given a complete explanation of the background and procedures to be used in the study and all details of the protocol as it involves the individual subjects. They will be interviewed in a group and individually in the presence of an investigator. Each participant will be given the opportunity to ask questions. Following this, at the individual interview, the consent form will be read and if the investigator believes the subject understands his participation adequately to give informed consent, the subject will be permitted to sign the consent form. On study day 1, the subject will reaffirm his consent in writing prior to his participation.

Study Plan:

The study plan is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Multiple Oral Dose Administration of WR 180,409

Day of Study	0*	1*	2*	3*	4*	5	7	9	11	14	17	21
Day of Week	M	T	W	TH	F	SA	M	W	F	M	TH	M
Physical Exam	X		X		X							X
Interview	X	X	X	X	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X			X		X
Lab Tests+	X		X		X		X			X		X
Dose		X---X										
Assay Sample++		X	X	X	X	X	X	X	X	X	X	X

* Controlled environment

+ glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices),platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

++ See "Sampling Schedule for Drug Assay"

The design is a 2 X 2, double-blind, rising dose level design with 8 subjects per level. Thirty-two subjects will be divided into 8 groups of 4 subjects each. In each group, by random assignment, 2 subjects will receive drug and 2 will receive placebo. Two groups of 4 subjects will be done at each dose level. The following table outlines the dosing schedule.

WR 180,409 DRUG ADMINISTRATION SCHEDULE

Time and Doses (in mg) of Drug or Placebo

Group	1st dose Day 1 0800	2nd dose Day 1 2000	3rd dose Day 2 0800	Total Dose
A	250	250	250	750
B	250	250	250	750
C	500	250	250	1000
D	500	250	250	1000
E	500	500	250	1250
F	500	500	250	1250
G	500	500	500	1500
H	500	500	500	1500

The drug will be supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, in the form of 250 mg tablets labelled "WR 180,409·H_3PO_4".

Whole blood samples of 6 ml per sample will be drawn. The sampling schedule is as follows:

EXPERIMENT #17 SAMPLING SCHEDULE FOR DRUG ASSAY

Study Day		Spec.#	Time	Cumulative Time (Hrs)	Interval (Hrs)
M	0	--	--	--	--
T	1	1	0755	0	--
		2	1400	6	6
		3	1955	12	6
W	2	4	0200	18	6
		5	0755	24	6
		6	0900	25	1
		7	1000	26	1
		8	1200	28	2
		9	1400	30	2
		10	1600	32	2
		11	2000	36	4
		12	2400	40	4
Th	3	13	0800	48	8
		14	1800	58	10
F	4	15	0600	70	12
		16	1800	82	12
S	5	17	1000	98	16
		18	1200	100	2
M	7	19	1200	148	48
W	9	20	1200	196	48
F	11	21	1200	244	48
M	14	22	1200	316	72
Th	17	23	1200	388	72
M	21	24*	1200	484	96

* Total blood drawn for assays = 144 ml

The blood will be drawn in disposable syringes, and specimens will be stored at 20^0c in teflon capped heparinized glass tubes pending transportation to Department of Pharmacology, WRAIR, for drug assay.

Special Procedures:

Diet:

WR 180,409 is highly soluble in lipids. Lipids taken by mouth may influence drug absorption and high concentration of blood lipids may interfere with extraction of drug from the blood.

For twelve hours preceding drug administration and for 12 hours following, all meals and snacks will be high in carbohydrates and low in fat and protein. To document compliance, dietary records will be maintained on each subject on study days 0-2 (inclusive).

Proposed Diet - High Carbohydrate, Low Fat, Low Protein:

No added fat. No meats with high fat content.

BREAKFAST	LUNCH	DINNER
As much fresh or canned fruit as desired 1 slice bread* Cereal (3/4 cup dry or 1/2 cup cooked) 1 egg 8 oz. skim milk	3 oz. lean meat 1 slice bread* Potato (noodles, rice) 1/2 cup 2 vegetables (1/2 cup each) - cooked in plain water As much fruit as desired Beverage	3 oz. lean meat 1 slice bread* 1/2 cup potato (or substitute) 2 vegetables (1/2 cup each) As much fruit as desired Beverage

MID-MORNING - MID-AFTERNOON - EVENING SNACKS

Sandwich (2 slices bread, 1 oz. lean meat).
As much fruit as desired.
Beverage

* Any item from bread exchange list may be substituted.

Monitoring:

Individual work sheets will be maintained on each subject. The following data will be recorded according to the schematic study plan: pulse, temperature, blood pressure, weight, clinical and laboratory test results, diet, symptoms and pertinent physical findings. In addition, a specimen schedule will be maintained for each subject to record exact dosing times and blood sample collections.

Signs or symptoms of possible drug intolerance will be carefully noted and thoroughly evaluated. Significant symptoms, physical findings, or laboratory deviations attributed to the drug shall be cause for suspension until BIO-MED and the COTR consult.

On the last study day for each subject, final physical and laboratory evaluation will be done. All abnormal findings will cause follow-up until normalcy, stabilization or proper medical disposition is assured.

Emergencies:

The first priority will be to care for any subject in emergent need from any cause. Appropriate medical consultation will be obtained and hospitalization arranged where indicated. The COTR will be informed of any emergent incident in writing within 24 hours.

RESULTS AND REPORTING:

All pertinent data for each subject will be logically assembled and submitted to the COTR for review prior to submission of a final report. When the results of the drug assays are available, the Division of Experimental Therapeutics, WRAIR, will analyze the data using a weighted non-linear regression technique for the estimation of pharmacokinetic parameters. Those results will be made available to BIO-MED, Inc.

BIO - MED, Inc.

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EXPLANATION FOR POTENTIAL SUBJECTS

EXPERIMENT #17

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

Gentlemen:

The study for which you have volunteered involves taking by mouth the antimalarial drug named WR 180,409. This is one of many antimalarial drugs being developed by the U.S. Army Medical Service, the sponsor of this study, in an effort to improve the treatment of drug resistant malaria. WR 180,409 has been approved for clinical testing in humans by both the sponsor and the Food and Drug Administration.

In a previous study with humans, 13 of 16 subjects who received a single dose of 750 mg. by mouth developed nausea and/or vomiting. Such reactions make administration of the drug in a single dose impractical. In this study, for which you are being considered, WR 180,409 will be administered in 3 doses of 250-500 mg. of the drug over a period of 24 hours in an attempt to avoid the undesirable clinical effects.

In order to monitor the safety of the drug, your tolerance to the drug, and the rate at which the drug builds up in the blood during this study, we will conduct interviews, physical examinations, blood tests for the level of the drug and its effects on you, urine tests, and measurements of your vital signs. These are summarized on the following page.

---

* WR 180,409·H_3PO_4 will be hereinafter designated as WR 180,409.

** Pharmacokinetics is the study of bodily absorption, distribution, metabolism and excretion of drugs.

SCHEMATIC STUDY PLAN

Multiple Oral Dose Administration of WR 180,409

Day of Study	0*	1*	2*	3*	4*	5	7	9	11	14	17	21
Day of Week	M	T	W	TH	F	SA	M	W	F	M	TH	M
Physical Exam	X		X		X							X
Interview	X	X	X	X	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X			X		X
Lab Tests[+]	X		X		X		X			X		X
Dose		X---X										
Assay Sample[++]		X	X	X	X	X	X	X	X	X	X	X

* Controlled environment

[+] glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglyceride, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

[++] See "Sampling Schedule for Drug Assay"

WR 180,409 DRUG ADMINISTRATION SCHEDULE

Time and Doses (in mg) of Drug or Placebo

Group	1st dose Day 1 0800	2nd dose Day 1 2000	3rd dose Day 2 0800	Total Dose
A	250	250	250	750
B	250	250	250	750
C	500	250	250	1000
D	500	250	250	1000
E	500	500	250	1250
F	500	500	250	1250
G	500	500	500	1500
H	500	500	500	1500

EXPERIMENT #17 SAMPLING SCHEDULE FOR DRUG ASSAY

Study Day		Spec.#	Time	Cumulative Time	Interval
M	0	--	--	--	--
T	1	1	0755	0	--
		2	1400	6	6
		3	1955	12	6
W	2	4	0200	18	6
		5	0755	24	6
		6	0900	25	1
		7	1000	26	1
		8	1200	28	2
		9	1400	30	2
		10	1600	32	2
		11	2000	36	4
		12	2400	40	4
Th	3	13	0800	48	8
		14	1800	58	10
F	4	15	0600	70	12
		16	1800	82	12
S	5	17	1000	98	16
		18	1200	100	2
M	7	19	1200	148	48
W	9	20	1200	196	48
F	11	21	1200	244	48
M	14	22	1200	316	72
Th	17	23	1200	388	72
M	21	24*	1200	484	96

* Total blood drawn for assays = 144 ml

At your discretion a small teflon catheter can be placed in one of your arm veins 15 minutes before drug administration. This will be used to obtain blood samples during the day you are dosed. In this way, repeated venipuncture may not be necessary on that day.

It is important that the blood be obtained at the times specified. On the days you come in for blood drawing, it is important that if you eat, it should be a light meal, (i.e., cereal, juice, coffee, bread - no milk or fatty foods because fat in the blood makes it more difficult to measure the drug). It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol. Such factors as time of day, meals, alcohol, other drugs and lack of proper sleep may affect the level of drug in your blood on any given day.

You must understand the risks to which you will be exposed in the course of this study. There are the risks, discomforts and inconveniences of residing in a clinical facility for a few days, and having routine measurements and venipunctures performed. In this study, there is a chance that you will develop nausea, vomiting, or abdominal discomfort. It is our expectation that if these symptoms develop, they will be minor and of short duration, and have no lasting effect upon your health. Finally, there is always the possibility of unexpected reactions to the drug. That possibility is minimal, but it should be taken into account.

You should know the policies and procedures followed at BIO-MED, Inc. to minimize the risk to your health and well-being. They are:

1. All procedures are conducted by a physician licensed in Maryland, or by a registered nurse or technician directly under the physician's supervision.

2. Each study to be conducted at BIO-MED, Inc. is reviewed by other agencies for compliance with Department of Health and Welfare Guidelines regarding volunteer participation in medical experiments. Those agencies are:

   a. The Food and Drug Administration. This arm of the Federal Government reviews study proposals for investigational new drugs.

   b. The Regulatory Agencies of the sponsoring bodies. In the case of studies sponsored by the U.S. Army, studies must be approved by the Human Use Committee of the Office of the Surgeon General of the U.S. Army.

c. The Institutional Review Board of BIO-MED, Inc. This board is made up of informed citizen's from the local community. The board reviews each proposed study to see that the risks to the subjects are minimal, that precautions are taken to avoid risk when possible, and that risks are fully disclosed to the subject. The members of this board occasionally visit the clinical facility to inspect the conduct of a study.

3. To further insure your personal protection the following standard procedures are established:

   a. Should you require emergency medical treatment you will be taken to nearby Doctor's Hospital of Prince Georges' County.

   b. As a temporary employee of BIO-MED, Inc., you are protected by Workmen's Compensation for disability resulting by reason of your employment.

   c. On your final day of participation, a complete physical examination and laboratory evaluation will be conducted. You will be informed of any abnormal findings, and should there be any, we will follow you until normalcy, stablization or proper medical disposition is assured.

After members of the investigating team have interviewed you individually and are satisfied that you understand the study and the written informed consent form you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent form, you signify that the study has been explained to you with regard to risks and requirements and that you wish to participate.

It should be clear to you that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to individuals who travel to these areas. Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent and your participation at anytime without prejudice to yourself.

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I,_____, hereby give my informed consent to participate as a study subject in the study entitled "WR 180,409·H_3PO_4: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr._____, and are set forth in the document titled "Explanation for Potential Subjects, Experiment Number 17: WR 180,409·H_3PO_4: Short Term Multiple Doses, Safety, Tolerance and Pharmacokinetics.", which I have initialed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at anytime; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____
Date

_____ _____
Signature Investigator Certification

_____ _____
Address Witness

REAFFIRMATION OF CONSENT:

_____ _____
Date Witness

_____
Signature

BMI-300

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BIO - MED, Inc.

INSTITUTIONAL CERTIFICATION

The professional staff of BIO-MED, Inc. has reviewed the protocol entitled: WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

We recommend to the appropriate reviewing agencies and committees that the protocol be approved for implementation at BIO-MED, Inc.

John A. Johnson, M.D., Principal Investigator

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

Leslie B. Altstatt, M.D., Assoc. Director

Concurrences:

Charles L. Pamplin, III, M.D.,
Major, MC
Contracting Officer Technical Representative (COTR)
DAMD 17-75-C-5036

TITLE: WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.

PURPOSE:

To establish the highest well-tolerated dose of WR 194,965·H_3PO_4 given in three divided doses at intervals of 12 hours.

RATIONALE OF STUDY:

WR 194,965·H_3PO_4 is an antimalarial of the Mannich base class.

In pre-clinical studies, the drug showed considerable promise as an antimalarial drug.

The drug has a CD_{50} of 163 mg/kg (subcutaneously in peanut oil) in the mouse with rodent malaria and a CD_{50} of 16.2 mg/kg (oral) in the Aotus monkey infected with the Smith Strain of falciparum malaria. Given orally to the Smith Strain infected Aotus at 35 mg/kg, it cured 100% of the animals studied in single doses or divided doses given over 3 or 5 days.

Animal toxicity studies show that the drug is well tolerated over the range of 8-35 mg/kg (oral). The curative dose for man has not been established. In a study of safety and tolerance with rising dose levels conducted at BIO-MED, Inc., single doses up to 1250 mg were given orally before intolerance was noted. At that dosing level, one of two subjects developed light-headedness, anorexia, nausea and self-induced emesis.

This drug is a promising candidate for studies of efficacy against induced malaria in man. However, safety and tolerance studies in man show that the top tolerated single oral dose is less than the dose that has cured 100% of Aotus monkeys infected with falciparum malaria. In this study, increasing doses of the drug will be given to subjects in three divided doses over a period of 24 hours, testing the assumption that higher total doses will be tolerated with divided doses than with single doses. A rising dose schedule will be followed with successive groups of subjects until intolerance* occurs or until the desired dose level is established.

* See "Monitoring" for discussion of intolerance.

METHODS:

Subject Acceptability Criteria

Subject acceptability criteria are based upon the precept that the risks of participation should be slight, and comparable for all subjects. Following this guideline, certain subjects are rejected routinely: for example, subjects with organic heart murmurs, splenomegaly or active lesions on chest x-ray. The presence of conditions which do not increase risk for the subject or potentially compromise the validity of the study as illustrated by epidermophytosis, "shotty lymphadenopathy", or scarred tympanic membranes are not routinely cause for rejection. Deviations of laboratory values of 3 standard deviations from the mean are cause for rejection. Deviations between 2 and 3 standard deviations from the mean are generally cause for rejection dependent upon the particular test and associated clinical and laboratory observations. For example, a serum calcium of 11.2 mg/dl would cause rejection, whereas a serum sodium of 153 mEq/L of itself would not. Subjects shall be between 60 and 90 kg in body weight, and within ten percent of ideal body weight.*

When doubt exists concerning acceptance of a subject for any reason, a decision is made following consultation with fellow M.D. investigators and other specialists, as appropriate. In this manner, questionable candidates are given full consideration and the integrity and ethics of the Research Team protected.

Subject Selection:

Approximately 32 male subjects between the ages of 18 and 35 will be recruited from the Washington, D.C. metropolitan area. No subject will participate more than once.

Candidates will be given a complete explanation of the background of the study, and of the procedures to be used in the study, and of all details of the protocol as it involves the individual subjects (see tab 1). They will be interviewed in a group and individually in the presence of an investigator. Each participant will be given the opportunity to ask questions. Following this, at the individual interview, the consent form (see tab 2) will be read and if the investigator believes the subject understands his participation adequately to give informed consent, the subject will be permitted to sign the consent form.

* Adapted from the Table of the Metropolitan Life Insurance Company. After Bray, G.A. Advances in Internal Medicine, Volume 21, page 270 Year Book Publishers 1976.

Following the consent process, candidates for employment will be medically evaluated to obtain the subjects for study. The medical evaluation will include a comprehensive history and physical examination, chest x-ray, electrocardiogram, urinalysis, white blood cell and differential counts, red blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, and total bilirubin.

Qualified candidates will be hired as temporary employees of BIO-MED, Inc.

Study Plan:

The study plan is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Three Divided Doses of WR 194,965·H_3PO_4

Day of Study	0*	1*	2*	3*	4	14
Day of Week	M	T	W	TH	F	M
Physical Exam	X		X**		X	X
Interview	X	X	X	X	X	X
Vital Signs+	X	X	X	X	X	X
Phototoxicity	X			X		
Lab Tests++	X		X		X	X
Dose		X---X				

* Controlled environment

** This examination to be done after 1400 hours.

\+ Temperature, pulse, respiration, blood pressure, every 6 hours.

++glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin,calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will be done as clinically indicated.

The design is a 2 X 2, double-blind, rising dose schedule with four subjects per level. The following table outlines the dosing schedule:

WR 194,965·H_3PO_4 DRUG ADMINISTRATION SCHEDULE

Group	1st dose Day 1 0800 hr	2nd dose Day 1 2000 hr	3rd dose Day 2 0800 hr	Total Dose (mg)
A	500*	250	250	1000
B	500	500	250	1250
C	500	500	500	1500
D	750	500	500	1750
E	750	750	500	2000
F	750	750	750	2250
G	1000	750	750	2500

*Doses (in mg) of Drug or Placebo

There will be an interval of at least one week between dose levels.

On study day 1, the subject will reaffirm his consent in writing prior to his participation. The drug or the placebo will be ingested at the scheduled times in the presence of a staff nurse.

The drug will be supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, in the form of 250 mg tablets labelled "WR 194,965·H_3PO_4". Unused drug and all containers will be returned to the Army Monitor.

SPECIAL PROCEDURES:

The standardized BIO-MED Phototoxicity Test (see tab 4) will be done on each subject on day 0 and day 3. Target sites will be examined 24 hours after exposure and re-examined until resolution if erythema develops. Codes revealing whether the subject received drug or placebo will not be broken until each respective subject has completed his participation in this study.

Monitoring:

Individual work sheets will be maintained on each subject. The following data will be recorded according to the schematic study plan: vital signs every 6 hours (including pulse, temperature, respiration, blood pressure, and weight), clinical and laboratory test results, symptoms and pertinent physical findings.

Signs or symptoms of possible drug intolerance will be carefully noted and thoroughly evaluated. Significant symptoms, physical findings, or laboratory deviations attributed to the drug shall be cause for suspension until BIO-MED and the COTR consult regarding continuation of the study. When ambiguity or uncertainty exists, the clinical director of BIO-MED, Inc. and the COTR may jointly decide to repeat any given dose level before proceeding to the next higher dose level.

On the last study day for each subject, final physical and laboratory evaluations will be done. All abnormal findings will cause follow-up until normalcy, stabilization or proper medical disposition is assured.

Emergencies:

The first priority will be to care for any subject in emergent need from any cause. Appropriate medical consultation will be obtained and hospitalization arranged where indicated. The COTR will be informed of any emergent incident in writing within 24 hours.

RESULTS AND REPORTING:

Individual summaries (see tab 3) will be prepared for each subject. All deviations from normal will be identified. Frequency distributions of inter-subject and intra-subject deviations will be prepared, providing a comparison of drug vs placebo effect at each dose level. BIO-MED, Inc. will prepare a final report when the study is completed.

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BIO - MED, Inc.

EXPERIMENT NUMBER 18

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

PRINCIPAL INVESTIGATOR: JOHN A. JOHNSON, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

INSTITUTIONAL REVIEW BOARD MEMBERS:

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JAMES A. DUKE, Ph.D.
JOSEPH J. D'ERASMO, LL.B.
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ANGELO J. TROISI

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BIO - MED, Inc.

EXPLANATION FOR POTENTIAL SUBJECTS

EXPERIMENT #18

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

Gentlemen:

The study for which you have applied involves taking by mouth the antimalarial drug WR 194,965·H_3PO_4. This is one of many antimalarial drugs being developed by the United States Army Medical Service, the sponsor of this study, in an effort to improve the treatment of drug resistant malaria. WR 194,965 has been approved for clinical testing in humans by both the sponsor and the Food and Drug Administration.

In a previous study of this drug conducted by BIO-MED, Inc., one subject who received a single dose of 1250 mg developed transitory nausea and self-induced vomiting. Several subjects experienced "light-headedness" which was not necessarily unpleasant and was not strictly related to the amount of drug. This symptom also occurred in a few subjects who received placebo (containing no active drug).

In this study a design called two by two, double-blind, rising dose schedule will be used. At each dose level, 4 subjects will be employed. Two will receive drug and 2 will receive placebo (no active drug). Neither the subjects nor the investigators know which subjects are receiving drug until the study for that dose level is completed. When that particular phase of the study is completed, codes will be broken and subjects will be told whether they received the drug or not. The amount of drug given is increased at each succeeding dose level. A new dose level is not started until the results of the seventh day of the previous dose level have been reported and evaluated.

In this study, the drug will be given by mouth in three doses at intervals of 12 hours, and the recipients will be closely monitored for well-being through vital signs (temperature, pulse, respirations, blood pressure), physical examinations and laboratory tests.

The plan of study is summarized in the following schematic:

SCHEMATIC STUDY PLAN

Three Divided Doses of WR 194,965·H_3PO_4

Day of Study	0*	1*	2*	3*	4	14
Day of Week	M	T	W	TH	F	M
Physical Exam	X		X		X	X
Interview	X	X	X	X	X	X
Vital Signs+	X	X	X	X	X	X
Phototoxicity	X			X		
Lab Tests++	X		X		X	X
Dose		X---X				

* Controlled environment

+ Temperature, pulse, respiration, blood pressure every 6 hours.

++glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, CBC (differential and indices), platelets, reticulocyte count, urinalysis. Additional studies will done as clinically indicated.

WR 194,965·H_3PO_4 DRUG ADMINISTRATION SCHEDULE

Group	1st dose Day 1 0800 hr	2nd dose Day 1 2000 hr	3rd dose Day 2 0800 hr	Total Dose (mg)
A	500*	250	250	1000
B	500	500	250	1250
C	500	500	500	1500
D	750	500	500	1750
E	750	750	500	2000
F	750	750	750	2250
G	1000	750	750	2500

*Doses (in mg) of Drug or Placebo

It is important that the blood be obtained at the times specified. It is also important that you avoid taking any other medication during the entire period and avoid the use of alcohol.

You must understand the risks to which you will be exposed in the course of this study. There are the risks, discomforts and inconveniences of residing in a clinical facility for a few days, and having routine measurements and venipunctures performed. Mild "sunburn" could develop at the site where your skin is exposed to a sun lamp in the phototoxicity test. In this study, there is a chance that you will develop nausea, vomiting, or abdominal discomfort. It is our expectation that if these symptoms develop, they will be minor and of short duration, and have no lasting effect upon your health. Finally, there is always the possibility of unexpected reactions to the drug. That possibility is minimal, but it should be taken into account.

You should know the policies and procedures followed at BIO-MED, Inc. to minimize the risk to your health and well-being. They are:

1. All procedures are conducted by a physician licensed in Maryland, or by a registered nurse or technician directly under the physician's supervision.

2. Each study to be conducted at BIO-MED, Inc. is reviewed by other agencies for compliance with Department of Health and Welfare Guidelines regarding volunteer participation in medical experiments. Those agencies are:

   a. The Food and Drug Administration. This arm of the Federal Government reviews study proposals for investigational new drugs.

   b. The Regulatory Agencies of the sponsoring bodies. In the case of studies sponsored by the U.S. Army, studies must be approved by the Human Use Committee of the Office of the Surgeon General of the U.S. Army.

   c. The Institutional Review Board of BIO-MED, Inc. This board is made up of informed citizens from the local community. The board reviews each proposed study to see that the risks to the subjects are minimal, that precautions are taken to avoid risk when possible, and that risks are fully disclosed to the subject. The members of this board occasionally visit the clinical facility to inspect the conduct of a study.

3. To further insure your personal protection the following standard procedures are established:

   a. Emergency medical treatment will be provided at nearby Doctors' Hospital of Prince George's County.

   b. As a temporary employee of BIO-MED, Inc., you are protected by Workmen's Compensation for disability resulting by reason of your employment.

   c. On your final day of participation, a complete physical examination and laboratory evaluation will be conducted. You will be informed of any abnormal findings, and should there be any, we will follow you until normalcy, stablization or proper medical disposition is assured.

After members of the investigating team have interviewed you individually and are satisfied that you understand the study and the written informed consent form, you will be permitted to sign it. No subject may participate without a signed consent. By signing the informed consent form, you signify that the study has been explained to you with regard to risks and requirements and that you wish to participate.

It should be clear to you that your participation in this study is of no therapeutic value to you personally. The benefit, rather, is to others who live in parts of the world where malaria is a serious problem and to individuals who travel to these areas. Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent and your participation at anytime without prejudice to yourself.

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I,_____, hereby give my informed consent to participate as a study subject in the study entitled "WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels."

The implications of my voluntary participation; the nature, duration and purpose; the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr._____, and are set forth in the document titled "EXPLANATION FOR POTENTIAL SUBJECTS, Experiment Number 18: WR 194,965·H_3PO_4: Short Term Safety and Tolerance to Three Divided Doses, Rising Dose Levels.", which I have initialed.

I understand that with all drug administration and clinical investigation there are associated potential discomforts and risks. The discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will attain no direct therapeutic benefits from participation in the study. I also understand that my participation may be as a control subject.

I understand that as a temporary employee of BIO-MED, Inc. that Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at anytime; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____
Date

_____ _____
Signature Investigator Certification

_____ _____
Address Witness

REAFFIRMATION OF CONSENT:

_____ _____
Date Witness

_____
Signature

BMI-300

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 18: WR 194,965·H_3PO_4: SHORT TERM SAFETY AND TOLERANCE TO: THREE DIVIDED DOSES, RISING DOSE LEVELS.

TOTAL DOSE:_____mg DOSING DATES:_____ CODE:_____
DOSE PER Kg:_____mg/kg _____ GROUP:____ AGE:____
HEIGHT:_____cm WEIGHT:_____kg

==========

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1981								
STUDY DAY:	Screen	0*	1*	2*	3*	4	14	
1. Symptoms								
2. Physical Exam								
3. Vital Signs								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								

KEY: X=abnormal (X)=abnormal, unchanged *=controlled environment

LABORATORY ABNORMALITIES SUMMARY:

ABNORMALITIES COMMENT:

CONCLUSION:

BIO - MED, Inc.

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PHOTOTOXICITY PROCEDURE

PURPOSE: To determine immediate or delayed toxic response to U.V. Light.

EQUIPMENT:
1. Blak-Ray B-100A U.V. Lamp with spot bulb.
2. Blak-Ray J-221 Long Wave Ultraviolet Meter with reduction screen.
3. A 12-inch ruler.
4. A Marking Pen.
5. Dark or smoked glasses.
6. An accurate timer.

CALIBRATION:
Calibration will be done prior to studies requiring Photo-toxicity Testing. Target distance in inches will be done at 5, 5 1/2, 6, 7, 8, 9, and 10 inches.

To determine Joules:
uW/cm^2 = B Scale Reading x 500 (To be recorded for each target distance).
$Watts/cm^2 = uW/cm^2 \times 10^{-6}$
Joules = $Watts/cm^2$ x time in seconds

Example:
Target Distance = 5 inches
B Scale Reading = 60

$uW/cm^2 = 60 \times 500$
$uW/cm^2 = 30,000$

$Watts/cm^2 = 30,000 \times 10^{-6}$
$Watts/cm^2 = 0.030000$

Joules = 0.030000 x 300 (5 minutes)
Joules = 9.0

METHODS:

1. Place lamp horizontally on counter approximately 5 1/2 inches from counter lip. Allow 10 minutes lapse after activating lamp. Measure and record intensity in microwatts (uW).

2. Have subject sit with back exposed and touching counter lip. Using ruler adjust lamp distance to proper distance for correct joules from lamp rim to target spot on subject's skin. Circle target spot with marking pen and set timer for 5 minutes for white-skinned subjects and 10 minutes for dark-skinned subjects.

3. Check target stop frequently to be certain subject did not change position. Swing lamp away from subject when timer rings.

4. Use skin surface below tip of right scapula for target #1 and skin surface below tip of left scapula for target #2.

5. Calibration results will be included in study results.

TEST INTERPRETATION:

Targets will be read as specified in protocol, usually 24, 48 and 72 hours.

CAUTION:

Subject and operator must wear protective glasses. Lamp handle remains cool; however, lamp bulb may cause a burn if touched. Instruct subject and personnel accordingly.

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