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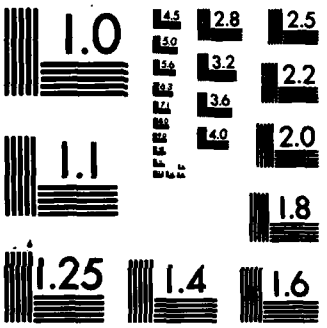

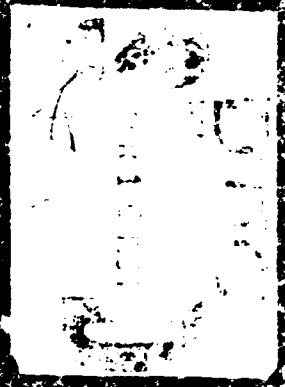

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Army Drug Development Program
Phase I
Clinical Testing

Annual Report

John A. Johnson, M.D.

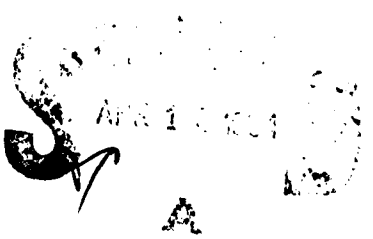
March 1980

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-75-C-5036

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



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Phase I Clinical Testing, Antimalarial, Antileishmanials, Human Subjects, Pharmacokinetics, Comparative Bioavailability, WR 149,024, WR 142,490, WR 180,409 WR 172,435, WR 171,669, WR 229,870, Automatic Data Processing.

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

From February 1979 through January of 1980, research was continued at BIO-MED, Inc. under contract DAMD17-75-C-5036 "Phase I Clinical Studies: The Army Drug Development Program" Programs and Activities under this contract include;

Experiment #11: WR 149,024 Short Term Dosage, Safety and Tolerance (Final Report)

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20. Abstract (continued)

Addendum Number 2 to Experiment 3: Short Term Safety and Tolerance To WR 142,490 HCl Clinical Evaluation of Two Formulations 1000 mg Dose Level

Addendum to Experiment Number 13: WR 172,435·CH_3SO_3H Short Term Dosage, Safety and Tolerance: Effect on the Total and Differential Leukocyte Counts Following a Single Oral Dose

Experiment Number 14: Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration

Experiment Number 15: Continuation of Single Dose Rising Dose Level Studies With Orally Administered WR 171,669: Short Term Safety and Tolerance. Preliminary Pharmacokinetics

Experiment Number 16: WR 229,870 (Sodium Stibogluconate Injection BP): Pharmacokinetics Following A Single Intravenous Dose

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AD_____

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SUMMARY

In this reporting period, the Army Drug Development Program produced an unusual level of demand for the services of BIO-MED, Inc.

Earlier studies of formulations of drugs from the drug development program evoked unanticipated questions of high priority. As a result, while new studies were designed and implemented, some scheduled studies were postponed.

Experiment Number 3 had shown that WR 142,490·HCl (Mefloquine) produced some untoward gastrointestinal side effects. Addendum Number 2 to Experiment Number 3 was designed and implemented to compare the tolerance and bioavailability of two Mefloquine formulations (E-443: INTERx and B-512: Lafayette). This study, a cross-over design with 8 subjects with a six-week wash-out period showed no appreciable difference in tolerance to either 1000 mg oral dose. Samples to permit determination of the differences in pharmacokinetics of the two preparations have been supplied to the Walter Reed Army Institute of Research.

The three-phase study of the Pharmacokinetics of WR 180,409 (Experiment 14) was completed through the second phase without untoward incident. Phase III is held in abeyance until Phase I and II yield the optimal dose levels for the concluding portion of the study.

Data from the study of WR 172,435 (Experiment 13) suggested that administration of the drug may be associated with gastrointestinal symptoms and leukocytosis. An addendum to Experiment Number 13 was designed and implemented to examine those possibilities. In the controlled, double-blind study 6 of 6 subjects receiving 1000 mg of the drug by mouth had gastrointestinal symptoms and significant leukocytosis (a polymorphonuclear response) while subjects receiving placebo were not affected.

In this reporting period, the drug blood levels from the 52 week study of safety and tolerance of Mefloquine (WR 142,490, Experiment 1) became available. It then became desirable to correlate these data with the myriad observations and measurements made of 46 subjects over the course of one year. In six months of sustained effort; under the guidance and supervision of the Division of Experimental Therapeutics of WRAIR, BIO-MED, Inc. wrote programs for the orderly storage and collation of the laboratory data (24, 288 Discreet laboratory observations spread over 52 weeks to be accounted for), and entered the formatted data into the Tektronic 4051 table top computer system. The data are now stored in an accessible format on floppy discs, compatible with the WRAIR and BIO-MED, Inc. system.

This system was the basis for the preparation of "Special Requested Report of Experiment 1 - BIOCHEMICAL ABNORMALITIES".

In this demanding year, it became apparent that two rate-limiting factors precluded an optimal response by BIO-MED, Inc. to increased Army requirements: 1) the inconstant supply of reliable volunteer subjects and 2) the 4-bed capacity of the Clinical Unit provided by the Washington Hospital Center. In December of 1979, BIO-MED, Inc. moved its operation to a new Clinical Facility in College Park, Maryland. This new facility provides a 20 bed capacity in a community densely populated by potential subjects. All previous safeguards for the health and well-being of subjects are available while BIO-MED, Inc. is disassociated from the rapidly escalating costs of hospitalization.

An appropriate Institutional Review Board has been established for the new Clinical Facility, and the response of volunteer subjects has been prompt and satisfactory. Site visits have been conducted by the Army Clinical Monitor, the Contracting Officer of Hqs. USADRDC and by the Human Use Review Office of the Surgeon General. BIO-MED, Inc. has received approval for its request for Special Assurance for the execution of this contract.

FOREWORD

Phase I Clinical Testing of drugs developed by the U.S. Army Research and Development Command were performed at the Washington Hospital Center under terms of contract DAMD 17-75-C-5036. All protocols were processed by the contractor's Institutional Review Board and Human Use Committee prior to submission to the Washington Hospital Center Research Committee.

All executed protocols were processed and approved by the Washington Hospital Center prior to implementation. The Washington Hospital Center is approved for performance of Clinical Research by the Department of Health and Welfare. (DHW Assurance No. GO 180)

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

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OBJECTIVES

General: The general objective of this contract was to continue to provide support to the Army Drug Development Program by conducting 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.

CONCLUSIONS

In this contract year, Phase I Studies at BIO-MED, Inc. continued to provide the bridge from the development of Army Drugs in the laboratory to the use of these drugs in humans. This past year has provided further demonstration that withthorough review of the data regarding a drug to be tested, careful selection of subjects and diligent execution of protocols, Phase I Studies can be conducted productively and safely.

With its new Clinical Facility and an augmented professional Staff, BIO-MED, Inc. can be expected to be even more productive in the coming year.

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FINAL REPORT

EXPERIMENT NUMBER 11

WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

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FINAL REPORT

ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 11

TITLE:	WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE
PRINCIPAL INVESTIGATOR:	RICHARD C. REBA, M.D.
CLINICAL DIRECTOR:	KEVIN G. BARRY, M.D.
CONSULTING AND INSTITUTIONAL REVIEW BOARD MEMBERS:	JAMES M. BACOS, M.D. JAMES A. CURTIN, M.D. STUART H. DANOVITCH, M.D.

Richard C. Reba

RICHARD C. REBA
PRINCIPAL INVESTIGATOR

DATE: August 9, 1979

K. G. Barry

KEVIN G. BARRY, M.D.
CLINICAL DIRECTOR

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WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TABLE OF CONTENTS

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FINAL REPORT

EXPERIMENT NUMBER 11

WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

ABSTRACT

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

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

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

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

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

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FINAL REPORT

EXPERIMENT NUMBER 11

WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

INTRODUCTION:

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

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

This compound is the symmetrical disulfide dimer of WR 2823. WR 2823 has been extensively studied for its alpha adrenergic blocking action which is shared by WR 149,024. WR 149,024, as well as WR 2823, has demonstrated efficacy in preventing morbidity and mortality in hemorrhagic, endotoxic, anaphylactic and traumatic injury shock in animal models. WR 149,024 appears to be about four times as potent as WR 2823 and about four times as toxic as WR 2823 in animal models. As with WR 2823 in all animal systems the nature of the toxicity is minimal, transient, and spontaneously reversible and can also be reversed therapeutically. WR 149,024 offers an advantage over WR 2823 in its greater stability in storage and ease of formulation. On the basis of the demonstrated efficacy in animals models as a lifesaving measure and on the basis of the lack of demonstrable irreversible toxicity, it was deemed proper to extend these studies to man.

The INDs for both WR 2823 and WR 149,024, with Supplements, were available at all processing committee meetings and were available at all times in the Office of the Clinical Director of BIO-MED, Inc.

METHODS AND MATERIALS:

Subject Selection - Acceptability Criteria:

Twenty-five subjects, 21 to 36 years of age, weighing 59-100 kg and within 10% of their ideal body weight, were employed for the study. They were recruited from the Washington, D.C. metropolitan area. Candidates were hired by BIO-MED, Inc. as temporary employees for study purposes.

Candidates for employment were screened to obtain the subjects for 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, and total bilirubin.

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 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 ordinarily cause for rejection. Deviations of laboratory values of 3 standard deviations or more 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 did not cause rejection, whereas a serum calcium of 11.2 mg/dl did cause rejection.

Whenever doubt existed concerning the eligibility of a subject, a decision was made following consultation wit 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.

Qualified candidates were presented with 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 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.

Drug Administration:

Each 53 mg vial of WR 149,024 was reconstituted by adding 5.3 ml sterile saline for injection U.S.P. to the vial. The resulting solution contained 10 mg drug per ml solution at pH 4.8 to 5.8. The appropriate amount of this drug solution was then withdrawn and diluted using sterile saline q.s. to 120 cc.

The infusion of WR 149,024 was discontinued if there was a decrease in either systolic blood pressure of more than 20% or a decrease diastolic blood pressure of more than 10% and at the discretion of the M.D. Investigator for any reason.

Supplies of norepinephrine and angiotensin were available for reversal of severe hypotension as needed.

A physician investigator supervised and remained in the study unit during the administration of the drug.

At each dose level two subjects completed the infusion. WR 149,024 was administered to one subject at a time. An interval of 7 days was required between testing at each dose level. Each subject participated only at one dose level.

Dose Level	Total Dose (mg)	Increment of Increase	Drug Infusion Rate* (mg/min)
1	1		0.0083
2	4	4	0.033
3	8	2	0.066
4	16	2	0.133
5	32	2	0.266
6	64	2	0.533
7	125	1.9	1.042
8	250	2	2.083
9	375	1.5	3.125
10	480	1.3	4.000
11	600	1.3	5.000
12	720	1.2	6.000

*The infusion time was 120 minutes and the volume 120 cc for each subject.

The subjects were housed in a controlled environment for the interval shown in the schematic on page 5. Each study was conducted as follows:

1. Subjects were admitted to the research unit 1 day prior to drug administration; baseline tests were done according to the schematic study plan. On the study day the drug was to be administered, an intravenous catheter was inserted in a forearm vein with initial infusion of U.S.P. Normal Saline at 100 cc/hr until blood pressure and pulse were stable for not less than 15 minutes. The catheter remained in place during and for 2 hours after drug administration infusing U.S.P. Normal Saline at 100 cc/hr.

2. Blood pressure and ECG (lead II) were recorded every 5 minutes for the first 15 minutes, every 10 minutes for the next 30 minutes, then every 15 minutes thereafter during the infusion period.

3. At the completion of drug administration the subject remained at bedrest for 12 hours, with blood pressure and ECG (lead II) monitored as follows:

   Every 15 minutes for the first 2 hours.
   Every 30 minutes for the next 2 hours.
   Every 1 hour for the last 8 hours.

4. Orthostatic tolerance was tested as follows: control measurements of heart rate and blood pressure were made supine, sitting, and 3 minutes after assuming the erect position every 10 minutes for 1 hour prior to commencement of the infusion, or until 3 consecutive measurements of heart rate and blood pressure did not differ by more than 10%.

5. Testing for orthostatic tolerance was performed immediately after drug administration; ECG (lead II) and testing for orthostatic hypotension was repeated at 2, 4, 6, and 12 hours after completion of drug administration.

6. The criteria for intolerance used for this study included a decrease in systolic pressure more than 10 mmHg and any decrease in diastolic pressure 3 minutes after assuming the upright position as compared with the pressure obtained in the supine position.* The abnormal results are presented in Table 3 for subjects intolerant prior to dosing, and Table 4 for subjects intolerant only after dosing.

*Reference: Foley, H.T.: Clinical Observations on the Value of the Orthostatic Tolerance Test in Normal Men. J. Aviation Med. 20: 230, 1949.

7. Schematic Study Plan - Single Dose Administration WR 149,024

Study Day	0*	1*	2*	3	7	14	28
Dose		X					
Physical Exam	X		X		X		X
Interview	X	X	X	X	X	X	X
Complete Vital Signs	X	X	X	X	X	X	X
ECG (Lead II)	X	X	X	X	X		X
Laboratory Tests+	X		X	X	X	X	X

*controlled environment

+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, 2-hour creatinine clearance on day 0, day 2, and day 7. Additional studies were done as clinically indicated.

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

9. The subjects did not use any drugs for 3 days prior to and 1 week following the study. Special emphasis was given regarding systemic and topical vasoactive agents. Smoking also was prohibited for 3 days prior to and 3 days following drug administration.

10. Emergencies: Immediate action was planned to first care for the subject in emergent need, including consultation and hospitalization if warranted and second to notify the Army Clinical Monitor and the Washington Hospital Center authorities immediately by telephone and by written communication within 24 hours.

Laboratory Data:

All laboratory data was recorded daily for each subject. Any deviation from normal was brought to the attention of the investigator.

Recording:

Individual Worksheets were maintained for each subject. The following was recorded on individual work forms: blood pressure, pulse, weight, clinical laboratory results, subjective symptoms, and physical examination. A cumulative master log for the study was also kept which included laboratory data and the results of a nondirected symptomatology interview. This provided for ongoing availability of data at all times to the Research Committee, Washington Hospital Center, and the Army Research and Development Command.

RESULTS:

Twenty-four subjects completed the infusion. In an additional subject (code no. 282), infusion of WR 149,024 was discontinued after 6.9 mg had been administered because of electrocardiographic variation of the p wave configuration. The variation was present in all electrocardiograms recorded prior to dosing and not considered significant nor attributable to drug administration by the cardiology consultant.

Symptoms and Physical Findings:

All symptoms and physical deviations occurring during the study are presented as Table 1, pages 17 through 19. Eleven subjects were asymptomatic during the study. The array of symptoms and signs was similar to that observed in safety and tolerance studies in general with the exception of pruritis and erythema of the skin overlying the infused vein in subject code no. 334 starting 20 minutes after initiation of the infusion of 720 mg WR 149,024. The erythema dissipated within 24 hours but a residual 1 x 1 cm area of induration followed by ecchymoses was observed at the puncture site. One other subject (code no. 292) demonstrated contact sensitivity to the adhesive tape used to secure the intravenous catheter with erythema persisting forapproximately 36 hours.

Neurosensory:

Five subjects had neurosensory symptoms during or following the infusion. One hour and fifteen minutes after the infusion was started subject code no. 274, receiving 1 mg drug, stated "my chest feels tight when I breathe". Examination suggested the symptom was a hyperventilation equivalent and the symptom responded to reassurance dissipating after 15 minutes. Subject code no. 279 complained that he felt as if he were "spinning" 20 minutes after the infusion of 8 mg WR 149,024 was initiated. Neurologic and cardiac examination were normal. The dizziness

gradually diminished but was replaced by a sensation of warmth in the cervicofacial area starting 1 hour and 45 minutes after infusion initiation and lasting for 15 minutes. Twenty-four hours post infusion the patient developed dermatographic patches in the areas used for electrode placement after a warm shower. The subject tested positively for dermatographia.

Subject code no. 280 reported his eyes "felt strained" 50 minutes after starting the infusion of 16 mg drug. Examination was normal and the symptoms lasted for 65 minutes. Twelve hours after the infusion the subject had difficulty "catching" his breath for 2 minutes while showering. Subject code no. 284 complained of dizziness starting 60 hours after the infusion of 32 mg drug. This subject was hyperactive and apparently slept very little from the time of study unit discharge, day 3, to examination, day 7, at which time he appeared fatigued and had trace pretibial edema which was absent on examination 3 days later. The patient was last examined 43 days after study entry at which time examination was normal but the patient complained of recurrent dizziness, sore throat, hoarseness, and general poor health.

Subject code no. 293 reported "my face tingles" 1 hour and 45 minutes after starting the infusion of 480 mg WR 149,024. The symptoms persisted for 10 minutes. Examination was normal. Subject code no. 294 receiving the same dose had transient nausea on standing immediately post infusion and momentary tingling of the back of his head on arising 10 minutes after the infusion was completed.

Finally, subject code no. 334 receiving the maximum dose of 720 mg WR 149,024 complained of perioral numbness and vague thoracic and abdominal sensations starting 45 minutes after initiation of the infusion. A degree of anxiety and hyperventilation symptoms continued during the infusion. Upon standing immediately post-infusion, the subject had a transient episode of nausea and emesis. Standing systolic blood pressure of questionable accuracy taken at the time of nausea and emesis was recorded as 102 mmHg. Orthostatic tolerance tested within 5 minutes of the episode was normal.

Gastrointestinal:

Four subjects had gastrointestinal symptoms or signs. Subject code no. 288 receiving 125 mg WR 149,024 had 3 loose stools between 8 and 12 hours after the initiation of the infusion. Subject code no. 291 had a loose stool 96 hours after the initiation of the infusion of 375 mg drug with a repeat episode 24 hours later. Neither subject had associated symptoms. Subject code no. 294, immediately upon the completion of the

infusion of 480 mg of drug, had nausea upon standing of approximately 2 minutes duration. Subject code no. 334, upon completion of the infusion of 720 mg WR 149,024, experienced an episode of nausea with a single emesis. As noted previously in the Neurosensory section, this subject also had symptoms of hyperventilation during the infusion interval and a blood pressure of questionable accuracy, taken at the time of the emesis, was recorded as 102 mmHg systolic. Orthostatic tolerance performed within 5 minutes was normal.

Miscellaneous:

All other symptoms and signs are tabulated in Table 1, and presented in detail in the Individual Final Summary Reports. They vary from the common cold to nonspecific urethral discharge and are not considered related to the infusion of WR 149,024.

Orthostatic Tolerance Testing:

Orthostatic intolerance test results for all subjects are presented as Table 2, pages 20 through 26. Eighteen subjects had positive results.

Eight subjects demonstrated intolerance prior to dosing (Table 3, pages 27 through 29). Six of these 8 subjects demonstrated intolerance during or within 12 hours after the infusion. Ten additional subjects (Table 4, pages 30 through 32) demonstrated orthostatic intolerance only after infusion of WR 149,024. Orthostatic intolerance was variable and not attributed to drug infusion.

Hematology:

All deviations are presented as Table 5b, pages 33 through 37. Minor deviations were present without a specific pattern related to drug administration or dose level. Deviations in hematocrit, hemoglobin, red blood cell counts and percent eosinophils were most common and are presented as Table 6, pages 38 through 39.

Biochemistry:

All deviations are presented as Table 5b, pages 33 through 37. Deviations were minimal and inconsistent except for occasional subjects displaying persistent minor deviations before and after drug administration.

Repetitive minimal elevation of serum carbon dioxide content was the most frequent deviation present before and after dosing and was present in subject code nos. 274, 276, 277, 278, 279, 281, 285, 286, 287, 288, 290, and 293. Subject code no. 280 had LDH

values ranging from 200 to 253 U/L without other associated abnormality. Similarly for subject code nos. 285 and 334, repetitive elevations of serum alkaline phosphatase and serum cholesterol respectively were reported before and after dosing.

Subject code no. 285 presented additional elevation of LDH 28 days and minimal elevations of serum bilirubin 16 and 28 days after administration of 64 mg WR 149,024 not considered drug related. This subject failed to report for further follow-up.

Three subjects had minimal to mild elevation of SGPT after drug administration presented in Table 7. The pattern does not suggest drug effect.

Serum bilirubin was similarly minimally elevated after drug administration in 4 subjects as presented in Table 7. In 2 subjects it was limited to an isolated determination 2 days (code no. 287) and 6 days (code no. 278) after dosing. Subject code nos. 279 and 285 had 2 successive mild elevations of serum bilirubin starting 6 and 16 days respectively after drug administration.

DISCUSSION:

WR 149,024 was well tolerated under conditions of this study. The incidence and character of signs and symptoms observed during the 28 day study interval were similar to those commonly present in control subjects participating in safety and tolerance testing with one exception. Subject code no. 334 developed temporary erythema of the skin overlying the infused vein after receiving 120 mg WR 149,024 during 20 minutes. The infusion was continued and a total dose of 720 mg drug administered as specified. This drug administration rate of 6 mg/min was the highest used. Although one other subject had no reaction to the same infusion rate, it is possible the local iritation was a rate related phenomenon. This subject also had symptoms compatible with hyperventilation starting 45 minutes after drug infusion initiation culminating in nausea and emesis on standing immediately after infusion completion. Orthostatic tolerance testing was normal. The hyperventilation symptoms are considered possibly but not probably drug induced.

This subject (code no. 334) is the only subject with probably drug related reaction of local irritation at the infusion site. The perioral numbness, anxiety, and vague thoraco-abdominal discomfort culminating in transient orthostatic nausea and emesis at the end of the infusion occurring in this subject and transient orthostatic nausea occurring in subject code no. 294 receiving 480 mg drug may have been systemic drug effect.

Results of orthostatic tolerance testing as performed were too variable before as well as after drug administration to assign any value in detecting drug effect.

Similarly creatinine clearance values reported were beyond credibility. Serum creatinine values appeared valid and showed no variation suggestive of drug effect.

Hematologic deviations in hematocrit, hemoglobin, red blood cell counts, and percent eosinophils occurred with a frequency warranting separate tabulation. Inspection of the tables demonstrated that the deviations were minor or inconsistent and of random distribution relative to time and dose level.

Biochemical deviations attributable to drug administration were not observed. Separate tabulations were made for SGPT and total bilirubin deviations. The time of occurrence and magnitude of deviations do not suggest a drug relationship.

CONCLUSIONS:

Under conditions of this study no pharmacologic effect of WR 149,024 was detected.

The drug was well tolerated and without significant adverse local reaction except for temporary irritation of the skin overlying the infused vein in one of two subjects at the highest dose level of 720 mg WR 149,024 administered at a rate of 6 mg/minute. The irritation was mild, temporary, and without sequelae.

In the same subject symptoms of hyperventilation during drug infusion culminating in transient orthostatic nausea and emesis immediately upon completion of the infusion occurred. One other subject receiving 480 mg WR 149,024 had transient nausea without emesis upon standing immediately after infusion completion. The foregoing are considered possible but not probable systemic effects of the drug infusion.

BIO - MED, Inc.

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EXPLANATION FOR PROSPECTIVE SUBJECTS
ANTI-SHOCK DRUG PROJECT
EXPERIMENT NUMBER 11
WR 149,024 Short-Term Dosage
Safety and Tolerance

GENTLEMEN:

The study for which you have applied as a temporary employee involves receiving the anti-shock compound WR 149,024 intravenously. The drug has been approved by the Food and Drug Administration for investigational studies.

WR 149,024 is being developed for the treatment of circulatory failure resulting from severe blood loss (hemorrhage), trauma, and certain bacterial infections. In various animal test systems this drug was shown to be effective in lessening circulatory failure and death rate due to these causes. There is evidence, in animals, that this compound may be effective in the above clinical applications where current modes of medical therapy have proved less than satisfactory. In all animal systems the nature of the toxicity is minimal, transient and spontaneously reversible and can also be reversed therapeutically.

Previous studies with a similar drug, WR 2823, have shown that symptoms (intolerance) may occur in certain individuals at various dose levels. The symptoms observed included increased heart rate and a fall in standing blood pressure sometimes associated with dizziness, headache, nausea, or vomiting. These effects were all short-lived and by 15-30 minutes post infusion they had dissipated. A transient inability to urinate was also seen in a few patients.

The clinical laboratory tests did not reveal any instances of overt toxicity relative to the organ systems monitored. However, there were small but statistically significant dose related changes in the serum calcium, phosphorus and creatinine seen on the second day after drug administration. These returned to pre-drug levels by the fourth day after drug administration. None of the subjects had symptoms referable to these changes but this is not surprising since the changes were mostly within the range of physiologic normality.

The purpose of this study is twofold: (1) To determine the maximum tolerated single dose of WR 149,024; and (2) To evaluate the effects of WR 149,024 on blood pressure and heart rate when administered intravenously.

The study method is a sequential rising single dose design. We will begin by giving WR 149,024 to a subject at a very low dose level. Two subjects will be studied at each dose level. The drug will be administered to one subject at a time. An interval of 7 days will be required between testing at each dose level. Each subject will be tested only once. We will proceed to the next higher dose level only after the data obtained at the previous lower level is analyzed and it is considered safe to proceed.

Specifically the study will be conducted as follows:

You will be admitted to the Hospital Research Unit on the day before you are to receive the drug. At this time certain baseline clinical and laboratory information will be obtained in a manner similar to that which was used to obtain the data in your preliminary screen for employment. The information to be collected throughout the study can be seen on the following schematic:

Schematic Study Plan - Single Dose Administration
WR 149,024

Study Day	0*	1*	2*	3	7	14	28
Dose		X					
Physical Exam	X		X		X		X
Interview	X	X	X	X	X	X	X
Complete Vital Signs	X	X	X	X	X	X	X
ECG (Lead II)	X	X	X	X	X		X
Laboratory Tests+	X		X	X	X	X	X

*Controlled environment

+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, 4-hour creatinine clearance on day 0, day 2, and day 7. Additional studies will be done as clinically indicated.

On the days indicated by *, the participants in the study will remain in a controlled environment. The entire group will remain together with a member of the research unit staff and will function according to their directions. Facilities provided while participating in the study include room and board with a study-lounge area.

To administer the drug solution a small teflon catheter will be inserted into a large vein in your forearm. The drug will then be administered to you as an infusion into your vein over a period of 120 minutes (2 hours). The catheter will remain in place following completion of drug administration for 2 hours. This is the standard method of administering intravenous fluids and medications in most hospitals. It is a safe and tried procedure an involves negligible risks including infection or inflammation of the vein wall. These complications are very rare and treatable. The infusion should not be painful. Starting the infusion will be associated with the same amount of discomfort as a venipuncture.

Both during and after receiving the test compound you will remain at bedrest for 12 hours while your blood pressure, electrocardiogram and pulse rate are checked. A doctor will be with you throughout the period of drug administration. You will remain under close observation in the hospital for 48 hours after the end of drug administration. Follow-up visits to the Research Unit clinic will be necessary on the seventh, fourteenth, and twenty-eighth day after drug administration. On these days we will proceed according to the schematic study plan. Should any questions arise at other times, a member of the research team will be available for information or aid.

You have already had many of the examinations listed on the schematic as part of your qualification examination. The laboratory tests to be performed require a urine sample and venipuncture to obtain blood samples. On study days 0, 2, and 7 a 4-hour urine collection for creatinine clearance is required. The procedure for collecting the 4-hour specimens will be as follows: At 6:01 AM empty your bladder completely and discard the specimen. Collect all urine voided after this for the next 4 hours and save in a collection container provided by the research unit. It is very important that you save all urine voided during the 4-hour period.

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 secured.

It is mandatory that you do not use drugs of any description for 3 days prior to admission to the unit through 1 week following the study. This applies not only to drugs you might take by mouth but to others such as ointments and particularly nose drops. Smoking will also be prohibited for 3 days prior

to and 3 days following drug administration. If you or your doctor believe you need medicine for any purpose be sure to call to obtain our approval.

Since WR 149,024 has never been given to humans before, there can be no guarantee that unexpected reactions will not occur and the drug might make you sick. However, past experience with WR 2823 and preclinical studies with WR 149,024 is that sickness due to intolerance is minor and of short duration. It is understood that, due to the nature of the drug being tested, you will receive no therapeutic benefit from your participation in this study.

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 and to answer any questions you might have. A member may also visit you at the hospital research unit. After members of the investigating team and Human Use Committee, at an individual interview with you, are satisfied 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 that you wish to participate.

It should be clear that your participation in this study is of no therapeutic value to you personally. 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.

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 149,024 Short Term Dosage, Safety and Tolerance".

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: ANTI-SHOCK DRUG PROJECT, Experiment No. 11, WR 149,024 Short-Term Dosage, Safety and Tolerance", 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	

EXPERIMENT NO. 11: WR 149,024
SHORT TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 1: Symptoms and Physical Findings - All Subjects

DOSE LEVEL	TOTAL DOSE	CODE NUMBER	Neurosensory		Nausea		Loose Stool		Headache		Other‡	
			Onset*	Duration†	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration
1	1 mg	274	Tightness bilaterally in chest wall 1.15††	0.15								
		275					No Symptoms					
2	4 mg	276					No Symptoms					
		277					No Symptoms					
3	8 mg	278					No Symptoms					
		279	"Bed swims" and "spinning" sensation 0.20	1.40							Opthalmic pruritis macular erythema-upper torso after shower ~24.0	~0.20
			Warm sensation in cervicofacial area 1.45	0.15							Areas of erythema 2-3cm with central white papulation of ±0.5cm after shower ~26.5	~0.20
4	16 mg	280	Eye strain 0.50	1.05							Difficulty "catching" breath during shower ~12.0	~0.02
		281	"Bizzare dreams" ~17.0	~0.5							Fatigue and hunger 2° to travel ~600.0	~48.0

* = Onset after dosing
† = Duration after onset
†† = hours . minutes
‡ = See Individual Subject Final Summary for details
~ = approximately

TABLE 1: Symptoms and Physical Findings - All Subjects (cont.)

DOSE LEVEL	TOTAL DOSE	CODE NUMBER	Neurosensory		Nausea		Loose Stool		Headache		Other‡	
			Onset*	Duration+	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration
5ex	6.916 mg	282							Retro-orbital and temporal -18.0	~54.0	Electrocardiographic variation of p-wave configuration -24.0	chronic
5	32 mg	283									Upper respiratory congestion 8.0	~3.0
	32 mg	284	Dizziness 80.0	~0.05							Trace pretibial and ankle edema ~92.0	~76.0
											Hoarseness and scratchy throat ~648.0	~360.0
6	64 mg	285					No Symptoms					
		286					No Symptoms					
7	125 mg	287					No Symptoms					
		288					3 loose stools 8.0	~4.0	~96.0	~3.0		
8	250 mg	289					No Symptoms					
		290					No Symptoms					
9	375 mg	291					2 loose stools 96.0	~24.0				

* = Onset after dosing
+ = Duration after onset
++= hours . minutes
‡ = See Individual Subject Final Summary for details
~ = approximately

TABLE 1: Symptoms and Physical Findings - All Subjects (cont.)

DOSE LEVEL	TOTAL DOSE	CODE NUMBER	Neurosensory		Nausea		Loose Stool		Headache		Other‡	
			Onset*	Duration+	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration
9	375 mg	292									"cold feet" -1.0	~1.10
											Mild erythema due to adhesive tape at I.V. site 24.0	~48.0
10	480 mg	293	"tingling" of face 1.45	0.10							mucoid urethral discharge 48.0	~24.0
		294	"tingling" at back of head 2.10	<0.01	2.0	<0.02						
11	600 mg	295					No Symptoms					
		296									coryza ~312.0	~48.0
12	720 mg	334	Perioral numbness & indefinable thoracic and abdominal sensations 0.45	~1.15	Nausea with emesis 2.0	<0.10					Mild erythema with pruritis over infusion vein 0.20	~24.0
											Area of ecchymosis at I.V. site 144.0	unknown
		335					No Symptoms					

* = Onset after dosing
+ = Duration after onset
++= hours . minutes
‡ = See Inditivual Subject Final Summary for details
~ = approximately

EXPERIMENT NO. 11: WR 149,024
SHORT TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 2: Orthostatic Tolerance:
Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
274	1 mg	baseline #1	120/74	76	128/78	84
		baseline #2	124/72	80	114/72	82
		baseline #3	130/76	86	118/78*	88
		immediate	114/74	62	122/74	72
		2 hrs p.i.+	122/72	78	124/76	78
		4 hrs p.i.	112/68	70	108/64*	80
		6 hrs p.i.	120/68	68	112/66*	84
		12 hrs p.i.	122/72	70	118/76	80
275	1 mg	baseline #1	122/72	60	120/82	64
		baseline #2	128/72	60	114/82*	66
		baseline #3	116/72	64	120/72	64
		immediate	118/72	56	108/72	68
		2 hrs p.i.	124/80	56	126/78*	64
		4 hrs p.i.	136/82	62	138/88	66
		6 hrs p.i.	126/78	66	124/80	64
		12 hrs p.i.	122/82	70	126/82	72
276	4 mg	baseline #1	108/64	48	120/94	84
		baseline #2	118/70	58	124/94	78
		baseline #3	118/74	58	126/78	76
		immediate	124/68	44	108/78*	60
		2 hrs p.i.	114/58	48	114/76	60
		4 hrs p.i.	106/64	50	128/94	70
		6 hrs p.i.	114/62	52	120/88	70
		12 hrs p.i.	110/58	48	108/74	76

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance: Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
277	4 mg	baseline #1	106/60	60	124/80	68
		baseline #2	120/66	60	126/70	64
		baseline #3	128/64	58	130/74	74
		immediate	118/78	56	104/70*	68
		15 min p.i.+	116/68	52	108/72	62
		30 min p.i.	112/78	52	118/78	68
		60 min p.i.	120/78	52	118/66	68
		2 hrs p.i.	118/64	60	130/84	72
		4 hrs p.i.	124/66	56	120/82	76
		6 hrs p.i.	118/64	56	118/72	72
		12 hrs p.i.	124/76	52	114/84	64
278	8 mg	baseline #1	114/62	52	122/78	70
		baseline #2	116/62	56	126/80	72
		baseline #3	112/60	58	128/78	72
		immediate	124/76	50	126/74*	72
		2 hrs p.i.	134/70	64	136/82	78
		4 hrs p.i	132/80	60	136/92	64
		6 hrs p.i.	122/72	50	126/84	62
		12 hrs p.i.	134/70	58	128/78	64
279	8 mg	baseline #1	128/66	68	132/88	82
		baseline #2	130/76	68	140/88	80
		baseline #3	130/76	74	138/90	84
		immediate	116/62	64	132/94	82
		2 hrs p.i.	116/66	60	132/88	88
		4 hrs p.i.	114/62	64	122/84	76
		6 hrs p.i.	116/68	64	128/84	84
		12 hrs p.i.	120/80	64	130/88	68

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance: Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
280	16 mg	baseline #1	120/68	64	128/80	70
		baseline #2	122/70	60	128/86	68
		baseline #3	130/66	64	132/88	66
		immediate	150/92	62	114/72*	78
		15 min p.i.+	118/60	60	128/88	72
		2 hrs p.i.	128/72	64	142/88	78
		4 hrs p.i.	124/72	62	102/70*	80
		4 hr 5min p.i.	118/60	-	122/80	-
		6 hrs p.i.	122/66	60	122/82	72
		12 hrs p.i.	136/56	60	122/72*	68
281	16 mg	baseline #1	110/74	52	122/80	66
		baseline #2	112/74	54	128/86	74
		baseline #3	114/62	60	122/80	80
		immediate	114/64	60	118/82	82
		2 hrs p.i.	124/60	56	120/80	76
		4 hrs p.i.	114/68	50	118/78	86
		6 hrs p.i.	126/72	56	128/76	82
		12 hrs p.i.	122/80	50	92/78*	60
282	32 mg	baseline #1	110/60	72	112/80	86
		baseline #2	110/60	76	112/72	84
		baseline #3	102/60	66	106/72	88
		immediate	108/62	64	110/62	80
		2 hrs p.i.	102/60	68	110/72	76
		4 hrs p.i.	106/60	60	114/74	80
		6 hrs p.i.	108/72	60	120/78	78
		12 hrs p.i.	104/60	60	108/84	68

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance: Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
283	32 mg	baseline #1	128/92	80	118/88*	82
		baseline #2	122/90	72	128/98	88
		baseline #3	128/90	76	122/96	96
		immediate	122/84	68	122/82*	76
		2 hrs p.i.+	126/90	78	128/86*	88
		4 hrs p.i.	130/72	72	132/92	78
		6 hrs p.i.	124/84	72	132/90	76
		12 hrs p.i.	118/84	72	104/92*	84
284	32 mg	baseline #1	124/74	56	128/96	68
		baseline #2	124/82	64	124/94	72
		baseline #3	150/90	60	120/80*	76
		immediate	132/84	64	138/80*	76
		2 hrs p.i.	142/92	64	132/92	80
		4 hrs p.i.	134/78	64	142/94	76
		6 hrs p.i.	130/78	60	132/94	76
		12 hrs p.i.	138/84	72	136/98	74
285	64 mg	baseline #1	110/70	48	118/72	52
		baseline #2	112/76	52	108/74*	52
		baseline #3	110/70	50	114/72	56
		immediate	106/66	56	116/78	62
		2 hrs p.i.	112/66	52	112/8C	70
		4 hrs p.i.	108/70	52	110/78	64
		7 hrs p.i.	114/78	60	120/80	66
		12 hrs p.i.	118/68	52	118/84	60
286	64 mg	baseline #1	114/64	48	118/76	64
		baseline #2	110/68	50	110/78	60
		baseline #3	116/72	48	112/82	56
		immediate	112/80	44	118/80	62
		2 hrs p.i.	108/78	48	110/84	54
		4 hrs p.i.	112/80	44	120/84	56
		6 hrs p.i.	110/72	48	118/90	68
		12 hrs p.i.	98/70	44	108/86	64

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance: Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
287	125 mg	baseline #1	106/62	60	90/60*	72
		baseline #2	102/62	58	108/78	72
		baseline #3	110/64	60	110/78	78
		baseline #4	106/60	58	110/70	80
		immediate	102/62	52	114/80	68
		2 hrs p.i.+	104/62	68	128/72	78
		4 hrs p.i.	116/72	60	114/78	72
		6 hrs p.i.	116/74	56	116/78	78
		12 hrs p.i.	120/72	58	118/80	78
288	125 mg	baseline #1	128/72	74	124/72	72
		baseline #2	120/72	68	122/80	70
		baseline #3	120/68	70	120/80	74
		immediate	122/68	68	118/68	72
		2 hrs p.i.	128/72	68	126/78	76
		4 hrs p.i.	128/78	76	128/80	78
		6 hrs p.i.	120/68	70	126/80	76
		12 hrs p.i.	138/70	78	124/80*	80
289	250 mg	baseline #1	132/70	76	120/68*	88
		baseline #2	118/58	64	114/70	78
		baseline #3	120/68	68	116/72	78
		immediate	112/70	64	112/72	84
		2 hrs p.i.	118/70	68	122/78	80
		4 hrs p.i.	132/70	64	112/68*	92
		6 hrs p.i.	138/70	58	122/78*	70
		12 hrs p.i.	118/68	52	108/82	76
290	250 mg	baseline #1	118/66	52	120/74	62
		baseline #2	118/68	52	120/70	76
		baseline #3	120/62	58	118/72	78
		immediate	118/74	64	112/74	88
		2 hrs p.i.	116/76	56	112/82	84
		4 hrs p.i.	118/62	56	112/84	78
		6 hrs p.i.	122/80	52	122/88	84
		12 hrs p.i.	126/68	64	124/78	90

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance:
Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
291	375 mg	baseline #1	122/68	74	120/80	90
		baseline #2	130/68	80	136/82	88
		baseline #3	120/58	72	122/80	88
		immediate	130/80	78	138/94	90
		2 hrs p.i.+	128/78	88	126/92	84
		4 hrs p.i.	132/72	78	154/92	108
		6 hrs p.i.	142/78	90	140/92	94
		12 hrs p.i.	122/80	78	128/82	82
292	375 mg	baseline #1	116/60	64	112/70	72
		baseline #2	112/62	60	118/80	80
		baseline #3	108/62	64	114/72	78
		immediate	110/60	60	118/88	64
		2 hrs p.i.	112/62	60	108/70	80
		4 hrs p.i.	108/62	62	112/84	68
		6 hrs p.i.	110/60	60	96/68*	76
		12 hrs p.i.	110/64	56	104/70	66
293	480 mg	baseline #1	120/72	84	134/94	84
		baseline #2	120/76	84	142/94	84
		baseline #3	124/76	84	128/86	84
		immediate	118/76	76	122/86	88
		2 hrs p.i.	120/78	72	130/92	84
		4 hrs p.i.	110/62	68	120/68	74
		6 hrs p.i.	120/68	66	120/84	86
		12 hrs p.i.	120/70	64	124/80	84
294	480 mg	baseline #1	122/54	64	112/68	76
		baseline #2	120/58	60	126/58	74
		baseline #3	120/58	64	124/74	76
		immediate	112/62	68	128/72	78
		2 hrs p.i.	118/64	68	120/68	62
		4 hrs p.i.	124/76	80	120/60*	62
		6 hrs p.i.	112/74	72	118/66*	84
		12 hrs p.i.	124/70	72	112/68*	72

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

TABLE 2: Orthostatic Tolerance:
Test Results - All Subjects

CODE NUMBER	DOSE LEVEL	TIME	SUPINE		UPRIGHT (after 3 min)	
			B/P	Pulse	B/P	Pulse
295	600 mg	baseline #1	128/72	84	126/76	84
		baseline #2	126/76	84	136/84	92
		baseline #3	122/72	84	126/86	84
		immediate	124/84	78	136/96	82
		2 hrs p.i.+	124/84	84	136/74*	92
		4 hrs p.i.	130/82	84	132/102	88
		6 hrs p.i.	132/86	80	138/100	88
		12 hrs p.i.	122/78	78	138/100	88
296	600 mg	baseline #1	120/80	44	118/78*	52
		baseline #2	122/70	48	124/64*	46
		baseline #3	124/80	48	124/80	52
		immediate	132/80	62	124/86	60
		2 hrs p.i.	136/60	60	138/80	60
		4 hrs p.i.	136/58	56	130/70	64
		12 hrs p.i.	138/68	58	138/76	60
334	720 mg	baseline #1	112/76	64	112/84	80
		baseline #2	106/66	64	118/78	78
		baseline #3	118/76	64	124/88	84
		immediate	118/76	72	112/88	78
		2 hrs p.i.	114/70	68	110/82	78
		4 hrs p.i.	110/68	66	122/86	84
		6 hrs p.i.	116/66	68	128/84	86
		12 hrs p.i.	108/70	66	108/88	76
335	720 mg	baseline #1	122/74	80	130/92	78
		baseline #2	120/82	72	128/90	80
		baseline #3	120/76	72	128/90	84
		immediate	122/74	72	122/72*	94
		10 min p.i.	122/74	84	114/68*	96
		2 hrs p.i.	124/78	76	136/84	84
		4 hrs p.i.	118/70	84	120/82	84
		6 hrs p.i.	124/82	92	140/90	92
		12 hrs p.i.	120/80	78	130/88	92

* = orthostatic intolerance, underlined value abnormal
+ = post infusion completion

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SHORT TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 3: Orthostatic Tolerance: Abnormals Prior to Dosing

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
274	1 mg	baseline #1	120/74	128/78
		baseline #2	124/72	114/72
		baseline #3	130/76	118/78*
		immediate	114/74	122/74
		2 hrs post infusion	122/72	124/76
		4 hrs post infusion	112/68	108/64*
		6 hrs post infusion	120/68	112/66*
		12 hrs post infusion	122/72	118/76
275	1 mg	baseline #1	122/72	120/82
		baseline #2	128/72	114/82*
		baseline #3	116/72	120/72
		immediate	118/72	108/72
		2 hrs post infusion	124/80	126/78*
		4 hrs post infusion	136/82	138/88
		6 hrs post infusion	126/78	124/80
		12 hrs post infusion	122/82	126/82
283	32 mg	baseline #1	128/92	118/88*
		baseline #2	122/90	128/98
		baseline #3	128/90	122/96
		immediate	122/84	122/82*
		2 hrs post infusion	126/90	128/86*
		4 hrs post infusion	130/72	132/92
		6 hrs post infusion	124/84	132/90
		12 hrs post infusion	118/84	104/92*

* = orthostatic intolerance, underlined value abnormal

TABLE 3: Orthostatic Tolerance:
Abnormals Prior to Dosing (cont.)

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
284	32 mg	baseline #1	124/74	128/96
		baseline #2	124/82	124/94
		baseline #3	150/90	120/80*
		baseline #4	134/86	138/88
		immediate	132/84	138/80*
		2 hrs post infusion	142/92	132/92
		4 hrs post infusion	134/78	132/92
		6 hrs post infusion	130/78	132/94
		12 hrs post infusion	138/34	136/98
285	64 mg	baseline #1	110/70	118/72
		baseline #2	112/76	108/74*
		baseline #3	110/70	114/72
		immediate	106/66	116/78
		2 hrs post infusion	112/66	112/80
		4 hrs post infusion	108/70	110/78
		6 hrs post infusion	114/78	120/80
		12 hrs post infusion	118/68	118/84
287	125 mg	baseline #1	106/62	90/60*
		baseline #2	102/62	108/78
		baseline #3	110/64	110/78
		baseline #4	106/60	110/70
		immediate	102/62	114/80
		2 hrs post infusion	104/62	128/72
		4 hrs post infusion	116/72	114/78
		6 hrs post infusion	116/74	114/78
		12 hrs post infusion	120/72	118/80
289	250 mg	baseline #1	132/70	120/68*
		baseline #2	118/58	114/70
		baseline #3	120/68	116/72
		immediate	112/70	112/72
		2 hrs post infusion	118/70	122/78
		4 hrs post infusion	132/70	112/68*
		6 hrs post infusion	138/70	122/78*
		12 hrs post infusion	118/68	108/82

* = orthostatic intolerance, underlined value abnormal

TABLE 3: Orthostatic Tolerance:
Abnormals Prior to Dosing (cont.)

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
296	600 mg	baseline #1	120/80	118/76*
		baseline #2	122/70	124/64*
		baseline #3	124/80	124/80
		immediate	132/80	124/86
		2 hrs post infusion	136/60	138/80
		4 hrs post infusion	136/58	130/70
		12 hrs post infusion	138/68	138/76

* = orthostatic intolerance, underlined value abnormal

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TABLE 4: Orthostatic Tolerance: Abnormals Post Dosing

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
276	4 mg	baseline #1	108/64	120/94
		baseline #2	118/70	124/94
		baseline #3	118/74	126/78
		immediate	124/68	108/78*
		2 hrs post infusion	114/58	114/76
		4 hrs post infusion	106/64	128/94
		6 hrs post infusion	114/62	120/88
		12 hrs post infusion	110/58	108/74
277	4 mg	baseline #1	106/60	124/80
		baseline #2	120/66	126/70
		baseline #3	128/64	130/74
		immediate	118/78	104/70*
		15 min post infusion	116/68	108/72*
		30 min post infusion	112/78	118/78
		2 hrs post infusion	118/64	130/84
		4 hrs post infusion	124/66	120/82
		6 hrs post infusion	118/64	118/72
		12 hrs post infusion	124/76	114/84
278	8 mg	baseline #1	114/62	122/78
		baseline #2	116/62	126/80
		baseline #3	112/60	128/78
		immediate	124/76	126/74*
		2 hrs post infusion	134/70	136/82
		4 hrs post infusion	132/80	136/92
		6 hrs post infusion	122/72	126/84
		12 hrs post infusion	134/70	128/78

* = orthostatic intolerance, underlined value abnormal

TABLE 4: Orthostatic Tolerance: Abnormals Post Dosing (cont.)

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
280	16 mg	baseline #1	120/68	128/80
		baseline #2	122/70	128/86
		baseline #3	130/66	132/88
		immediate	150/92	114/72*
		15 min post infusion	118/60	128/88
		2 hrs post infusion	128/72	142/88
		4 hrs post infusion	124/72	102/70*
		4 hr 5 min post inf.	118/60	122/88
		6 hrs post infusion	122/66	122/82
		12 hrs post infusion	136/56	122/74*
281	16 mg	baseline #1	110/74	122/80
		baseline #2	112/74	128/86
		baseline #3	114/62	122/80
		immediate	114/64	118/82
		2 hrs post infusion	124/60	120/80
		4 hrs post infusion	114/68	118/78
		6 hrs post infusion	126/72	128/76
		12 hrs post infusion	122/80	92/78*
288	125 mg	baseline #1	128/72	124/72
		baseline #2	120/72	122/80
		baseline #3	120/68	120/80
		immediate	122/68	118/68
		2 hrs post infusion	128/72	126/78
		4 hrs post infusion	128/78	128/80
		6 hrs post infusion	120/68	126/80
		12 hrs post infusion	138/70	124/80*
292	375 mg	baseline #1	116/60	112/70
		baseline #2	112/62	118/80
		baseline #3	108/62	114/72
		immediate	110/60	118/88
		2 hrs post infusion	112/62	108/70
		4 hrs post infusion	108/62	112/84
		6 hrs post infusion	110/60	96/68*
		12 hrs post infusion	110/64	104/70

* = orthostatic intolerance, underlined value abnormal

TABLE 4: Orthostatic Tolerance: Abnormals Post Dosing (cont.)

CODE NUMBER	DOSE LEVEL	TIME	SUPINE	UPRIGHT (after 3 min)
294	480 mg	baseline #1	122/54	112/68
		baseline #2	120/58	126/58
		baseline #3	120/58	124/74
		immediate	112/62	128/72
		2 hrs post infusion	118/64	120/68
		4 hrs post infusion	124/76	120/60*
		6 hrs post infusion	112/74	118/66*
		12 hrs post infusion	124/70	112/68*
295	600 mg	baseline #1	128/72	126/76
		baseline #2	126/76	136/84
		baseline #3	122/72	126/86
		immediate	124/84	136/96
		2 hrs post infusion	124/84	136/74*
		4 hrs post infusion	130/82	132/102
		6 hrs post infusion	132/86	136/100
		12 hrs post infusion	122/78	138/100
335	720 mg	baseline #1	122/74	130/92
		baseline #2	120/82	118/90
		baseline #3	120/76	128/90
		immediate	122/74	122/72*
		10 min post infusion	122/74	114/68*
		2 hrs post infusion	124/78	136/84
		4 hrs post infusion	118/70	120/82
		6 hrs post infusion	124/82	140/90
		12 hrs post infusion	120/80	130/88

* = orthostatic intolerance, underlined value abnormal

TABLE 5a: LABORATORY VALUES, NORMAL RANGE
April - June 1975
AMDP Subjects
Age: 21-45 Sex: Male
Laboratory: National Health Laboratories

	n	$\bar{x}$	S.D.	± 2 S.D.	N.H.L. Normal Rang
Glucose (mg/dl)	142	90	12	66-114	65-110
BUN (mg/dl)	126	15	3.1	9-21	10-25
Creatinine (mg/dl)	129	1.1	0.16	0.8-1.4	0.7-1.4
Sodium (mEq/L)	137	144	3.5	137-151	135-145
Potassium (mEq/L)	136	4.4	0.41	3.6-5.2	3.5-5.0
Chloride (mEq/L)	133	104	3.0	98-110	95-105
Carbon Dioxide (mEq/L)	125	27	1.9	23-31	24-32
Uric Acid (mg/dl)	127	6.0	1.0	4-8	2.5-8.0
T. Protein (g/dl)	131	7.2	0.41	6.4-8.0	6.0-8.0
Albumin (g/dl)	132	4.6	0.25	4.1-5.1	3.5-5.0
Globulin (g/dl)	133	2.6	0.42	1.8-3.4	2.5-3.2
Calcium (mg/dl)	113	10	0.44	9.0-10.9	8.5-11.0
Phosphate (mg/dl)	126	3.5	0.50	2.5-4.5	2.5-4.5
Cholesterol (mg/dl)	127	176	33	110-242	150-300
Triglyceride (mg/dl)	131	111	58	*-5-207	30-200
Alka. Phos. (U/L)	127	60	17	26-94	30-115
SGOT (U/L)	128	23	12	*-1-47	7-40
SGPT (U/L)	128	17	15	*-13-47	7-40
LDH (U/L)	128	153	40	73-233	100-225
T. Bilirubin (mg/dl)	128	0.58	0.34	*-0.1-1.3	0.2-1.5
Hematocrit (Vol %)	125	45	2.52	40-50	42-52
Hemoglobin (GMS %)	125	15	0.84	13.3-16.7	14-18
WBC (thous/cu mm)	126	6.3	1.6	3.1-9.5	5-11
RBC (million/cu mm)	127	5.0	0.36	4.3-5.7	4.7-6.0
Lymph (%)	128	39	9.8	19-59	20-40
SEG (%)	128	58	11	36-80	50-70
MCV (cu microns)	128	90	3.85	82-98	80-94
MCHC (%)	127	33	2.0	29-37	32-36
MCH (micro micro GM)	128	30	1.45	27-33	27-31
Platelet Count(thous/cu mm)	128	264	81	102-426	150-300
Haptoglobin (mg/dl)					50-220

* "0" value will be used as lower limits normal range because of lack of statistical normal distribution.

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 5b: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES

GROUP	DOSE LEVEL	CODE NUMBER	TESTS	STUDY DAY Screen	0*	2*	3	7	14	28
1	1 mg	274	Glucose (mg/dl)	92	92	102	104	90	62---L	92
			Potassium (mEq/L)	3.9	3.9	3.9	4.2	3.7	4.2	3.5-L
			Carbon Dioxide (mEq/L)	28	28	30	31	27	32---H	32---H
			Triglyceride (mg/dl)	59	59	223---H	123	40	113	48
		275	Chloride (mEq/L)	105	105	106	111---H	105	101	104
			Carbon Dioxide (mEq/L)	29	29	28	31	30	27	32---H
			Uric Acid (mg/dl)	6.2	6.2	4.6	3.8-L	6.4	5.9	6.9
			Calcium (mg/dl)	10.9	10.9	11.0-H	10.5	10.3	10.7	9.7
			Triglyceride (mg/dl)	64	64	271---H	243---H	73	72	113
2	4 mg	276	Glucose (mg/dl)	97	91	44---L	83	73	69	87
			Creatinine (mg/dl)	0.8	0.7-L	1.0	0.9	0.8	0.9	0.8
			Carbon Dioxide (mEq/L)	30	33---H	36---H	32---H	34---H	31	24
			Uric Acid (mg/dl)	4.6	3.3-L	4.4	4.5	3.3-L	4.5	4.3
			Total Protein (g/dl)	6.8	6.5	7.1	6.8	6.8	6.2-L	6.7
			Albumin (g/dl)	4.3	4.0-L	4.3	4.3	4.2	3.9-L	4.2
			Calcium (mg/dl)	10.2	9.2	9.7	9.9	9.2	8.7-L	9.1
			Phosphate (mg/dl)	3.3	3.0	3.1	3.1	2.5	2.2-L	2.6
			Lymphocytes (%)	22	18---L	12---L	38	18---L	32	30
			Seg. Neutrophils (%)	74	80	86---H	60	80	66	66
		277	Glucose (mg/dl)	93	71	121---H	87	85	89	89
			Potassium (mEq/L)	4.6	3.9	5.5-H	4.0	4.7	5.1	4.8
			Carbon Dioxide (mEq/L)	32---H	37---H	34---H	32---H	31	33---H	34---H
			Albumin (g/dl)	4.4	4.0-L	4.3	4.4	4.1	4.2	4.2
			Hematocrit (Vol %)	49.2	44.7	49.8	51.2-H	43.0	46.6	47.9
			Hemoglobin (GMS %)	16.6	15.4	17.1-H	18.0-H	14.9	15.8	16.0
			MCH (micro micro GM)	31.3	31.8	31.5	32.7	33.1-H	31.3	31.8

* = controlled environment (Nursing Unit 5-W, WHC) L = below 2 SD H = above 2 SD

TABLE 5B: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

GROUP	DOSE LEVEL	CODE NUMBER	TESTS	STUDY DAY						
				Screen	0*	2*	3	7	14	28
3	8 mg	278	BUN (mg/dl)	11	11	13	15	12	16	22----H
			Sodium (mEq/L)	139	140	141	140	136----L	137	138
			Potassium (mEq/L)	4.0	5.2	5.4--H	4.7	4.8	3.9	3.8
			Chloride (mEq/L)	104	100	103	104	95----L	96----L	97----L
			Carbon Dioxide (mEq/L)	29	36----H	31	32----H	32----H	35----H	35----H
			Uric Acid (mg/dl)	5.2	5.3	3.7--L	3.7--L	5.4	5.6	5.9
			Albumin (g/dl)	4.4	4.3	4.0--L	4.4	4.7	4.4	4.4
			Calcium (mg/dl)	10.3	9.7	8.8--L	9.3	9.6	9.5	9.5
			Phosphate (mg/dl)	3.2	3.3	2.4--L	3.9	3.1	3.2	3.9
			Triglyceride (mg/dl)	44	133	245----H	138	52	93	74
			Total Bilirubin (mg/dl)	0.2	0.2	0.2	0.3	1.5--H	0.3	0.3
		279	Carbon Dioxide (mEq/L)	33----H	33----H	33----H	33----H	32----H	30	29
			Albumin (g/dl)	4.2	3.8--L	3.9--L	4.1	4.2	4.1	4.2
			Total Bilirubin (mg/dl)	1.0	1.1	0.9	1.0	1.7--H	2.0--H	1.1
			Lymphocytes (%)	27	37	30	32	30	17----L	34
4	16 mg	280	Uric Acid (mg/dl)	3.5--L	4.0	3.7--L	3.9--L	4.3	4.9	3.7--L
			Triglyceride (mg/dl)	39	102	89	143	186	63	254----H
			Hematocrit (Vol %)	48.7	49.0	49.7	52.0--H	48.3	49.0	47.7
			Hemoglobin (GMS %)	16.2	16.7	16.6	17.2--H	16.1	16.4	16.5
			RBC (million/cu mm)	5.69	5.75-H	5.68	6.02-H	5.56	5.72-H	5.63
		281	Carbon Dioxide (mEq/L)	32----H	27	35----H	30	33----H	32----H	30
			Phosphate (mEq/L)	2.7	2.4--L	3.5	3.9	3.1	4.0	3.9
			Triglyceride (mg/dl)	61	82	91	103	78	254----H	35
			Hematocrit (Vol %)	45.4	45.4	50.1--H	49.1	45.1	45.4	47.3

* = controlled environment (Nursing Unit 5-W, WHC) L = below 2 SD H = above 2 SD

TABLE 5b: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

GROUP	DOSE LEVEL	CODE NUMBER	TESTS	STUDY DAY						
				Screen	0*	2*	3	7	14	28
5	32 mg	282	No Abnormalities							
		283	Hematocrit (Vol %)	50.1--H	50.2--H	49.7	50.8--H	ND+	ND+	ND+
			Hemoglobin (GMS %)	16.7	16.8--H	17.0--H	17.5--H	ND+	ND+	ND+
			RBC (million/cu mm)	6.12-H	6.11-H	5.98-H	6.16-H	ND+	ND+	ND+
5b	32 mg	284	Sodium (mEq/L)	143	142	137	139	136----L	140	138
			Carbon Dioxide (mEq/L)	29	31	32----H	31	30	28	29
			Total Protein (g/dl)	7.8	7.2	7.9	8.4--H	5.9--L	6.5	6.7
			Albumin (g/dl)	4.9	4.4	4.6	5.2--H	3.9--L	4.1	4.1
			Calcium (mg/dl)	10.2	9.3	9.9	10.3	8.4--L	9.3	9.3
			LDH (U/L)	253----H	223	211	217	200	245----H	202
			Hematocrit (Vol %)	45.1	43.2	52.1--H	54.8--H	40.7	41.3	43.8
			Hemoglobin (GMS %)	15.3	14.9	17.5--H	18.1--H	13.3	13.3	14.8
			RBC (million/cu mm)	4.62	4.39	5.36	5.55	4.08-L	4.15-L	4.49
			MCV (cu microns)	98	96	98	99----H	99----H	98	96
6	64 mg	285	Sodium (mEq/L)	142	135----L	138	138	142	139	138
			Carbon Dioxide (mEq/L)	32----H	31	31	32----H	33----H	30	30
			Calcium (mg/dl)	9.8	8.9--L	9.4	9.6	9.4	10.0	9.8
			Alkaline Phosphatase (U/L)	102----H	99----H	92	96----H	99----H	76	105----H
			LDH (U/L)	204	158	156	148	173	172	246----H
			Total Bilirubin (mg/dl)	0.9	0.8	0.7	0.5	0.6	1.5--H	1.4--H
			Lymphocytes (%)	45	31	49	54	63----H	47	15----L
			Seg. Neutrophils (%)	47	60	49	38	33----L	48	80
			Eosinophils (%)	7----H	7----H	2	8----H	4	2	0
		286	Carbon Dioxide (mEq/L)	25	32----H	28	32----H	31	30	30
			Total Protein (g/dl)	6.4	6.5	6.5	6.8	6.2--L	6.7	6.6
			Eosinophils (%)	1	1	0	2	3	2	6----H

* = controlled environment (Nursing Unit 5-W, WHC) L = below 2 SD H = above 2 SD + = not drawn

TABLE 5b: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

GROUP	DOSE LEVEL	CODE NUMBER	TESTS	STUDY DAY						
				Screen	0*	2*	3	7	14	28
7	125 mg	287	Sodium (mEq/L)	138	136----L	140	139	135----L	140	141
			Carbon Dioxide (mEq/L)	30	26	34----H	32----H	25	29	31
			Total Bilirubin (mg/dl)	1.3	1.0	1.0	1.4--H	1.0	0.8	0.7
			Hemoglobin (GMS %)	16.2	15.9	16.8--H	16.5	15.5	15.7	15.8
		288	BUN (mg/dl)	11	22----H	22----H	22----H	12	14	16
			Carbon Dioxide (mEq/L)	30	30	30	31	33----H	32----H	29
			Uric Acid (mg/dl)	3.9--L	5.2	3.9--L	4.7	5.3	5.1	4.8
			Phosphate (mg/dl)	3.3	3.4	4.5	4.5	2.4--L	4.1	2.3--L
			SGPT (U/L)	20	22	40	68----H	39	32	35
			Hematocrit (Vol %)	45.7	38.3--L	43.3	43.5	41.6	39.2--L	40.1
			Hemoglobin (GMS %)	14.7	12.8--L	14.2	14.4	13.6	13.6	12.7--L
8	250 mg	289	BUN (mg/dl)	12	21	19	23----H	21	14	16
			Hematocrit (Vol %)	45.9	41.4	44.7	44.4	38.4--L	43.8	41.9
			Hemoglobin (GMS %)	15.2	14.3	15.1	14.9	13.1--L	14.6	13.9
			RBC (million/cu mm)	5.07	4.65	4.97	4.97	4.27-L	5.06	4.61
		290	Carbon Dioxide (mEq/L)	34----H	32----H	31	31	29	31	33----H
			Phosphate (mg/dl)	3.5	3.4	3.2	4.7--H	3.8	4.2	3.7
			Triglyceride (mg/dl)	124	77	181	147	216----H	87	59
			Hematocrit (Vol %)	40.0	40.1	40.2	41.7	36.9--L	40.3	38.4--L
			Hemoglobin (GMS %)	13.9	13.2--L	14.7	14.8	13.2--L	13.5	13.4
			MCV (cu microns)	85	83	82	82	81----L	84	84
			MCH (micro micro GM)	29.4	26.9--L	29.9	29.1	29.2	28.9	29.4
9	375 mg	291	Glucose (mg/dl)	94	111	103	81	140----H	99	100
			Calcium (mg/dl)	9.3	9.3	9.3	9.7	9.0	8.8--L	9.5
			Phosphate (mg/dl)	2.6	2.6	2.9	2.4--L	2.3--L	3.0	2.9
			Triglyceride (mg/dl)	99	68	148	268----H	73	89	110
			WBC (thous/cu mm)	5.4	7.4	8.0	11.4--H	8.6	8.6	6.9
			Lymphocytes (%)	44	27	20	13----L	20	34	27
			Seg. Neutrophils (%)	56	70	76	83----H	69	53	65
			Eosinophils (%)	0	0	0	0	0	11----H	5

* = controlled environment (Nursing Unit 5-W, WHC) L = below 2 SD H = above 2 SD

TABLE 5b: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

GROUP	DOSE LEVEL	CODE NUMBER	TESTS	STUDY DAY						
				Screen	0*	2*	3	7	14	28
9	375 mg	292	Carbon Dioxide (mEq/L)	29	30	30	31	32----H	26	29
10	480 mg	293	Glucose (mg/dl)	77	98	97	96	94	66	133----H
			Carbon Dioxide (mEq/L)	29	32----H	33----H	33----H	25	28	27
			Uric Acid (mg/dl)	7.2	7.2	6.0	5.0	7.2	7.7	8.6--H
			Phosphate (mg/dl)	3.6	2.5	3.8	4.1	3.0	3.0	2.4--L
			Triglycerides (mg/dl)	148	165	439----H	256----H	177	108	195
			SGPT (U/L)	31	34	49----H	59----H	37	29	12
			Hemoglobin (GMS %)	16.1	15.7	17.1--H	16.5	16.1	15.5	15.9
			Eosinophils (%)	2	6----H	7----H	0	0	4	4
		294	Chloride (mEq/L)	103	102	99	102	100	97----L	98
			Carbon Dioxide (mEq/L)	31	27	31	34----H	30	30	31
			Total Protein (g/dl)	7.8	7.6	7.6	7.6	7.2	8.5--H	7.8
			Globulin (g/dl)	3.1	3.0	3.2	3.0	2.8	3.5--H	3.2
			LDH (U/L)	193	171	132	145	172	226	235----H
11	600 mg	295	Creatinine (mg/dl)	1.3	1.3	1.5--H	1.3	1.3	1.3	1.0
			Sodium (mEq/L)	142	138	142	140	140	142	136----L
			SGPT (U/L)	45	20	41	41	35	50----H	33
			Eosinophils (%)	0	1	0	ND+	0	6----H	1
		296	Uric Acid (mg/dl)	6.3	7.3	7.0	7.0	8.4--H	7.0	7.0
			Hematocrit (Vol %)	49.4	50.0	48.7	ND+	50.2--H	48.5	48.8
12	720 mg	334	Glucose (mg/dl)	92	88	91	87	64----L	54----L	87
			Total Protein (g/dl)	8.5--H	7.8	8.3--H	8.1--H	8.2--H	7.5	8.2--H
			Cholesterol (mg/dl)	273----H	261----H	277----H	268----H	259----H	238	240
		335	Glucose (mg/dl)	81	65----L	78	84	78	90	94
			Hemoglobin (GMS %)	15.6	16.9--H	16.2	16.8--H	15.7	16.1	15.6
			Eosinophils (%)	0	3	0	12----H	7----H	2	8----H

* = controlled environment (Nursing Unit 5-W, WHC) L = below 2 SD H = above 2 SD

EXPERIMENT NO. 11: WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 6: Hematologic Deviations

SUBJECTS WITH DEVIATIONS OF HEMATOCRITS‡

GROUP	CODE NUMBER	TOTAL DOSE	STUDY DAYS						
			Screen	0	[illegible]	3	7	14	28
2	276	4 mg	49.2	44.7	49.8	51.2--H	43.0	46.6	47.9
4	280	16 mg	48.7	49.0	49.7	52.0--H	48.3	49.0	47.7
4	281	16 mg	45.4	45.4	50.1--H	49.1	45.1	45.4	47.3
5	283	32 mg	50.1--H	50.2--H	49.7	50.8--H	ND*	ND*	ND*
5b	284	32 mg	45.1	43.2	52.1--H	54.8--H	40.7	41.3	43.8
7	288	125 mg	45.7	38.3--L	43.3	43.5	41.6	39.2--L	40.1
8	289	250 mg	45.9	41.4	44.7	44.4	38.4--L	43.8	41.9
8	290	250 mg	40.6	40.1	40.2	41.7	36.9--L	40.3	38.4--L
11	296	600 mg	49.4	50.0	48.7	ND*	50.2--H	48.5	48.8

‡normal range: 40-50 Vol %

SUBJECTS WITH DEVIATIONS OF HEMOGLOBINS†

2	277	4 mg	16.6	15.4	17.1--H	18.0--H	14.9	15.8	16.0
4	280	16 mg	16.2	16.7	16.6	17.2--H	16.1	16.4	16.5
5	283	32 mg	16.7	16.8--H	17.0--H	17.5--H	ND*	ND*	ND*
5b	284	32 mg	15.3	14.9	17.5--H	18.1--H	13.3	13.3	14.8
7	287	125 mg	16.2	15.9	16.8--H	16.5	15.5	15.7	15.8
7	288	125 mg	14.7	12.8--L	14.2	14.4	13.6	13.6	12.7--L
8	289	250 mg	15.2	14.3	15.1	14.9	13.1--L	14.6	13.9
8	290	250 mg	14.1	13.2--L	14.7	14.8	13.2--L	13.5	13.4
10	293	480 mg	16.1	15.7	17.1--H	16.5	16.1	15.5	15.9
12	335	720 mg	15.6	16.9--H	16.2	16.8--H	15.7	16.1	15.6

†normal range: 13.3-16.7 GMS %

SUBJECTS WITH DEVIATIONS OF RED BLOOD CELL COUNTS††

4	280	16 mg	5.69	5.75-H	5.68	6.02-H	5.56	5.72-H	5.63
5	283	32 mg	6.12-H	6.11-H	5.98-H	6.16-H	ND*	ND*	ND*
5b	284	32 mg	4.62	4.39	5.36	5.55	4.08-L	4.15-L	4.48
8	289	250 mg	5.07	4.65	4.97	4.97	4.27-L	5.06	4.61

††normal range: 4.3-5.7 million cu/mm

L = below 2 SD H = above 2 SD * = not drawn

TABLE 6: Hematologic Deviations (cont.)

SUBJECTS WITH DEVIATIONS OF EOSINOPHILS‡

GROUP	CODE NUMBER	TOTAL DOSE	STUDY DAYS						
			Screen	0	2	3	7	14	28
6	285	64 mg	7-H	7-H	2	8-H	4	2	0
6	286	64 mg	1	1	0	2	3	2	6-H
9	291	375 mg	0	0	0	0	0	11-H	5
10	293	480 mg	2	6-H	7-H	0	0	4	4
11	295	600 mg	0	1	0	ND*	0	6-H	1
12	335	720 mg	0	3	0	12-H	7-H	2	8-H

‡normal range: 0-6%

H = above 2 SD * = not drawn

EXPERIMENT NO. 11: WR 149,024 SHORT TERM DOSAGE, SAFETY AND TOLERANCE

TABLE 7: Biochemical Deviations

SUBJECTS WITH DEVIATIONS OF SGPTs‡

GROUP	CODE NUMBER	TOTAL DOSE	STUDY DAYS						
			Screen	0	2	3	7	14	28
7	288	125 mg	20	22	40	68-H	39	32	35
10	293	480 mg	31	34	49-H	59-H	37	29	12
11	295	600 mg	45	20	41	41	35	50-H	33

‡normal range: 0-47 U/L

SUBJECTS WITH DEVIATIONS OF TOTAL BILIRUBINS+

3	278	8 mg	0.2	0.2	0.2	0.3	1.5-H	0.3	0.3
3	279	8 mg	1.0	1.1	0.9	1.0	1.7-H	2.0-H	1.1
6	285	64 mg	0.9	0.8	0.7	0.5	0.6	1.5-H	1.4-H
7	287	125 mg	1.3	1.0	1.0	1.4-H	1.0	0.8	0.7

+normal range: 0.0-1.3 mg/dl

H = above 2 SD * = not drawn

APPENDIX

INDEX

INDIVIDUAL SUBJECT FINAL SUMMARIES

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 1 mg CODE: 274 GROUP: 1 AGE: 26
DOSE PER Kg: 0.0127 mg/kg HEIGHT: 184.15 cm WEIGHT: 78.33 kg
INFUSION DATE: 3/7/78 TIME DOSED: 0920 TOTAL: 0.0083 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	3/6	3/6	3/7	3/8	3/13	3/20	4/3	5/1
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	56
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28	56
Glucose (mg/dl)	92	92	102	104	80	82---L	92	ND+
Potassium (mEq/L)	3.9	3.9	3.9	4.2	3.7	4.2	3.5-L	4.0
CO_2 (mEq/L)	28	28	30	31	27	32---H	32---H	31
Triglyceride(mg/dl)	59	59	223--H	123	40	113	48	ND+

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: One hour and fifteen minutes after starting the infusion, subject experienced a sensation of "tightness" bilaterally in the chest wall of 15 minutes duration described by the subject as "my chest feels tight when I breathe". Physical examination at that time was normal and no ECG monitor changes occurred. Thereafter, the subject was asymptomatic throughout the study interval. Physical examination was unchanged during study participation.

Abnormalities Comment: There were minimal and inconsistent laboratory deviations not considered of clinical significance.

Conclusion: No adverse effect from infusion of 1 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 1 mg **CODE:** 275 **GROUP:** 1 **AGE:** 32
DOSE PER Kg: 0.0146 mg/kg **HEIGHT:** 170.18 cm **WEIGHT:** 68.49 kg
INFUSION DATE: 3/7/78 **TIME DOSED:** 1135 **TOTAL:** 0.0083 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	3/6	3/6	3/7	3/8	3/9	3/13	3/20	4/3	6/14
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	100
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28	100
Chloride (mEq/L)	105	105	106	111---H	105	101	104	ND+
CO_2 (mEq/L)	29	29	28	31	30	27	32---H	33---H
Uric Acid (mg/dl)	6.2	6.2	4.6	3.8-L	6.4	5.9	6.9	ND+
Calcium (mg/dl)	10.9	10.9	11.0-H	10.5	10.3	10.7	9.7	ND+
Triglyceride(mg/dl)	64	64	271---H	243---H	73	72	113	ND+

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: The subject was asymptomatic during the study interval and physical examination remained unchanged.

Abnormalities Comment: Mild elevation of serum triglycerides to 271 mg/dl and 243 mg/dl was manifest on day 2 and day 3 respectively. On day 7, the serum triglyceride was reported as normal with a value of 73 mg/dl. Other abnormalities were minimal and inconsistent. Observed deviations not considered of clinical significance.

Conclusion: No adverse effect from infusion of 1 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 4 mg **CODE:** 276 **GROUP:** 2 **AGE:** 36
DOSE PER Kg: 0.0541 mg/kg **HEIGHT:** 182.88 cm **WEIGHT:** 73.94 kg
INFUSION DATE: 3/28/78 **TIME DOSED:** 0900 **TOTAL:** 0.033 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	3/8	3/27	3/28	3/29	3/30	4/3	4/10	4/24	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
Glucose (mg/dl)	97	91	44---L	83	73	69	87
Creatinine (mg/dl)	0.8	0.7-L	1.0	0.9	0.8	0.9	0.8
CO_2 (mEq/L)	30	33---H	36---H	32---H	34---H	31	24
Uric Acid (mg/dl)	4.6	3.3-L	4.4	4.5	3.3-L	4.5	4.3
T. Protein (g/dl)	6.8	6.5	7.1	6.8	6.8	6.2-L	6.7
Albumin (g/dl)	4.3	4.0-L	4.3	4.3	4.2	3.9-L	4.2
Calcium (mg/dl)	10.2	9.2	9.7	9.9	9.2	8.7-L	9.1
Phosphate (mg/dl)	3.3	3.0	3.1	3.1	2.5	2.2-L	2.6
Lymphocytes (%)	22	18---L	12---L	38	18---L	32	30
Seg.Neutrophils(%)	74	80	86---H	60	80	66	66

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic during the study interval and the physical examination remained unchanged.

Abnormalities Comment: There was a tendency to minimal depression of percent lymphocytes before and after drug administration. Other laboratory abnormalities were minor and inconsistent. Deviations not considered of clinical significance.

Conclusion: No adverse effect from infusion of 4 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 4 mg **CODE:** 277 **GROUP:** 2 **AGE:** 24
DOSE PER Kg: 0.0598 mg/kg **HEIGHT:** 172.72 cm **WEIGHT:** 66.91 kg
INFUSION DATE: 4/4/78 **TIME DOSED:** 0900 **TOTAL:** 0.033 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	3/8	4/3	4/4	4/5	4/6	4/10	4/17	5/1	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance			X						

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
Glucose (mg/dl)	93	71	121---H	87	85	89	89
Potassium (mEq/L)	4.6	3.9	5.5-H	4.0	4.7	5.1	4.8
CO_2 (mEq/L)	32---H	37---H	34---H	32---H	31	33---H	34---H
Albumin (g/dl)	4.4	4.0-L	4.3	4.4	4.1	4.2	4.2
Hematocrit (Vol %)	49.2	44.7	49.8	51.2-H	43.0	46.6	47.9
Hemoglobin (GMS %)	16.6	15.4	17.1-H	18.0-H	14.9	15.8	16.0
MCH(micro micro GM)	31.3	31.8	31.5	32.7	33.1-H	31.3	31.8

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic during study participation. Immediately upon completion of drug administration minimal orthostatic intolerance was noted: supine 118/78, standing after 3 minutes 104/70. Upon repeating 15 minutes later, supine 116/68, sitting 122/70, standing 108/72. Thirty minutes after completion of drug infusion: supine 112/78, sitting 112/68, standing after 3" 118/78. Sixty minutes after completion of drug infusion supine B/P 120/78, sitting 124/72, standing after 3" 118/66. Two hours after completion of drug infusion: supine 118/64, sitting 124/72, and standing 130/84. Thereafter no change was noted in orthostatic tolerance.

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

Conclusion: No adverse effect from infusion of 4 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 8 mg **CODE:** 278 **GROUP:** 3 **AGE:** 24
DOSE PER Kg: 0.0991 mg/kg **HEIGHT:** 180.34 cm **WEIGHT:** 80.74 k
INFUSION DATE: 4/18/78 **TIME DOSED:** 0900 **TOTAL:** 0.066 mg/mi

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	3/22	4/17	4/18	4/19	4/20	4/24	5/1	5/15	6/1
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	45
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28	45
BUN (mg/dl)	11	11	13	15	12	16	22---H	17
Sodium (mEq/L)	139	140	141	140	136---L	137	138	ND+
Potassium (mEq/L)	4.0	5.2	5.4-H	4.7	4.8	3.9	3.8	ND+
Chloride (mEq/L)	104	100	103	104	95---L	96---L	97---L	102
CO_2 (mEq/L)	29	36---H	31	32---H	32---H	35---H	35---H	33--
Uric Acid (mg/dl)	5.2	5.3	3.7-L	3.7-L	5.4	5.6	5.9	ND+
Albumin (g/dl)	4.4	4.3	4.0-L	4.4	4.7	4.4	4.4	ND+
Calcium (mg/dl)	10.3	9.7	8.8-L	9.3	9.6	9.5	9.5	ND+
Phosphate (mg/dl)	3.2	3.3	2.4-L	3.9	3.1	3.2	3.9	ND+
Triglyceride (mg/dl)	44	133	245---H	138	52	93	74	ND+
T. Bilirubin (mg/dl)	0.2	0.2	0.2	0.3	1.5-H	0.3	0.3	ND+

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: The subject was asymptomatic during the study interval and physical examination remained unchanged.

Abnormalities Comment: The subject manifested an isolated occurrence of an elevated total bilirubin of 1.5 mg/dl on day 7. The upper limits of normal are 1.3 mg/dl. All abnormalities were marginal and inconsistent.

Conclusion: No adverse effect from infusion of 8 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 8 mg CODE: 279 GROUP: 3 AGE: 23
DOSE PER Kg: 0.1336 mg/kg HEIGHT: 177.80 cm WEIGHT: 59.87 kg
INFUSION DATE: 5/2/78 TIME DOSED: 0930 TOTAL: 0.066 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	4/26	5/1	5/2	5/3	5/4	5/8	5/15	5/30	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	29	
1. Symptoms			X	X					
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	29
CO_2 (mEq/L)	33---H	33---H	33---H	33---H	32---H	30	29
Albumin (g/dl)	4.2	3.8-L	3.9-L	4.1	4.2	4.1	4.2
T.Bilirubin (mg/dl)	1.0	1.1	0.9	1.0	1.7-H	2.0-H	1.1
Lymphocytes (%)	27	37	30	32	30	17---L	23

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: Twenty minutes after onset of infusion, the subject stated he had the "bed-swims". He felt as if he was "spinning". Physical examination showed no nystagmus, no arrhythmia, and no associated change in blood pressure. The symptoms subsided and disappeared by the time the infusion was completed. One hour and forty-five minutes after onset of infusion, the subject felt warm in cervicofacial area "like being embarrassed" lasting approximately 15 minutes. Twenty-four hours after infusion of drug, the subject experienced ophthalmic pruritis and a macular erythematous patchy rash of upper torso after taking a luke-warm shower. Twenty-six and one-half hours after drug infusion following a luke-warm shower a few areas of erythema of 2-3 cm with central white papulation ± 0.5 cm were produced. Test for dermatographia was positive. Thereafter, the subject was asymptomatic and no change was noted in physical examination.

Abnormalities Comment: The total bilirubin was elevated to 1.7 mg/dl and 2.0 mg/dl on day 7 and day 14 respectively. Repeated on days 18 and day 29 the total bilirubin values were 1.4 and 1.1 mg/dl respectively. Other laboratory abnormalities were minimal and inconsistent and not considered of clinical significance. Lightheadedness, skin rash, and increase in serum bilirubin not considered related to infusion of 8 mg WR 149,024.

Conclusion: No adverse effect from infusion 8 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 16 mg CODE: 280 GROUP: 4 AGE: 23
DOSE PER Kg: 0.2328 mg/kg HEIGHT: 182.88 cm WEIGHT: 68.72 kg
INFUSION DATE: 5/9/78 TIME DOSED: 0900 TOTAL: 0.133 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	5/1	5/8	5/9	5/10	5/11	5/15	5/22	6/6	6/13
STUDY DAY:	Screen	0*	1*	2*	3	7	14	29	38
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	29	38
Uric Acid (mg/dl)	3.5--L	4.0	3.7--L	3.9--L	4.3	4.9	3.7--L	6.1
Triglyceride(mg/dl)	39	102	89	143	186	63	254----H	66
Hematocrit (Vol %)	48.7	49.0	49.7	52.0--H	48.3	49.0	47.7	ND+
Hemoglobin (GMS %)	16.2	16.7	16.6	17.2--H	16.1	16.4	16.5	ND+
RBC (million/cu mm)	5.69	5.75-H	5.68	6.02-H	5.56	5.72-H	5.63	ND+

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: Approximately 50 minutes after starting the drug infusion, the subject reported that his eyes "felt strained", as though he had had his eyeglasses on too long. Examination was normal. The symptom lasted for 65 minutes. Approximately 12 hours after drug infusion initiation the subject experienced difficulty "catching" his breath for 2 minutes while in the shower. The subject remained asymptomatic thereafter and physical examination remained unchanged.

Abnormalities Comment: There was a tendency towards a depressed uric acid both before and after drug administration, however, it was reported as normal (6.0 mg/dl) on day 38.

Conclusion: No adverse effect from infusion of 16 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 16 mg **CODE:** 281 **GROUP:** 4 **AGE:** 21
DOSE PER Kg: 0.250 mg/kg **HEIGHT:** 173.99 cm **WEIGHT:** 63.96 kg
INFUSION DATE: 7/18/78 **TIME DOSED:** 0845 **TOTAL:** 0.133 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/12	7/17	7/18	7/19	7/20	7/24	7/31	8/14	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms								X	
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
CO_2 (mEq/L)	32---H	27	35---H	30	33---H	32---H	30
Phosphate (mEq/L)	2.7	2.4-L	3.5	3.3	3.1	4.0	3.3
Triglyceride(mg/dl)	61	82	91	103	78	254---H	35
Hematocrit (Vol %)	45.4	45.4	50.1-H	49.1	45.1	45.4	47.3

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: During close-out examination on day 28, subject stated that he had been experiencing fatigue, feeling "worn-out", and hunger over the past 7 days. The subject stated that he had spent that time in England. Physical examination at this time was normal. Subject was otherwise asymptomatic during the study interval, and physical examination remained unchanged.

Abnormalities Comment: Abnormalities were minimal and inconsistent, and not considered to be of clinical significance.

Conclusion: No adverse effect from infusion of 16 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 6.916 mg CODE: 282 GROUP: 5ex AGE: 28
DOSE PER Kg: 0.1146 mg/kg HEIGHT: 170.18 cm WEIGHT: 60.33 kg
INFUSION DATE: 7/25/78 TIME DOSED: 1115 TOTAL: 0.266 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/17	7/24	7/25	7/26	7/27	8/28			
STUDY DAY:	Screen	0*	1*	2*	3	35			
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:

No Abnormalities

Symptoms and Physical Findings: Starting 18 hours prior to drug administration the subject experienced a mild retro-orbital and temporal headache which resolved completely within 54 hours. The subject attributed the symptoms to reading. Twenty-eight minutes after starting the drug infusion p wave irregularity was noted and the infusion terminated. The cardiology consultant's opinion was subject "appears to have normal sinus rhythm with sinus arrhythmia and variations in p waves 2° to vagal tone .... during infusion additional variation probably 2° to normal vagal tone." The subject did not return for scheduled follow-up visits after repeated attempts by phone and mail, however, the subject did return for a close-out physical examination 34 days after drug administration without symptoms or change in physical examination.

Abnormalities Comment: Variation in p wave and sinus arrhythmia considered secondary to normal vagal tone for this subject.

Conclusion: No adverse effect related to infusion of 6.916 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 32 mg CODE: 283 GROUP: 5 AGE: 21
DOSE PER Kg: 0.3207 mg/kg HEIGHT: 179.07 cm WEIGHT: 99.79 kg
INFUSION DATE: 7-25-78 TIME DOSED: 0910 TOTAL: 6.266 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/19	7/24	7/25	7/26	7/27				
STUDY DAY:	Screen	0*	1*	2*	3				
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3
Hematocrit (Vol %)	50.1--H	50.2--H	48.7	50.8--H
Hemoglobin (GMS %)	16.7	16.8--H	17.0--H	17.5--H
RBC (million/cu mm)	6.12-H	6.11-H	5.98-H	6.16-H

H = above 2 SD

Symptoms and Physical Findings: Eight hours after initiation of drug infusion, subject experienced some upper respiratory congestion with associated sneezing and coughing lasting for 2-3 hours. Minimal orthostatic intolerance was present before and after the infusion. Physical examination on day 2 was within normal limits. The subject failed to return for any follow-up visits, despite numerous attempts to reach him.

Abnormalities Comment: There was a tendency towards a slightly elevated hematocrit, hemoglobin, and RBC both before and after drug administration considered to be an individual variant. No other laboratory abnormalities were observed.

Conclusion: No adverse effects from drug infusion.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 32 mg CODE: 284 GROUP: 5 AGE: 23
DOSE PER Kg: 0.4672 mg/kg HEIGHT: 189.87 cm WEIGHT: 68.49 kg
INFUSION DATE: 8/1/78 TIME DOSED: 0930 TOTAL: 0.266 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/26	7/31	8/1	8/2	8/3	8/7	8/14	8/28	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms								X	
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
Sodium (mEq/L)	143	142	137	139	136----L	140	139
CO_2 (mEq/L)	29	31	32----H	31	30	28	29
Total Protein(g/dl)	7.8	7.2	7.9	8.4--H	5.9--L	6.5	6.7
Albumin (g/dl)	4.9	4.4	4.8	5.2--H	3.9--L	4.1	4.1
Calcium (mg/dl)	10.2	9.3	9.9	10.3	8.4--L	9.3	9.3
LDH (U/L)	225	223	211	217	200	245----H	202
Hematocrit (Vol %)	45.1	43.2	52.1--H	54.8--H	40.7	41.3	43.8
Hemoglobin (GMS %)	15.3	14.9	17.5--H	18.1--H	13.8	13.3	14.8
RBC (million/cu mm)	4.62	4.39	5.36	5.55	4.08-L	4.15-L	4.49
MCV (cu microns)	98	96	98	99----H	99----H	98	96

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic except for pruritis from electrode paste until 60 hours post dosing when "finally felt effects of the drug .... Thursday night felt dizzy and my feet swelled up .... you know my pace is fast and I felt like I was moving in slow motion .... felt that way off and on over the weekend". The subject apparently was very active and slept little from discharge day 3 until return day 7. At that time the examiner noted "bags under both eyes" and trace pre-tibial and ankle edema not present on examination 3 days later. Physical exam unchanged thereafter. Advised to obtain more rest and elevate feet. Neither prescription followed and subject continued to complain of recurrent dizziness, sore throat, and returned for the last time 9/13/78, 43 days after the drug infusion complaining of hoarseness and generally poor health since study participation. Examination was normal.

Abnormalities Comment: It is difficult to explain the sudden increase in hematocrit and hemoglobin on study days 2 and 3 with abrupt decrease to pre-dosing levels thereafter. In the absence of correlating evidence to suggest otherwise, the elevated values are considered a laboratory error. Other laboratory deviations were minor and inconsistent.

Conclusion: No adverse effect from drug infusion.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 64 mg CODE: 285 GROUP: 6 AGE: 26
DOSE PER Kg: 0.8500 mg/kg HEIGHT: 190.54 cm WEIGHT: 75.30 kg
INFUSION DATE: 8/8/78 TIME DOSED: 0845 TOTAL: 0.533 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/31	8/7	8/8	8/9	8/10	8/14	8/24	9/5	
STUDY DAY:	Screen	0*	1*	2*	3	7	17	29	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	17	29
Sodium (mEq/L)	142	135---L	138	138	142	139	138
CO_2 (mEq/L)	32---H	31	31	32---H	33---H	30	30
Calcium (mg/dl)	9.8	8.9-L	9.4	9.6	9.4	10.0	9.8
Alka.Phos. (U/L)	102---H	99---H	92	96---H	99---H	76	105---H
LDH (U/L)	204	158	156	148	173	172	246---H
T.Bilirubin (mg/dl)	0.9	0.8	0.7	0.5	0.6	1.5-H	1.4-H
Lymphocytes (%)	45	31	49	54	63---H	47	15---L
Seg.Neutrophils (%)	47	60	49	38	33---L	48	80
Eosinophils (%)	7---H	7---H	2	8---H	4	2	0

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic during the study interval. Physical examination remained unchanged.

Abnormalities Comment: There was a tendency to minimal elevation of alkaline phosphatase and eosinophil percentage both before and after drug administration. The total bilirubin was 1.5 mg/dl and 1.4 mg/dl on day 17 and 29 respectively. Other deviations were minimal and inconsistent. The subject was requested to return for follow-up biochemistry, but has failed to do so.

Conclusion: No adverse effect from infusion of 64 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 64 mg CODE: 286 GROUP: 6 AGE: 31
DOSE PER Kg: 0.9406 mg/kg HEIGHT: 177.80 cm WEIGHT: 68.04 kg
INFUSION DATE: 8/8/78 TIME DOSED: 1100 TOTAL: 0.533 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	7/31	8/7	8/8	8/9	8/10	8/14	8/21	9/5	9/9
STUDY DAY:	Screen	0*	1*	2*	3	7	14	29	33
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	29	33
CO_2 (mEq/L)	25	32---H	28	32---H	31	30	30	ND+
T. Protein (g/dl)	6.4	6.5	6.5	6.8	6.2-L	6.7	6.6	ND+
Eosinophils (%)	1	1	0	2	3	2	6---H	141‡

L = below 2 SD H = above 2 SD + = not drawn ‡ = total eosin count (normal 100-300)

Symptoms and Physical Findings: The subject was asymptomatic during the study interval. Physical examination remained unchanged.

Abnormalities Comment: Abnormalities were minimal and inconsistent and not considered to be of clinical significance.

Conclusion: No adverse effect from infusion of 64 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 125 mg CODE: 287 GROUP: 7 AGE: 21
DOSE PER Kg: 1.5658 mg/kg HEIGHT: 177.80 cm WEIGHT: 79.83 kg
INFUSION DATE: 9/12/78 TIME DOSED: 0855 TOTAL: 1.042 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	9/7	9/11	9/12	9/13	9/14	9/18	9/25	10/10	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	29	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	29
Sodium (mEq/L)	138	136---L	140	139	135---L	140	141
CO_2 (mEq/L)	30	26	34---H	32---H	25	29	31
T.Bilirubin (mg/dl)	1.3	1.0	1.0	1.4-H	1.0	0.8	0.7
Hemoglobin (GMS %)	16.2	15.3	16.8-H	16.5	15.3	15.7	15.3

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic during the study interval. Physical examination remained unchanged.

Abnormalities Comment: Deviations were minor and inconsistent, and not considered of clinical significance.

Conclusion: No adverse effect from infusion of 125 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 125 mg CODE: 388 GROUP: 7 AGE: 22
DOSE PER Kg: 1.8071 mg/kg HEIGHT: 167.01 cm WEIGHT: 69.17 kg
INFUSION DATE: 10/25/78 TIME DOSED: 0945 TOTAL: 1.042 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	10/16	10/24	10/25	10/26	10/27	11/	11/6	11/	
STUDY DAY:	Screen	0*	1*	2*	3	6	13	27	
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	6	13	27
BUN (mg/dl)	11	22---H	22---H	22---H	12	14	16
CO_2 (mEq/L)	30	30	30	31	33---H	32---H	29
Uric Acid (mg/dl)	3.9-L	5.2	3.9-L	4.7	5.3	5.1	4.8
Phosphate (mg/dl)	3.3	3.4	4.5	4.5	2.4-L	4.1	2.3-L
SGPT (U/L)	20	22	40	68---H	39	32	35
Hematocrit (Vol %)	45.7	38.3-L	43.3	43.5	41.6	39.2-L	40.1
Hemoglobin (GMS %)	14.7	12.8-L	14.2	14.4	13.6	13.6	12.7-L

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: Loose stools without associated symptoms occurred 8 and 9 hours after initiation of the drug infusion and following evening meal. The subject had a headache which lasted for "several hours" beginning 96 hours after onset of drug infusion. Physical examination at this time was normal. Subject was otherwise asymptomatic and physical examination was unchanged.

Abnormalities Comment: There was a tendency to minimal elevation of serum BUN before and after drug administration. Isolated elevation of the SGPT to 68 U/L was reported on day 3. Other abnormalities were minimal and inconsistent. The deviations are not considered of clinical significance. Occurrence of 2 loose stools 8 and 9 hours after infusion of 125 mg of WR 149,024 not considered drug related. Headache beginning 96 hours after drug infusion with a duration of several hours not considered drug related.

Conclusion: No adverse effect from infusion of 125 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 250 mg CODE: 289 GROUP: 8 AGE: [illegible]
DOSE PER Kg: 4.0377 mg/kg HEIGHT: 176.53 cm WEIGHT: 61.92 kg
INFUSION DATE: 11/7/78 TIME DOSED: 1145 TOTAL: 2.083 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	11/2	11/6	11/7	11/8	11/9	11/13	11/20	12/4	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
BUN (mg/dl)	12	21	19	23----H	21	14	16
Hematocrit (Vol %)	45.9	41.4	44.7	44.4	38.4--L	43.8	41.9
Hemoglobin (GMS %)	15.2	14.3	15.1	14.9	13.1--L	14.6	13.9
RBC(million/cu mm)	5.07	4.65	4.97	4.97	4.27-L	5.06	4.61

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic during the study interval. Physical examination remained unchanged.

Abnormalities Comment: Abnormalities were minimal and inconsistent, and not considered to be of clinical significance.

Conclusion: No adverse effect from infusion of 250 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 250 mg CODE: 290 GROUP: 8 AGE: 26
DOSE PER Kg: 3.3403 mg/kg HEIGHT: 180.98 cm WEIGHT: 74.84 kg
INFUSION DATE: 11/7/78 TIME DOSED: 0915 TOTAL: 2.083 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	10/30	11/6	11/7	11/8	11/9	11/13	11/20	12/4	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	11	14	28
CO_2 (mEq/L)	34---H	32---H	31	31	29	ND+	31	33---H
Phosphate (mg/dl)	3.5	3.4	3.2	4.7-H	3.8	ND+	4.2	3.7
Triglyceride (mg/dl)	124	77	181	147	216---H	ND+	87	59
Hematocrit (Vol %)	40.0	40.1	40.2	41.7	36.9-L	40.0	40.3	38.4-L
Hemoglobin (GMS %)	13.9	13.2-L	14.7	14.8	13.2-L	13.4	13.5	13.4
MCV (cu microns)	85	83	82	82	81---L	ND+	84	84
MCH (micro micro GM)	29.4	26.9-L	29.9	29.1	29.2	ND+	28.9	29.4

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: Subject was asymptomatic during the study interval. Physical examination remained unchanged.

Abnormalities Comment: There were minimal and inconsistent laboratory deviations not considered of clinical significance.

Conclusion: No adverse effect from infusion of 250 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 375 mg CODE: 291 GROUP: 9 AGE: 33
DOSE PER Kg: 6.0789 mg/kg HEIGHT: 170.18 cm WEIGHT: 61.69 kg
INFUSION DATE: 11/14/78 TIME DOSED: 0915 TOTAL: 3.125 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	10/31	11/13	11/14	11/15	11/16	11/20	11/27	12/11	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
Glucose (mg/dl)	94	111	103	81	140---H	99	100
Calcium (mg/dl)	9.3	9.3	9.3	9.7	9.0	8.8-L	9.5
Phosphate (mg/dl)	2.6	2.6	2.9	2.4-L	2.3-L	3.0	2.9
Triglyceride(mg/dl)	99	68	148	268---H	73	89	110
WBC (thous/cu mm)	5.4	7.4	8.0	11.4-H	8.6	8.6	6.3
Lymphocytes (%)	44	27	20	13---L	20	34	27
Seg.Neutrophils (%)	56	70	76	83---H	69	53	65
Eosinophils (%)	0	0	0	0	0	11---H	0

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: Subject passed loose stools without abdominal discomfort 96 hours and 120 hours after onset of drug infusion. Subject was otherwise asymptomatic during study interval, and physical examination remained unchanged.

Abnormalities Comment: Subject manifested an isolated occurrence of an elevated eosin of 11% on day 14, which was reported as a normal of 0% on day 28. Other abnormalities were minimal and inconsistent, and not considered of clinical significance. Passage of 2 loose stools over a 48 hour period not considered related to drug infusion.

Conclusion: No adverse effect from infusion of 375 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 375 mg CODE: 292 GROUP: 9 AGE: 29
DOSE PER Kg: 4.6315 mg/kg HEIGHT: 185.42 cm WEIGHT: 80.97 kg
INFUSION DATE: 11/28/78 TIME DOSED: 1005 TOTAL: 3.125 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	11/15	11/27	11/28	11/29	11/30	12/4	12/11	1/2/79	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
CO_2 (mEq/L)	29	30	30	31	32-H	26	29

H = above 2 SD

Symptoms and Physical Findings: Before initiation of drug infusion, subject experienced a vague sensation of cold feet without physical findings for approximately 10 minutes after infusion started. Fifty-five minutes after starting drug infusion, subject experienced itching under the tape at the I.V. site. Physical examination revealed mild erythema (2 x 2) at the I.V. site, considered to be sensitivity to tape. Erythema persisted for approximately 48 hours. Subject was otherwise asymptomatic during the study interval, and physical examination remained unchanged.

Abnormalities Comment: No laboratory abnormalities were observed during the study interval.

Conclusion: No adverse effect from infusion of 375 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 480 mg CODE: 293 GROUP: 10 AGE: 28
DOSE PER Kg: 5.4477 mg/kg HEIGHT: 181.61 cm WEIGHT: 88.11 kg
INFUSION DATE: 12/5/78 TIME DOSED: 1000 TOTAL: 4.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	11/27	12/4	12/5	12/6	12/7	12/11	12/18	1/2/79	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	29	
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis				X	(X)	(X)			
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	29
Glucose (mg/dl)	77	98	97	96	94	66	133---H
CO_2 (mEq/L)	29	32---H	33---H	33---H	25	28	27
Uric Acid (mg/dl)	7.2	7.2	6.0	5.0	7.2	7.7	8.6-H
Phosphate (mg/dl)	3.6	2.5	3.8	4.1	3.0	3.0	2.4-L
Triglycerides(mg/dl)	148	165	439---H	256---H	177	108	195
SGPT (U/L)	31	34	49---H	59---H	37	29	12
Hemoglobin (GMS %)	16.1	15.7	17.1-H	16.5	16.1	15.5	15.3
Eosinophils (%)	2	6---H	7---H	0	0	4	4
Urine: WBC's	occ.	3.8	20.0-H	TNTC--H	18.2-H	2.1	rare

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: One hour and forty-five minutes after starting infusion, the subject experienced "tingling of face" lasting approximately 10 minutes. Physical examination at this time was normal. Forty-eight hours after drug administration subject noticed mucoid uretheral discharge. Smear and culture of discharge was reported as normal. Uretheral discharge was completely resolved within 24 hours.

Abnormalities Comment: Elevation of serum triglycerides to 439 mg/dl and 256 mg/dl and SGPT to 49 U/L and 54 U/L was reported on days 2 and 3 respectively: both values were normal when repeated on day 7. The changes are not considered drug related. Urinary sediment contained 20 WBC's pHpF on day 2, TNTC on day 3, and 18 pHpF on day 7. The subject was referred to a urologist on day 7 concerning discharge and urinary sediment. Urologist and investigators conclude subject had recurrent episode of nonspecific urethritis not related to drug infusion.

Conclusion: No adverse effect from infusion of 480 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 480 mg **CODE:** 294 **GROUP:** 10 **AGE:** 24
DOSE PER Kg: 7.9565 mg/kg **HEIGHT:** 176.53 cm **WEIGHT:** 60.33 kg
INFUSION DATE: 12/12/78 **TIME DOSED:** 1000 **TOTAL:** 4.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1978	11/27	12/11	12/12	12/13	12/14	12/18	1/3/79	1/8/79	
STUDY DAY:	Screen	0*	1*	2*	3	7	23	28	
1. Symptoms			X						
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	23	28
Chloride (mEq/L)	103	102	99	102	100	97---L	98
CO_2 (mEq/L)	31	27	31	34---H	30	30	31
T.Protein (g/dl)	7.8	7.6	7.6	7.6	7.2	8.5-H	7.8
Globulin (g/dl)	3.1	3.0	3.2	3.0	2.8	3.5-H	3.2
LDH (U/L)	193	171	132	145	172	226	235---H

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: Immediately upon completion of drug infusion, subject experienced nausea without emesis upon standing with a duration of less than 2 minutes. Ten minutes later, when the subject stood for orthostatic tolerance testing he experienced a "tingling" in the back of his head which lasted for several seconds. Orthostatic tolerance was normal as was physical examination. Subject was asymptomatic during the remainder of the study interval and physical examination remained unchanged.

Abnormalities Comment: Laboratory deviations were minimal and inconsistent, and not considered to be of clinical significance.

Conclusion: Transient nausea immediately following drug infusion possibly related to infusion of 480 mg WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 600 mg CODE: 295 GROUP: 11 AGE: 28
DOSE PER Kg: 6.7488 mg/kg HEIGHT: 187.96 cm WEIGHT: 88.91 kg
INFUSION DATE: 1/3/79 TIME DOSED: 1010 TOTAL: 5.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	12/18/78	1/2	1/3	1/4	1/5	1/8	1/15	1/29	
STUDY DAY:	Screen	0*	1*	2*	3	6	13	27	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	6	13	27
Creatinine (mg/dl)	1.3	1.3	1.5-H	1.3	1.3	1.3	1.3
Sodium (mEq/L)	142	138	142	140	140	142	136---L
SGPT (U/L)	45	20	41	41	35	50---H	33
Eosinophils (%)	0	1	0	ND+	0	6---H	1

L = below 2 SD H = above 2 SD + = not drawn

Symptoms and Physical Findings: The subject was asymptomatic during the study interval, and the physical examination remained unchanged.

Abnormalities Comment: There were minimal and inconsistent laboratory deviations not considered of clinical significance.

Conclusion: No adverse reaction from infusion of 600 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 600 mg CODE: 296 GROUP: 11 AGE: 35
DOSE PER Kg: 7.7809 mg/kg HEIGHT: 177.17 cm WEIGHT: 77.11 kg
INFUSION DATE: 1/9/79 TIME DOSED: 0950 TOTAL: 5.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	1/4	1/8	1/9	1/10	1/11	1/15	1/24	1/31	
STUDY DAY:	Screen	0*	1*	2*	3	7	16	23	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	16	23
Uric Acid (mg/dl)	6.3	7.3	7.0	7.0	8.4-H	7.0	7.0
Hematocrit (Vol %)	49.4	50.0	48.7	ND+	50.2-H	48.5	48.8

H = above 2 SD

Symptoms and Physical Findings: Subject had mild symptoms of the common cold from day 14 to day 16. He was afebrile and otherwise asymptomatic. Physical examination was unchanged during the study interval.

Abnormalities Comment: Abnormalities were marginal and inconsistent and not considered to be of clinical significance.

Conclusion: No adverse reaction from infusion of 600 mg of WR 149,024.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 720 mg CODE: 334 GROUP: 12 AGE: 29
DOSE PER Kg: 10.4773 mg/kg HEIGHT: 182.88 cm WEIGHT: 68.72 kg
INFUSION DATE: 1/16/79 TIME DOSED: 1000 TOTAL: 6.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	1/4	1/15	1/16	1/17	1/18	1/22	1/29	2/12	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms			X	(X)					
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	28
Glucose (mg/dl)	92	88	91	87	64---L	54---L	87
T. Protein (g/dl)	8.5-H	7.8	8.3-H	8.1-H	8.2-H	7.5	8.2-H
Cholesterol(mg/dl)	273---H	261---H	277---H	268---H	259---H	238	240

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: Twenty minutes after initiation of drug infusion, an area of erythema was noted along course of vein in left forearm which was slightly pruritic initially. The area of erythema cleared within 24 hours but a 1 cm x 1 cm indurated nontender area persisted. One hundred forty-four hours after drug infusion a small area of ecchymosis but no evidence of thrombophlebitis was present at the IV site. Forty-five minutes after onset of infusion the subject complained of perioral numbness and indefinable thoracic and abdominal sensations. The subject exhibited mild hyperventilation during the episode. Some degree of anxiety and the hyperventilation symptoms continued throughout infusion. Immediately following infusion orthostatic tolerance testing was initiated. On standing, the subject became nauseated and vomited approximately 25 cc. Systolic blood pressure was recorded as 102 (questionable accuracy) during period of emesis. Orthostatic tolerance testing was promptly repeated and recorded as follows: supine 118/76 and standing 118/88. The subject was asymptomatic thereafter.

Abnormalities Comment: There was a tendency to elevated serum cholesterol and serum total protein before and after drug administration attributed to individual variation. The subject has been asked to return for repeat biochemical testing but has failed to do so at this time.

Conclusion: Erythema at infusion site related to venous irritation of intravenous catheter. Symptoms of hyperventilation, nausea, and emesis possibly but not probably a WR 149,024 effect.

INDIVIDUAL SUBJECT FINAL SUMMARY

EXPERIMENT NO. 11: WR 149,024 SHORT-TERM DOSAGE, SAFETY AND TOLERANCE

TOTAL DOSE: 720 mg CODE: 335 GROUP: 12 AGE: 24
DOSE PER Kg: 11.5862 mg/kg HEIGHT: 167.54 cm WEIGHT: 62.14 kg
INFUSION DATE: 1/23/79 TIME DOSED: 0945 TOTAL: 6.000 mg/min

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	1/4	1/22	1/23	1/24	1/25	1/29	2/5	2/22	
STUDY DAY:	Screen	0*	1*	2*	3	7	14	28	
1. Symptoms									
2. Physical Exam									
3. ECG									
4. Urinalysis									
5. Biochemistry									
6. CBC									
7. Platelets									
8. Creatinine Clearance									
9. Orthostatic Tolerance									

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

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0*	2*	3	7	14	31
Glucose (mg/dl)	81	65---L	78	84	78	90	94
Hemoglobin (GMS %)	15.6	16.9-H	16.2	16.8-H	15.7	16.1	15.6
Eosinophils (%)	0	3	0	12---H	7---H	2	8---H

L = below 2 SD H = above 2 SD

Symptoms and Physical Findings: The subject was asymptomatic throughout study interval. One hundred and twenty hours post dosing, the subject presented with a non-tender ecchymosis distal to the antecubital fossa on the right arm attributed to venipuncture. Physical exam otherwise remained unchanged throughout study interval. One hundred and twenty minutes after starting the infusion diastolic blood pressure decreased from 74 to 72 in orthostatic tolerance testing. Repeated 10 minutes later intolerance was still present (diastolic decrease 6 mmHg), but absent when checked promptly by the physician investigator.

Abnormalities Comment: Minor elevation of hemoglobin was present before and after drug administration and not considered drug related. Forty-eight hours after drug infusion the subject manifested eosinophilia of 12%. One hundred-twenty hours after drug infusion the eosinophil count was reported normal at 2%. Total eosinophil count at the same time was reported normal at 156 with a normal range of 200-400. The eosinophil count was elevated to 7% on day 7 and 8% on day 31. The subject has been requested to return for repeat eosinophil count but has failed to do so.

Conclusion: No adverse effect from infusion of 720 mg WR 149,024.

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FINAL REPORT

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3

TITLE:	SHORT-TERM SAFETY AND TOLERANCE TO WR 142,490·HCl CLINICAL EVALUATION OF TWO FORMULATIONS 1000 mg DOSE LEVEL
PRINCIPAL INVESTIGATOR	JOHN A. JOHNSON, M.D.
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CONSULTING AND INSTITUTIONAL REVIEW BOARD MEMBERS:	JAMES A. CURTIN, M.D. STUART H. DANOVITCH, M.D.

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PRINCIPAL INVESTIGATOR

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FINAL REPORT

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3

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

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FINAL REPORT

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3

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

ABSTRACT

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

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

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

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FINAL REPORT

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3

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

INTRODUCTION

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

In an attempt to find an optimal combination of bioavailability and tolerance, two formulations of Mefloquine Hydrochloride have been studied in humans: 250 mg tablets, Lafayette Pharmacal (Lot 443) and 250 mg tablets, INTERx (Lot B512). In the most recent study[1] WR 142,490·HCl as formulated in Lots B512 and E443 was not well tolerated at a single oral dose of 1750 mg.

Intolerance was manifested by combinations of nausea, lightheadedness, abdominal cramps and loose stools. Symptoms were mild and transitory. The frequency and duration of symptoms were less with E443.

Although the intolerance found at 1750 mg was not incapacitating, it was determined that the experiment should be repeated using a 1000 mg dose level, in a 2 x 2 balanced latin square crossover design.

This is a final report of the short-term safety and tolerance of WR 142,490·HCl given orally to volunteer subjects at the 1000 mg dose level in two formulations.

[1] Final Report: Addendum to Experiment 3: WR 142,490·HCl SHORT TERM SAFETY AND TOLERANCE Clinical Evaluation of Two Formulations, 18 October 1976

METHODS AND MATERIALS

1. Procurement of Subjects and Subject Acceptability Criteria:

   Nine healthy male subjects, age 21 to 40 years, weighing 64.410-90.265 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 for employment 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 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 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.

2. Two groups of 4 subjects each designated Groups C and D were studied in sequence in accordance with the following table:

SEQUENCE OF DRUG ADMINISTRATION

Group	Subject	1st Week	2nd Week	7th Week	8th Week
C	9	E443*		B512+	
C	10	E443		B512	
C	11	B512		E443	
C	12	B512		E443	
D	13		E443		B512
D	14		E443		B512
D	15		B512		E443
D	16		B512		E443

*Lafayette Pharmacal, Inc. 250 mg tablets

+INTERx 250 mg film-coated tablets

At 6:00 a.m., on the day of dosing, the subject drank 360ml of Sustacal(Mead-Johnson product) containing 360 calories. At 8:00 a.m., 1000mg of the scheduled drug was administered in the presence of a member of the investigating team.

Water was taken ad lib until 5:00 p.m. at which time the subjects were allowed to have the regular diet they selected from the hospital menu.

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

SCHEMATIC STUDY PLAN (For Each Dosing)

STUDY DAY	0*	1*	2*	3*	4	5	7	42
Dose		X						
Physical Exam	X		X				X	X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X		X	X
ECG (Rhythm Strip LII)	X	X	(post dose)					X
Laboratory Tests+	X		X				X	X
Blood for Drug Assay†		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, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, T.Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies were done as clinically indicated.

†Drug Assay: Each subject immediately prior to drug administration, and after dosing at 30 minutes and at 1, 2, 4, 6, 8, 10, 11, 12, 13, 15, 20, 24, 28, 34, 48, 56, 63, 72, 76, and 80 hours; and on study days, 5, 7, 8, 14, 21, 28, 35, and 42.

4. Ten ml of venous blood was drawn by a staff nurse for each drug assay. Six ml of the blood was 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 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 was centrifuged and the serum separated. The serum was transported to the Department of Pharmacology, WRAIR, for bioassay for antimalarial activity.

   For the hematologic and biochemical testing, a staff nurse obtained 27 ml of venous blood while the subject was fasting before breakfast. Seven ml of whole blood was placed in a test tube containing anticoagulant and used to determine the values for the white blood cell and differential count, red blood cell count, hematocrit, hemoglobin, MCV, MCH, MCHC, and platelet count. The remaining blood was centrifuged and the serum separated. The serum was divided into 2 samples. One sample was stored in the refrigerator as a "back-up" until the biochemical laboratory report was received. It was then stored in the freezer until released by the investigator. The other 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.

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

6. Emergencies: No medical emergencies occurred.

RESULTS

Number of Subjects:

Nine subjects were accepted into the study in accordance with the qualifying and regulatory procedures previously noted.

Compliance:

Eight of nine subjects completed the protocol as designed. One subject (#338) withdrew for personal reasons. That subject was administered only the B512 formulation.

Symptoms:

Symptoms are summarized in Table 1 (page 15). One subject (#339) had loose stools within 12 hours after ingestion of each formulation. Various symptoms occured - "twitching", "fuzzy spots on ceiling", "feeling hot" and "bad dreams" - which could not be related to drug administration. No unequivocal symptoms of intolerance were reported.

Physical Findings:

No abnormal physical findings related to drug administration were observed.

Laboratory Values:

Table 2 lists those laboratory values found to be abnormal for each subject. Where any value was abnormal, all values for that laboratory test are reported for that subject. All abnormal values were minimal or inconsistent, and were not clearly related to drug administration.

Electrocardiogram:

No cardiac electrical activity abnormalities were noted.

DISCUSSION

This study was designed to compare two formulations of WR 142,490·HCl regarding their safety, tolerance and bioavailability with a single oral dose of 1000 mg.

The outcome of this study cannot be adequately appreciated without considering the rationale for the study design. The two drug formulations had been compared previously in volunteer subjects with single oral doses of 1750 mg. Gastrointestinal symptoms were noted with each formulation.

It is readily apparent that pharmacokinetic studies of an orally administered drug are suspect if the absorptive phase is disrupted by gastrointestinal symptomatology. Thus, the comparative bioavailability of the two preparations at oral doses of 1750 mg is confounded with pathophysiological phenomena.

Furthermore, logistical and economic considerations mandate that small numbers of subjects are used in Phase I studies. It follows logically that with small numbers of subjects, individual variation in the way a given subject tolerates and metabolizes a drug can introduce Type I and Type II statistical errors of inference.

To cope with these two considerations, the investigators decided 1) To reduce the dosage to the point that the formulations were likely to be tolerated, yet were still an order of magnitude over the minimal prophylactic dose; 2) to use a crossover design so that each subject would be challenged with each preparation, and 3) to minimize order of administration effect by reversing the order in half of the subjects in each group, and by introducing a six week wash-out period between each drug administration.

The strategy of the design then depended upon the 1000 mg dose being well-tolerated and "safe" by biochemical and physiological measurements, thus permitting a valid comparison of the pharmacokinetics of the drug. Furthermore, the design permitted the identification and measurement of any residual effect from prior drug administration.

The strategy of the experiment was successful in that the 1000 mg dose in each formulation was well tolerated, and no physical or biochemical findings suggested adverse physiological effects.

CONCLUSIONS AND RECOMMENDATIONS

In this study, Mefloquine Hydrochloride given in oral doses of 1000 mg, produced no evidence of intolerance given as INTERx tablets (Lot B512) or Lafayette tablets (Lot E443), regardless of the order of administration.

Any decision regarding these preparations, *vis a vis* this experiment, should be based on the comparative bioavailability as determined by the blood samples supplied by BIO-MED, Inc., to the WRAIR.

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EXPLANATION: ANTIMALARIAL DRUG PROJECT
Addendum Number 2 to Experiment Number 3
Short-Term Safety and Tolerance to WR 142,490·HCl
Clinical Evaluation of Two Formulations
1000 mg Dose Level

GENTLEMEN:

The study for which you have applied involves taking by mouth two formulations of the drug, WR 142,490·HCl, Mefloquine Hydrochloride. Mefloquine is similar to Quinine and has been approved by the Food and Drug Administration for investigational studies. The drug has been administered to more than 100 subjects to determine its safety and tolerance, ability to prevent malaria, and ability to cure malaria.

Previous studies with this drug established that oral administration to humans was well tolerated in single oral doses of 2000 mg. Complaints of transient light-headedness occurred in both dosed and control subjects at single oral doses of 1500 mg and 1750 mg but not at 2000 mg.

Experiment Number 3 entitled, "WR 142,490·HCl: Short-Term Safety and Tolerance, Single Dose Levels" was designed to extend the Phase I tolerance human study to 2500 mg in a rising dose double-blind study. The study was initiated at an oral dose of 1750 mg dose. Watery diarrhea occurred 30 to 45 minutes after the drug was administered and continued for 3 to 4 hours. There was no nausea, vomiting, abdominal pain or other complaints by the subjects. An additional human study was conducted to test the tolerance in subjects administered the drug on two different occasions, one week apart. In this study, diarrhea, starting 30 to 60 minutes after dosing and lasting to 3 hours, occurred at both the 1250 mg and 1500 mg dose levels. In two subjects, the diarrhea occurred after both doses, in one subject after only the first dose and in one subject after only the second dose. There was no associated nausea, vomiting, or abdominal pain in most subjects.

Results of the Addendum to Experiment No. 3:WR 142,490·HCl, Short-Term Safety and Tolerance; Clinical Evaluation of Two Formulations, showed that administration of both formulations of WR 142,490·HCl as a single 1750 mg oral dose to be associated with combinations of mild and temporary nausea, abdominal cramps, and loose stools. Additionally, non-incapacitating light-headedness occurred in four instances in three subjects: following administration of drug formulation E443 on two occasions, and drug formulation B512 on two occasions.

There are two purposes for conducting the present study:

1. Since previous studies were associated with diarrhea, it is important to determine whether the present formulation will produce diarrhea when compared to previous formulations.

2. To accurately determine the pattern in which the drug appears and disappears from your body.

We will do this by doing a simple cross-over study. You will be assigned to one of two groups of four subjects each. You will receive one 1000 mg. dose of each of the drug formulations designated according to the sequence shown in Table I (below). In addition, blood will be drawn at the times specified in Table III (page 13), to measure the amount of drug present in your body.

TABLE I: SEQUENCE OF DRUG ADMINISTRATION

Group	Subject	1st Week	2nd Week	7th Week	8th Week
C	9	E443*		B512+	
C	10	E443		B512	
C	11	B512		E443	
C	12	B512		E443	
D	13		E443		B512
D	14		E443		B512
D	15		B512		E443
D	16		B512		E443

*Lafayette Pharmacal, Inc. 250 mg tablets

+INTERx 250 mg film-coated tablets

You will be admitted to the research unit for the first five days of the study. You will be seen on brief visits thereafter for a period of five weeks. On the seventh week, you will be readmitted to the research unit for a second five day period, after which you will be seen on brief visits for a period of five weeks. On the last day of the study you will have a complete physical examination.

The specifics for the study are presented in the schematic on the following page:

TABLE II: SCHEMATIC STUDY PLAN (For Each Dosing)
WR142,490·HCl - CLINICAL EVALUATION OF TWO FORMULATIONS

STUDY DAY	0*	1*	2*	3*	4	5	7	42
Dose		X						
Physical Exam	X		X				X	X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X		X	X
ECG (Rhythm Strip LII)	X	X	(post dose)					X
Laboratory Tests+	X		X				X	X
Blood for Drug Assay†		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, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, T.Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies were done as clinically indicated.

†Drug Assay: Each subject immediately prior to drug administration, and after dosing at 30 minutes and at 1, 2, 4, 6, 8, 10, 11, 12, 13, 15, 20, 24, 28, 34, 48, 56, 63, 72, 76, and 80 hours; and on study days, 5, 7, 8, 14, 21, 28, 35, and 42. (See Table III).

On the days indicated by *, the participants in the study will remain in a controlled environment. The entire group will remain together with a member of the Research 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 may have water as you wish until 5:00 p.m., at which time you may resume the normal diet you select from the hospital menu until you are discharged from the ward.

At your discretion, fifteen minutes before drug administration, a small teflon catheter can be placed in one of your arm veins. This can be used to obtain blood samples during the first fifteen hours; in this way, repeated venipunctures may not be necessary on that day.

During the eighty-four day study interval (twelve weeks), approximately eight hundred ml of whole blood will be obtained for study purposes. This is equivalent to a unit of blood that many people donate at Red Cross Center Blood Banks.

It is important that the blood be obtained as nearly as possible to the times specified in Table III, and that you eat a light breakfast (i.e., cereal, milk, juice, coffee, bread -- no eggs or bacon) on the days you come in for blood drawing. It is also important that you 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 body on any given day.

It is expected that at the dose level of 1000 mg, the amount of drug remaining in your blood on the last day of the study will be very low. However, the late specimens are just as important as the early specimens in obtaining an overall accurate assessment of the way the drug is handled by the body. Therefore, please do not start the study if you anticipate difficulty in adhering to the schedule.

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, both civlian 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.

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.

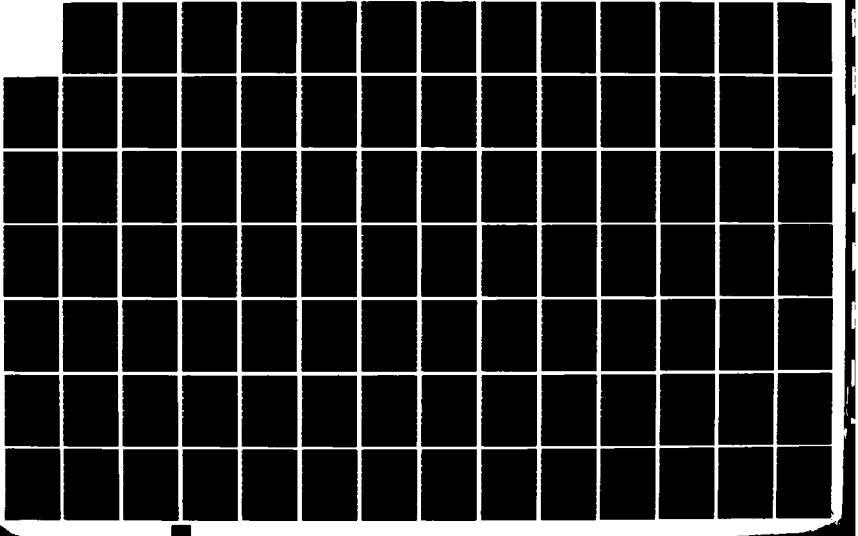
If after reading this document you have any additional questions, please ask them before affixing your initials below and signing the consent form.

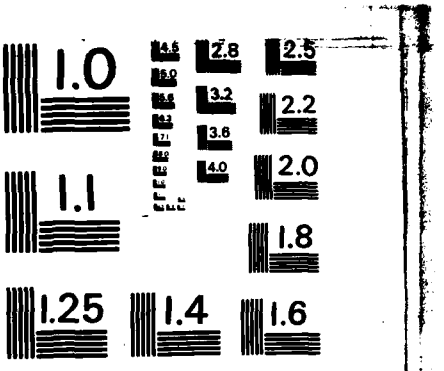
_____

Initial

AD-A139 980 ARMY DRUG DEVELOPMENT PROGRAM PHASE I CLINICAL TESTING 2/3
(U) BIO-MED INC COLLEGE PARK MD J JOHNSON MAR 80
DAMD17-75-C-5036

UNCLASSIFIED F/G 6/15 NL





MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

TABLE II: SCHEMATIC STUDY PLAN (For Each Dosing)
WR142,490·HCl - CLINICAL EVALUATION OF TWO FORMULATIONS

STUDY DAY	0*	1*	2*	3*	4	5	7	42
Dose		X						
Physical Exam	X		X				X	X
Interview	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X		X	X
ECG (Rhythm Strip LII)	X	X (post dose)						X
Laboratory Tests+	X		X				X	X
Blood for Drug Assay†		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, Triglycerides, Alkaline Phosphatase, SGOT, SGPT, LDH, T.Bilirubin, CBC (differential and indices), Platelets, Urinalysis. Additional studies were done as clinically indicated.

†Drug Assay: Each subject immediately prior to drug administration, and after dosing at 30 minutes and at 1, 2, 4, 6, 8, 10, 11, 12, 13, 15, 20, 24, 28, 34, 48, 56, 63, 72, 76, and 80 hours; and on study days, 5, 7, 8, 14, 21, 28, 35, and 42. (See Table III).

On the days indicated by *, the participants in the study will remain in a controlled environment. The entire group will remain together with a member of the Research 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 may have water as you wish until 5:00 p.m., at which time you may resume the normal diet you select from the hospital menu until you are discharged from the ward.

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During the eighty-four day study interval (twelve weeks), approximately eight hundred ml of whole blood will be obtained for study purposes. This is equivalent to a unit of blood that many people donate at Red Cross Center Blood Banks.

It is important that the blood be obtained as nearly as possible to the times specified in Table III, and that you eat a light breakfast (i.e., cereal, milk, juice, coffee, bread -- no eggs or bacon) on the days you come in for blood drawing. It is also important that you 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 body on any given day.

It is expected that at the dose level of 1000 mg, the amount of drug remaining in your blood on the last day of the study will be very low. However, the late specimens are just as important as the early specimens in obtaining an overall accurate assessment of the way the drug is handled by the body. Therefore, please do not start the study if you anticipate difficulty in adhering to the schedule.

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If after reading this document you have any additional questions, please ask them before affixing your initials below and signing the consent form.

_____

Initial

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3:
SHORT-TERM SAFETY AND TOLERANCE TO WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS

1000 mg DOSE LEVEL

TABLE III: DRUG ASSAY COLLECTION

DAY OF THE STUDY	SPECIMEN NUMBER			BLOOD VOLUME (ml)
1	1	0	Prior to dosing	10
	2	30min	8:30 AM	10
	3	1 hr	9:00 AM	10
	4	2 hr	10:00 AM	10
	5	4 hr	NOON	10
	6	6 hr	2:00 PM	10
	7	8 hr	4:00 PM	10
	8	10 hr	6:00 PM	10
	9	11 hr	7:00 PM	10
	10	12 hr	8:00 PM	10
	11	13 hr	9:00 PM	10
	12	15 hr	11:00 PM	10
	13	20 hr	4:00 AM	10
2	14	24 hr	8:00 AM	10
	15	28 hr	NOON	10
	16	34 hr	6:00 PM	10
3	17	48 hr	8:00 AM	10
	18	56 hr	4:00 PM	10
	19	63 hr	11:00 PM	10
4	20	72 hr	8:00 AM	10
	21	76 hr	NOON	10
	22	80 hr	4:00 PM	10
HOME				
5	23	96-98 hr	8:00-10:00 AM	10
7	24	144-146 hr	8:00-10:00 AM	10
8	25	168-170 hr	8:00-10:00 AM	10
14	26	312-314 hr	8:00-10:00 AM	10
21	27	480-482 hr	8:00-10:00 AM	10
28	28	648-650 hr	8:00-10:00 AM	10
35	29	816-818 hr	8:00-10:00 AM	10
42	30	984-986 hr	8:00-10:00 AM	10
			TOTAL	300 ml

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

DAY	HEMATOLOGY	CHEMISTRY	BLOOD ASSAY	TOTAL (ml)
0	7	20		27
1			130	130
2	7	20	30	57
3			30	30
4			30	30
5			10	10
7	7	20	10	37
8			10	10
14			10	10
21			10	10
28			10	10
35			10	10
42	7	20	10	37
			TOTAL	408 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 "Addendum No. 2 to Experiment No. 3: Short-Term Safety and Tolerance to WR 142,490-HCl; Clinical Evaluation of Two Formulations, 1000 mg Dose Level".

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: ANTIMALARIAL DRUG PROJECT, Addendum No. 2 to Experiment No. 3: Short-Term Safety and Tolerance to WR 142,490-HCl: Clinical Evaluation of Two Formulations, 1000 mg Dose Level"., 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.

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	

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3
WR 142,490·HCl: SHORT TERM SAFETY AND TOLERANCE
SINGLE DOSE LEVELS
TABLE 1 - SIGNS AND SYMPTOMS: ALL SUBJECTS

GROUP & SUBJ#	Formulation 1st Dose	Formulation 2nd Dose	GASTROINTESTINAL	OTHER
I 336		B512	None	"fuzzy spots" before eyes when looking up starting 7 hrs. post dosing and recurrent for 52 hrs. Normal eye examination. Pain in ribcage Day 21 following fall with residual tenderness on Day 43.
	E443		None	Diaphoretic feet 30 hrs. after dosing for 30 minutes-exam normal."Twitching" muscles left forearm from 6 hours to 18 hrs. post dosing - exam normal. Generalized headache from 11 hrs. to 14 hrs. post dosing.
I 337		B512	None	Lumbo-sacral discomfort following strenous exercise on day 39 lasting 3 days.
	E443		None	Temperature 99.4°F-99.6°F at 33 hours post dosing with return to normal at 43 hours at which time patient had transient slight sore throat. Normal examination.
I 338	B512		SUBJECT WITHDREW FROM STUDY	Mild left temporal headache 6 hrs. post dosing of 2 hrs. duration.
I 339	B512		One loose stool 10 hrs. post dosing.	
		E443	Transient "hunger pains" 1 hr. after dosing: 5 hrs. later flatus and one watery stool. Five days after dosing passed 6-8 watery stools after food indiscretion.	Temporary pain inner aspect right arm following exercise 6 days post dosing.

ADDENDUM NUMBER 2 TO EXPERIMENT NUMBER 3
WR 142,490·HCl: SHORT TERM SAFETY AND TOLERANCE
SINGLE DOSE LEVELS

TABLE 1 - SIGNS AND SYMPTOMS: ALL SUBJECTS

GROUP & SUBJ#	Formulation 1st Dose	Formulation 2nd Dose	GASTROINTESTINAL	OTHER
I 344	B512		"Abdominal discomfort 36 hrs. post dosing lasting for 2 hrs. At 48 hrs post dosing slight nausea and abdominal "tightness" for 1 hr.	"bizarre dreams" and fatigue starting 38 hrs. post dosing of 8 hrs. duration.
		E443	None	Slight "tickle in throat" 48 hrs. post dosing of 3 hrs. duration. Examination normal.
II 431		B512	None	
	E443		None	
II 341		B512	None	Injured hand 18 days post dosing.
	E443		None	Auto accident residual prior to dosing with painful knee exacerbated by striking bed rail 2 days post dosing: Exam normal. Recurrent orthostatic symptoms before and after study entry: exam normal including orthostatic tolerance test.
II 342	B512		None	Common cold for 12 days starting 25 days post dosing.
		E443	None	Traumatic conjunctivitis 4 days post dosing. Sprained ankle 5 days post dosing.
II 343	B512		None	Transient vasovagal reaction to bloodletting on day 0
		E443	None	Splinter right thumb 4 days prior to dosing. Gingival difficulty with recurrent minor bleeding before and after dosing. History of contact dermatitis, temporary approximately 4 weeks after dosing.

ADDENDUM NO.2 TO EXPERIMENT NO.3: SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl, CLINICAL EVALUATION OF OF TWO FORMULATIONS - 1000 MG DOSE LEVEL

TABLE 2: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES

GROUP-CODE NUMBER	FORMULATION 1st Dose	FORMULATION 2nd Dose	TESTS	Normal Range	1st Dose Study Day Screen	1st Dose Study Day 0	1st Dose Study Day 2	1st Dose Study Day 7	2nd Dose Study Day 0+	2nd Dose Study Day 2+	2nd Dose Study Day 7+	2nd Dose Study Day 42+
I 336	E-443	B-512	LDH	73-233 U/L	238*	397*	239*	261*	253*	244*	269*	288*
I 337	E-443	B-512	Glucose	66-114 mg/dl	66	67	79	81	85	92	64*	68
			Carbon Dioxide	23-31 mEq/L	32*	31	29	32*	32*	32*	32*	30
			Phosphate	2.5-4.5 mg/dl	3.7	3.6	4.7*	3.9	3.1	3.4	3.4	3.5
			Eosinophilia	0-5 %	2	0	0	0	6*	1	1	5
I 338	B-512	E-443	Cholesterol	110-242 mg/dl	218	266*	260*	218	ND†	ND	ND	ND
			Triglycerides	0-207 mg/dl	82	70	558*	114	ND	ND	ND	ND
			LDH	73-233 U/L	256*	288*	257*	257*	ND	ND	ND	ND
			White Blood Cell Count	3.1-9.5 th/cc mm	10.3*	8.5	9.9*	8.2	ND	ND	ND	ND
I 339	B-512	E-443	Carbon Dioxide	23-31 mEq/L	31	28	31	29	29	32*	31	27
			Total Protein	6.4-8.0 g/dl	6.8	6.5	6.6	6.4	6.2*	6.8	6.7	6.3*
			Calcium	9.0-10.9 mg/dl	9.5	8.9*	9.3	8.7*	8.4*	8.9*	9.2	9.1
			SGPT	0-47 U/L	29	29	32	57*	43	37	28	15
I 344	B-512	E-443	Glucose	66-114 mg/dl	77	87	92	83	62*	86	72	117*
			BUN	9-21 mg/dl	16	14	16	22*	23*	15	22*	15
			Carbon Dioxide	23-31 mEq/L	26	26	33*	29	26	27	26	26
			Uric Acid	4-8 mg/dl	3.7*	4.0	3.5*	4.6	5.2	4.4	4.1	4.9
			Phosphate	2.5-4.5 mg/dl	2.2*	3.0	2.9	2.1*	2.8	3.4	2.9	2.6
			Triglycerides	0-207 mg/dl	60	286*	74	61	30	81	62	76
			SGOT	0-47 U/L	27	16	14	12	19	23	88*	10
			LDH	73-233 U/L	175	187	149	150	182	171	247*	144

+indicates 2nd study interval (7 weeks after day 1, 1st study interval)
*denotes abnormality
†not done

TABLE 2: ABNORMAL BIOCHEMICAL and HEMATOLOGY VALUES (cont.)

GROUP-CODE NUMBER	FORMULATION 1st Dose	FORMULATION 2nd Dose	TESTS	Normal Range	1st Dose Study Day Screen	1st Dose Study Day 0	1st Dose Study Day 2	1st Dose Study Day 7	2nd Dose Study Day 0+	2nd Dose Study Day 2+	2nd Dose Study Day 7+	2nd Dose Study Day 42+
II 340	E-443	B-512	Carbon Dioxide	23-31 mEq/L	29	32*	31	27	29	28	27	29
			Calcium	9.0-10.9 mg/dl	9.6	9.1	9.9	8.9*	9.3	9.5	9.1	9.4
			Phosphate	2.5-4.5 mg/dl	3.0	2.4*	3.1	2.8	3.1	3.2	3.2	2.9
II 341	E-443	B-512	Potassium	3.6-5.2 mEq/L	4.9	3.6	4.5	3.5*	4.2	4.2	3.8	3.6
			Total Protein	6.4-8.0 g/dl	7.2	7.1	6.4	6.8	6.7	6.2*	6.3*	7.9
			Globulin	1.8-3.4 g/dl	2.1	2.2	2.0	2.0	2.0	1.7*	1.8	2.5
			Phosphate	2.5-4.5 mg/dl	2.8	2.2*	3.1	2.7	2.8	2.2*	2.5	1.8*
			Lymphocytes	19-59 %	20	17*	29	38	33	30	23	24
			Monocytes	0-10 %	0	3	3	11*	3	1	3	7
II 342	B-512	E-443	LDH	73-233 U/L	241*	212	178	196	188	192	247*	204
			Total Bilirubin	0.0-1.3 mg/dl	1.6*	1.7*	1.4*	1.2	1.6*	0.6	0.9	0.6
			Hemoglobin	13.3-16.7 GMS %	16.6	15.1	15.5	16.8*	14.9	15.0	15.1	15.9
			White Blood Cell Count	3.1-9.5 th/cc mm	4.3	4.1	5.5	4.3	3.9	5.9	9.9*	4.0
			Lymphocytes	19-59 %	41	46	43	53	41	42	17*	34
II 343	B-512	E-443	Glucose	66-114 mg/dl	83	114	82	90	89	94	98	56*
			Carbon Dioxide	23-31 mEq/L	29	28	31	26	32*	29	29	30
			LDH	73-233 U/L	189	211	185	254*	222	197	244*	243*
			Hemoglobin	13.3-16.7 GMS %	17.0*	15.6	16.4	16.1	14.9	14.7	15.1	16.8*

+indicates 2nd study interval (7 weeks after day 1, 1st study interval)
*denotes abnormality

SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing		
FORMULATION:	E-443	B-512	CODE:	336
DOSING DATE:	2-27-79	4-17-79	GROUP:	I
TIME DOSED:	1100	0800	AGE:	23
DOSE(mg/kg):	13.333	13.333	HEIGHT:	184.15 (c
			WEIGHT:	75.00 (k

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	2-1	2-26	2-27	2-28	3-5	4-16	4-17	4-18	4-23	5-29
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	43+
1. Symptoms										
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	43+	Normal Range
LDH	238*	397*	293*	261*	253*	244*	269*	288*	73-233 U/L

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: Approximately 7 hours after drug ingestion, while laying in bed looking at the ceiling, the subject noted "fuzzy spots". No associated symptomatology was present. Thirty hours post dosing the patient, during the physical examination, stated that he had "more fuzzies - guess it's still there". Physical examination was normal. Fifty-two hours after drug ingestion the patient complained "floaters were worse". The subject then inquired as to whether or not the increase in number of "floaters" could be related to the phototoxocity testing. Following an explanation of phototoxicity testing, the subject no longer noted an increase in the number of "floaters". Finally, it should be noted that complete opthalmalogic evaluation on Days 2 and 3 was normal. It is the opinion of the investigator that the subject fixed on the normal phenomenon of obtaining retinal images when gazing at a white ceiling from the supine position. Finally, approximately 20 days after drug administration, the subject fell down some bleachers and experience pain in the left lateral anterior rib cage. Some residual tenderness was present on pressure over the lower left 3 ribs anterior. 41 days after drug ingestion. Physical examination was otherwise unchanged.

Code: 336 (contd)

Formulation E 443: Approximately 30 minutes after drug ingestion the subject noted increased perspiration of his feet which persisted for approximately 30 hours. Physical examination was unremarkable and the degree of perspiration present within normal limits. The subject also noted "twitching" and "fibrillation" of the muscles of the left forearm starting approximately 6 hours after drug ingestion not observed by the staff. There was no involuntary movement of the fingers of the left hand except perhaps the little finger, the episodes were fleeting and recurrent during the 18 hours following onset. The subject stated that he had had such episodes in the past perhaps associated with tension. Physical examination 20 hours after onset was normal. Finally, 11 hours post dosing a mild generalized headache was present attributed to fasting and relieved when food was ingested.

Abnormalities Comment:

Persistent elevation of lactic acid dehydrogenase was present both before and after drug administration. It is probably an individual variant; the subject has been referred for follow-up to his private physician. The symptoms enumerated are not considered significant nor related to ingestion of the WR 142,490·HCl preparations.

Conclusion:

No adverse effects from ingestion of either formulation of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing		
FORMULATION:	E-443	B-512	CODE:	337
DOSING DATE:	2/27/79	4/17/79	GROUP:	I
TIME DOSED:	1100	0800	AGE:	21
DOSE(mg/kg):	15.494	15.494	HEIGHT:	170.18 (cm
			WEIGHT:	64.54 (kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	2/12	2/26	2/27	2/28	3/5	4/16	4/17	4/18	4/23	5/29
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	43+
1. Symptoms										
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	43+	Normal Range
Glucose	66	67	79	81	85	92	64*	68	66-114 mg/dl
Carbon Dioxide	32*	31	29	32*	32*	32*	32*	30	23-31 mEq/L
Phosphate	3.7	3.6	4.7*	3.9	3.1	3.4	3.4	3.5	2.5-4.5 mg/dl
Eosinophils	2	0	0	0	6*	1	1	5	0-5 %

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: The subject was asymptomatic throughout study interval until close out physical exam, at which time he complained of lumbosacral discomfort for approximately 72 hours attributed to strenuous exercise. Physical examination was unchanged throughout study interval.

Formulation E-443: Approximately 46 hours after ingestion of Formulation E-443 the subject experienced transient mild sore throat. No pharyngitis or adenopathy were noted on physical exam. A slight elevation of temperature (99^6 orally) was noted 33 hours post drug ingestion which was normal (97 orally) 43 hours after drug administration. Approximately 54 hours after drug administration the subject complained of "feeling hot" transiently. Thereafter the subject remained asymptomatic and physical examination remained unchanged.

Code: 337 (cont.)

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

Conclusion: No adverse effect attributed to ingestion of either formulation of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	B-512		CODE: 338
DOSING DATE:	2/27/79		GROUP: I
TIME DOSED:	1100		AGE: 35
DOSE(mg/kg):	13.968		HEIGHT: 167.64 (cm
			WEIGHT: 71.59 (kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	2/1	2/26	2/27	2/28	3/5					
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	
1. Symptoms			X							
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	Normal Range
Cholesterol	218	266*	260*	218	110-242 mg/dl
Triglycerides	82	70	558*	114	0-207 g/dl
LDH	256*	288*	257*	257*	73-233 U/L
White Blood Count	10.3*	8.5	9.9*	8.2	3.1-9.5 th/cu mm

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: Six hours after ingestion of Formulation B-512 the subject experienced a mild left temporal headache lasting two hours which the subject attributed to fasting. The subject was asymptomatic throughout remainder of his study participation. The subject withdrew from study participation 27 days after drug ingestion. There was no change in physical examination during the study interval.

Formulation E-443: The subject did not return for the second study interval.

Abnormalities Comment: Moderate elevation of serum lactic acid dehydrogenase is considered an individual variant for this subject and not related to study participation. The subject was requested to return for repeat biochemical testing but has failed to do so.

Conclusion: No adverse effect from administration of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	B-512	E-443	CODE: 339
DOSING DATE:	2/27/79	4/17/79	GROUP: I
TIME DOSED:	1100	0800	AGE: 39
DOSE(mg/kg):	12.790	12.790	HEIGHT: 186.055(cm
			WEIGHT: 78.18 (kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	2/1	2/26	2/27	2/28	3/5	4/16	4/17	4/18	4/23	5/29
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	43+
1. Symptoms			X				X			
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval. (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY	Screen	0	2	7	0+	2+	7+	43+	50+	Normal Range
CO_2	31	28	31	29	29	32*	31	27	-	23-31 mEq/L
Total Protein	6.8	6.5	6.6	6.4	6.2*	6.8	6.7	6.3*	6.1*	6.4-8.0 g/dl
Calcium	9.5	8.9*	9.3	8.7*	8.4*	8.9*	9.2	9.1	-	9.0-10.9mg/dl
SGPT	29	29	32	57*	43	37	28	18	-	0-47 U/L

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: Ten hours after ingestion of 1000 mg Formulation B-512 the subject passed one loose to semi-formed stool without associated abdominal cramps. Thereafter the subject remained asymptomatic throughout the study interval.

Formulation E-443: One hour after ingestion of 1000 mg Formulation E-443 the subject experienced "hunger pains" lasting less than one hour. Six hours after drug ingestion the subject experienced "gas in stomach" followed by one watery stool without associated abdominal cramps. Approximately 5 days after drug ingestion the subject had 6 to 8 watery stools without abdominal cramps over a 3 hour period. The subject relates this symptom to increased ingestion of salt and celery. Approximately 6 days after drug administration the subject manifest pain

Code: 339 (cont.)

in the inner aspect of right arm lasting 2 hours related to cleaning machines with a rotary motion. Thereafter, the subject remained asymptomatic throughout the study interval.
Physical examination remained unchanged throughout both study intervals.

Abnormalities Comment: Minimal depression of serum calcium is considered a normal variant for this subject and not related to drug ingestion. Other laboratory deviations were minimal and inconsistent and not considered of clinical significance.

Conclusion: One loose stool without abdominal cramping 10 hours after ingestion of Formulation B-512 and 1 loose stool 6 hours after ingestion of Formulation E-443 possibly related to ingestion of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-443	B-512	CODE: 340
DOSING DATE:	3/6/79	4/24/79	GROUP: II
TIME DOSED:	0800	0800	AGE: 40
DOSE(mg/kg):	14.570	14.570	HEIGHT: 180.34 (cm)
			WEIGHT: 68.63 (kg)

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	11/6	3/5	3/6	3/7	3/12	4/23	4/24	4/25	4/30	6/4
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	42+
1. Symptoms										
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7	42+	Normal Range
Carbon Dioxide	29	32*	31	27	29	28	27	29	23-31 mEq/L
Calcium	9.6	9.1	9.9	8.9*	9.3	9.5	9.1	9.4	9.0-10.9 mg/dl
Phosphate	3.0	2.4*	3.1	2.8	3.1	3.2	3.2	2.9	2.5-4.5 mg/dl

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: The subject was asymptomatic and physical examination unchanged during the study interval.

Formulation E-443: The subject was asymptomatic and physical examination remained unchanged throughout the study.

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

Conclusion: No adverse effect attributed to ingestion of either formulation of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY
ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	E-443	B-512	CODE: 341
DOSING DATE:	3-6-79	4-24-79	GROUP: II
TIME DOSED:	0800	0800	AGE: 34
DOSE(mg/kg):	11.055	11.055	HEIGHT: 193.04 (
			WEIGHT: 90.45 (

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	2-12	3-5	3-6	3-7	3-12	4-23	4-24	4-25	4-30	6-
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	42
1. Symptoms			X	X						
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	42+	49+	Normal Range
Potassium	4.9	3.6	4.5	3.5	4.2	4.2	3.8	3.6	-	3.6-5.2mEq/L
T.Protein	7.2	7.1	6.4	6.8	6.7	6.2*	6.3*	7.9	-	6.4-8.0 g/dl
Globulin	2.1	2.2	2.0	2.0	2.0	1.7*	1.8	2.5	-	1.8-3.4 g/dl
Phosphate	2.8	2.2*	3.1	2.7	2.8	2.2*	2.5	1.8*	2.3*	2.5-4.5mg/dl
Lymphocytes	20	17*	29	38	33	30	23	24	-	19-59%
Monocytes	0	3	3	11*	3	1	3	7	-	0-10%

* denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: The subject was asymptomatic during this study interval except for injuring his hand on rusty nails 18 days after drug ingestion without significant sequelae.

Formulation E-443: Shortly before admission to the study the subject had an automobile accident with laceration and ecchymosis above the left eye and pain and tenderness about the right knee joint. Forty-eight hours after drug ingestion he struck the right knee on a bed rail with temporary increase in pain. X-rays were within normal limits, and there was no evidence of joint effusion or inflammation.

Code: 341 (cont.)

From 13 to 15 hours after drug ingestion the subject had 3 ephemeral episodes of "white out" on sudden assumption of the upright from the supine position. The subject described the episodes as "everything going white" and had noted such episodes in the past. Eight days following drug ingestion there was a recurrence of the "white out" when the subject arose quickly from the floor while watching television to answer the doorbell, he "for first time ever felt like I wasn't standing up straight - just to make sure, I touched the wall - felt like my feet wouldn't hold me." The duration was 10-15 seconds, the subject did not stagger. There were 2 recurrences on the same day. Physical examination on day 2 and day 13 was within normal limits. On day 13 orthostatic tolerance was tested times 3 with normal results. The "white outs" are not considered related to drug ingestion since the most impressive episodes occurred 8 days after drug ingestion and the subject had experienced such symptomatology in the past.

Abnormalities Comment:

Abnormalities reported in laboratory values were minimal or inconsistent and are not considered drug related.

Conclusion:

"White out" episodes occurring 13 hours after administration of Formulation E-443 possibly but not probably related to drug ingestion.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	B-512	E-443	CODE: 342
DOSING DATE:	3/6/79	4/24/79	GROUP: II
TIME DOSED:	0800	0800	AGE: 22
DOSE(mg/kg):	14.667	14.667	HEIGHT: 156.21 (cm)
			WEIGHT: 68.18 (kg)

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	1/22	3/5	3/6	3/7	3/12	4/23	4/24	4/25	4/30	6/4
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	42+
1. Symptoms										
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	42+	Normal Range
LDH	241	212	178	196	188	192	247	204	73-233 U/L
T. Bilirubin	1.6*	1.7*	1.4*	1.2	1.6*	0.6	0.9	0.6	0.0-1.3 mg/dl
Hemoglobin	16.6	15.1	15.5	16.8*	14.9	15.0	15.1	15.9	13.3-16.7GMS%
White Blood Count	4.3	4.1	5.5	4.3	3.9	5.9	9.9*	4.0	3.1-9.5th/cu mm
Lymphocytes	41	46	43	53	41	42	17*	34	19-59 %

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: The subject had symptoms of the common cold occurring 25 days after drug ingestion of 12 days duration. Throat culture was performed and was negative. Subject was otherwise asymptomatic and physical examination unchanged.

Formulation E-443: Four days after drug ingestion the subject experienced a traumatic conjunctivitis o.d. which cleared within 3 days. Five days after drug ingestion the subject sprained his ankle, examination was normal except for local tenderness and the subject became asymptomatic within a few days. Physical examination remained unchanged during the entire study except as noted above.

Code: 342 (cont.)

Abnormalities Comment: Laboratory abnormalities were minimal or inconsistent and not considered to be of clinical significance.

Conclusion: No adverse effect from ingestion of either formulation of WR 142,490·HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing	
FORMULATION:	B-512	E-443	CODE: 343
DOSING DATE:	3/6/79	4/24/79	GROUP: II
TIME DOSED:	0800	0800	AGE: 21
DOSE(mg/kg):	14.619	14.619	HEIGHT: 180.34 (cm
			WEIGHT: 68.40 (kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	1/23	3/5	3/6	3/7	3/12	4/23	4/24	4/25	4/30	6/4
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	42+
1. Symptoms		X								
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	42+	Normal Range
Glucose	83	114	82	90	89	94	98	56*	66-114 mg/dl
Carbon Dioxide	29	28	31	26	32*	29	29	30	23-31 mEq/L
LDH	189	211	185	254*	222	197	244	243*	73-233 U/L
Hemoglobin	17.0*	15.6	16.4	16.1	14.9	14.7	15.1	16.8*	13.3-16.7 GMSZ

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: On day 0 the subject experienced vasovagal reaction during venipuncture lasting 10-15 seconds. He was asymptomatic and the physical exam remained unchanged for the remainder of the study interval.

Formulation E-443: On admission for the second study interval the subject related that he had a splinter embedded under the right thumbnail 4 days previously and had received a tetanus toxoid injection. Examination revealed an abrasion of the right thumb at the nail. When interviewed 5 days after drug ingestion the subject stated that he noted, either before or after drug ingestion, ever since he bit into a hard apple, a tendency for his gums to bleed. The investigator, using a paper towel, abraded the gums and there was minimal bleeding from between the teeth of the lower jaw anteriorly. It was the impression of the investigator that

Code: 343 (cont.)

this was a local mechanical problem. Prothrombin time and partial thromboplastin times were performed which were normal. Platelet counts were normal throughout the study and the bleeding is considered to be a local dentist problem. There were no further gingival problems following the examination 5 days after drug ingestion. On final examination 40 days after drug ingestion the subject stated he had had a skin rash of the right upper and lower extremities and neck approximately 2 weeks previously. Examination by a local physician yielded a diagnosis of contact dermatitis. No specific therapy was used and no residual was present at the time of examination.

Abnormalities Comment:

Laboratory abnormalities were minimal or inconsistent and not considered of clinical significance.

Conclusion

No adverse effect attributed to ingestion of either formulation of WR 142,490 •HCl.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM NO.2 TO EXPERIMENT NO.3
SHORT-TERM SAFETY AND TOLERANCE OF WR 142,490·HCl
CLINICAL EVALUATION OF TWO FORMULATIONS
1000 mg DOSE LEVEL

	1st Dosing	2nd Dosing		
FORMULATION:	B-512	E-443	CODE:	344
DOSING DATE:	4/17/79	6/5/79	GROUP:	I
TIME DOSED:	0800	0800	AGE:	23
DOSE(mg/kg):	15.494	15.494	HEIGHT:	182.245(cr
			WEIGHT:	64.54 (k

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	4/12	4/16	4/17	4/18	4/24	6/4	6/5	6/6	6/1	7/16
STUDY DAY:	Scr	0	1	2	7	0+	1+	2+	7+	42+
1. Symptoms				X						
2. Physical Exam										
3. ECG										
4. Urinalysis										
5. Biochemistry										
6. CBC										
7. Platelets										

KEY: X=abnormal (X)=abnormal, unchanged
+indicates 2nd study interval (7 weeks after day 1, 1st study interval)

LABORATORY ABNORMALITIES SUMMARY:

STUDY DAY:	Screen	0	2	7	0+	2+	7+	42+	Normal Range
Glucose	77	87	92	83	62	86	72	117*	66-114 mg/dl
BUN	16	14	16	22*	23*	15	22*	15	9-21 mg/dl
CO_2	26	26	33*	29	26	27	26	26	23-31 mEq/L
Uric Acid	3.7*	4.0	3.5*	4.6	5.2	4.4	4.1	4.9	4-8 mg/dl
Phosphate	2.2*	3.0	2.9	2.1*	2.8	3.4	2.9	2.6	2.5-4.5mg/dl
Triglycerides	60	286*	74	61	30	81	62	76	0-207 mg/dl
SGOT	27	16	14	12	19	23	88*	10	73-233 U/L
LDH	175	187	149	150	182	171	247*	144	72-233 U/L

*denotes abnormality

Symptoms and Physical Findings:

Formulation B-512: Thirty-six hours post dose the subject reported abdominal discomfort which lasted 1-2 hours. Forty-eight hours post dose the subject reported slight nausea and "tightness" in the abdomen which lasted 1 hour. The physical examination was normal at this time, and it was not considered to be drug related. The subject also experienced "bizzare" dreams and fatigue during the night of day 2. Thereafter, the subject was asymptomatic and the physical examination remained unchanged during the study interval.

Code: 344 (cont.)

Formulation E-443: Forty-eight hours post dose the subject reported a slight "tickle" in his throat upon awakening; oral temperature was normal at this time and the symptom lasted 3-4 hours. The subject was otherwise asymptomatic and the physical examination remained unchanged during the study interval.

Abnormalities Comment: The subject had an elevated SGOT of 88 U/L on day 7, which remained abnormal on day 8, but was normal at 16 U/L when repeated on day 14. The serum LDH was also elevated on day 7 and upon repeat on day 8, but was normal at 153 U/L when drawn on day 14. Other deviations were minimal and inconsistent and not considered to be of clinical significance.

Conclusion: Elevated SGOT and LDH on day 7 of second study interval possibly but not probably related to ingestion of Formulation E-443 of WR 142,490·HCl.

BIO - MED, Inc.

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FINAL REPORT

ADDENDUM TO EXPERIMENT NUMBER 13

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

ADDENDUM TO EXPERIMENT NUMBER 13

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

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FINAL CLINICAL REPORT

ADDENDUM TO EXPERIMENT NUMBER 13

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

ABSTRACT

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

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

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

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

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

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

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FINAL REPORT

ADDENDUM TO EXPERIMENT NUMBER 13

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

INTRODUCTION:

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

WR 172,435·CH_3SO_3H clinical testing was initiated in a prior study by us using a standard double-blind, rising single dose level method. Eighteen oral administrations of drug and of placebo were used in a 2 x 2 design study. Eight dose levels were used ranging from 5 mg through 1000 mg. (Experiment Number 13: WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Single Oral Dose, Rising Dose Levels, 6 December 1978).

Transient lightheadedness or gastrointestinal symptoms occurred occasionally in subjects administered either placebo or drug at the lower dose levels. Temporary mild gastrointestinal symptoms were the only symptoms attributed to drug and occurred in 1 of 2 subjects receiving 800 mg and 2 of 4 subjects receiving 1000 mg WR 172,435·CH_3SO_3H. Leukocytosis without change in the differential count occurred in 9 study subjects. Seven of these received WR 172,435·CH_3SO_3H. Three of 4 subjects receiving 1000 mg had leukocytosis 24 hours post dosing which returned to normal by 48 hours: leukocytosis in these subjects was observed on day 2 with a return to normal leukocyte counts on day 3. The data suggest a dose effect, but the circumstances of the observations are inadequate for definite conclusions.

Preclinical toxicology studies in male rats also revealed leukocytosis, but this occurred only with drug schedules that produced severe tissue damage.* Leukocytosis is an expected finding in this situation. In rats receiving single oral doses of WR 172,435·CH_3SO_3H leukocytosis was not observed, but leukocyte counts were determined only at 72 hours.*

* Investigational New Drug Application, WR 172,435·CH_3SO_3H, the Walter Reed Army Institute of Research, October, 1977.

Two of four dogs receiving single oral doses of drug developed changes in differential white counts, one relative neutrophilia, and the other an increase in the number of band neutrophils. Both animals received doses of drug (420mg/kg, 620mg/kg) far in excess of those which would be used in humans.

METHODS AND MATERIALS:

Subject Selection and Qualification:

Twenty-four subjects, 21 to 45 years of age, weighing 50-100 kg and within 10% of their ideal body weight, 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 phosphatase, SGOT, SGPT, LDH, and total bilirubin.

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 in the presence of the investigator and a member of the Human Use Committee. Each participant was given the opportunity to ask questions. Following this, at the individual interview, the consent form was read and if the investigator and Human Use Committee member believed the subject understood his participation adequately to given informed consent, the subject was permitted to sign the consent form.

The subjects were housed in a controlled environment on Nursing Unit 5-W at the Washington Hospital Center for the intervals shown on the attached schematic.

Subject Assignment - Drug Administration:

1. A 2 x 2 double-blind design was used. A single dose level of 1000 mg was used.

2. One group of four subjects was tested during each study interval. Two subjects received active drug and two were given placebo.

3. Assignment to the double-blind study was random through lottery with the code sealed and available only for emergencies to the investigator and his staff.

4. The tablets were ingested in the presence of a member of the investigating team.

5. Emergencies: No medical emergencies occurred.

6. On the last study day for each subject final physical and laboratory evaluation was done. All abnormal findings were followed until normalcy, dependent upon subject compliance.

7. The schedule for drug administration is presented below:

DRUG ADMINISTRATION SCHEDULE

WR 172,435·CH_3SO_3H was given as follows, as a single oral dose:

STUDY GROUP	PLACEBO*	DRUG**	TOTAL DOSE (mg)
1	2	2	1000
2	2	2	1000
3	2	2	1000

As each group finished its dosing schedule, the individuals were observed through the 7th day of the study before the next dosing was initiated.

Drug administration by subject number is presented in Table 5, Page 34.

Each subject received four placebo tablets or four 250 mg tablets of the drug as provided by the Division of Experimental Therapeutics, WRAIR.

* WR 172,435·CH_3SO_3H, Lot #E-564, Tablets, 250 mg

**WR 172,435·CH_3SO_3H, Lot #E-562, Tablets, 250 mg

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

SCHEMATIC STUDY PLAN - SINGLE ORAL DOSE ADMINISTRATION
WR 172,435·CH_3SO_3H

Study Day	0*	1*	2*	3	4	7	14
Dose		X					
Physical Examination	X		X				X
Interview	X	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				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, CO_2, 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 were done as clinically indicated.

++CBC (differential and indices), Platelets, and Reticulocyte Count. Seven ml blood for these studies were obtained by venipuncture on day 0, on day 1 prior to and immediately after dosing, and at 4, 8, 12, 24, 48, 72 hours, and at 6 and 13 days after dosing.

Hematology Methods:

Subjects were asked to refrain from smoking one half hour prior to and until 24 hours after drug administration. Blood specimens were collected by venipuncture from the antecubital veins with care taken to minimize trauma and tourniquet time. Blood was collected in Becton-Dickinson® vacutainer tubes. EDTA was used as the anticoagulant for the hematology studies.

The determinations were performed in the hematology laboratory of the Washington Hospital Center. Tests were done within 6 hours of receipt of the blood. Red cell counts, hemoglobin level, hematocrit level, red cell indices and white cell counts were determined using a Coulter Counter, Model S. Scientific Product diluents were used for diluting the blood samples (Isotonic Buffered Saline; Automated Lysing and Hemoglobin Reagent). All white cell counts were determined in duplicate. Platelet counts were determined on a Coulter Thrombocounter. Blood films for differential white cell counting were made by the slide method and stained with Wright's stain as outlined in William's Textbook of Hematology.[1] Three-hundred cells were counted to determine the white cell differential. Reticulocyte count was done according to the method outlined in William's Textbook of Hematology.[1]

RESULTS:

Each of the 12 subjects enrolled completed the study. By the time 12 subjects were completed, subjects were apparently separable into two groups on the basis of symptoms and white blood counts. With the concurrence of the Clinical Monitor, the codes were broken after 12 subjects were observed, and the apparent separation into drug and placebo group was confirmed. Therefore, the study was terminated.

Symptoms:

Symptoms for each subject are tabulated in Table 1.

In this 12 subject double blind study, symptomatology was strikingly different in the two groups. There were no clinically significant symptoms reported by the subjects receiving placebo. Each subject receiving drug had complaints. All had gastrointestinal discomfort. Complaints included abdominal pain, nausea, diarrhea and headache, another diarrhea alone, another had nausea, diarrhea and headache.

Symptoms were transitory; all subjects felt well at the conclusion of the study.

Physical Findings:

No changes attributed to drug administration occurred in any subject.

[1] William J. Williams et al., Hematology, (New York, New York, McGraw-Hill Book Co., 1977)

Laboratory Values:

All post-dosing, white blood cell counts and differentials were done in duplicate.

Table 2 (pages 15 through 20) lists those laboratory values found to be abnormal for each subject. Where any value was found to be abnormal, all values for that laboratory test are reported for that subject.

Values for each total white cell count and differential count for each subject are displayed on pages 21-32.

Electrocardiography and Phototoxicity:

Findings are reported on Table 4 (page 33). No abnormalities of the electrocardiogram were detected and phototoxicity was not seen.

DISCUSSION

Twelve subjects were admitted to the study. Six subjects were given 1000 mg of WR 172,435·CH_3SO_3H; Six were given placebo. The study was double-blind, conducted in groups of 4 subjects each. Total white blood cell counts and differentials were performed immediately before dosing (T_0), and repeated at 5 minutes, 4, 8,12, 24, 48 and 72 hours.

Table A highlights the differences in total white blood cell counts between the drug and placebo groups:

The mean white count at time zero was slightly higher in the Drug group than in the placebo group. Twelve hours later, the mean white count in the group receiving drug had more than doubled while in the placebo group, the mean white count increased by one-third. Examination of the discreet values at T_0 and T_{12} shows this trend to be evident for each subject (See "change" and "T_{12}/T_0" columns").

TABLE A

Addendum to Experiment Number 13

Total White Blood Cell Counts (x 1000) Prior to Dosing(PTD) and 12 Hours after Ingestion (T_{12h}) of WR 172,435·CH_3SO_3H or Placebo

	DRUG (WR 172,435·CH_3SO_3H)					PLACEBO				
Group	Subj.#	T_0*	T_{12h}	Change	T_{12}/T_0	Subj.#	T_0	T_{12h}	Change	T_{12}/T_0
I	(372)	8.7	16.25	+7.55	1.9	(373)	6.25	9.25	+3.0	1.48
	(375)	4.7	11.1	+6.4	2.3	(374)	7.5	7.85	+0.35	1.0
II	(377)	5.8	14.6	+8.8	2.5	(376)	5.1	6.6	+1.5	1.2
	(379)	6.15	14.5	+8.35	2.3	(378)	4.7	7.2	+2.4	1.5
III	(380)	6.2	13.75	+7.55	2.2	(382)	4.2	6.35	+2.15	1.5
	(381)	7.45	13.85	+6.4	1.8	(383)	5.2	6.1	+0.9	1.2
TOTALS		39.0	84.05	45.5	13.00		32.95	43.35	10.3	7.88
	Mean	6.50	14.00	7.46	2.16		5.49	7.22	1.71	1.31
	SD	1.39	1.68	1.00	.26		1.19	1.17	.98	0.21
	Error	.56	.68	.41	.10		0.48	0.48	0.40	0.08

* PTD

The proximity of the leukocytosis to drug administration (within twelve hours), and the regularity of occurrences (six of six subjects), along with the absence of leukocytosis in the placebo group, lead to the conclusion that the leukocytosis was induced by the drug formulation administered.

Table B "Change in the ratio of Neutrophils and Lymphocytes, T_0 to T_{12}" (page 9) was constructed to examine the nature of the observed leukocytosis.

In every instance of drug ingestion the ratio of neutrophils/lymphocytes increased by an order of magnitude. In no instance did that occur in the placebo group. Thus the leukocytosis is marked by an increase in circulating neutrophils.

Other variables related to hematopoesis were inspected for trends. Reticulocyte counts were highly variable in both groups, and must be discounted as unreliable. Platelet counts showed no discernible trends.

Table B

Addendum to Experiment Number 13

Change in the Ratio of % Neutrophils and Lymphocytes from T_0 to T_{12} after Ingestion of WR 172.435·CH_3SO_3H or Placebo

DRUG (WR 172,435·CH_3SO_3H)					PLACEBO			
Subj. #	T_0	%Lymphs	%Neutrophils	Neutrophil/Lymphs	Subj. #	%Lymphs	%Neutrophils	Neutrophil/Lymphs
381	T_0	25.5	70	2.74	383	24.5	62	2.53
	T_{12}	17.5	73.5	4.2		29.5	60.5	2.05
380	T_0	29.5	65	2.20	382	31	64	2.06
	T_{12}	9.5	84	8.89		23.5	70.5	3.00
379	T_0	31	54	1.74	378	62	29	.46
	T_{12}	17.5	73.5	4.20		71	23.5	.33
377	T_0	43.5	46	1.05	376	24	72	3.0
	T_{12}	12	80.5	6.7		35	57	1.62
375	T_0	34	52	1.52	374	29	65	2.24
	T_{12}	14.5	83.5	5.75		36.5	56	1.53
372	T_0	28	61	2.17	373	45	54	1.25
	T_{12}	14	83.5	5.96		54	36.5	.67

CONCLUSIONS AND RECOMMENDATIONS

This study was discontinued after only 12 of 24 subjects had participated because the investigators suspected that leukocytosis and gastrointestinal symptoms were occurring in the drug group. The code was broken, and as the preceding data attest, the suspicion of the investigators is borne out.

Thus, the gastrointestinal symptoms and leukocytosis associated with the drug at 1000 mg p.o. as previously reported in Experiment Number 13 are confirmed.

There are several possible explanations for the transitory leukocytosis with an absolute increase in neutrophils strongly associated with administration of the subject drug.

1) An increase in bone marrow production of neutrophils.

2) An increase in the half-life of circulating neutrophils with normal bone marrow production,

3) A mobilization of sequestered mature neutrophils into the circulating pool from extra-vascular and/or intravascular spaces.

Increased bone marrow production seems unlikely in that bands and other immature forms of neutrophils were not seen in association with the leukocytosis. One cannot rule out sudden release of mature neutrophils from the marrow.

An increased half-life of the neutrophil seems unlikely in that the peak of leukocytosis occurred 12 hours after drug administration, too soon for a longer half-life to produce a doubling of the leukocyte count.

The last possibility is the most attractive, although one could only speculate about the nature of the drug effect were it proven to be the case.

Each possibility could be explored and any could well represent some interesting attributes of the drug or of the drug formulation.

From a practical point of view of WR 172,435·CH_3SO_3H as an anti-malarial, the issue is whether repeated administration of the drug produces a sustained or even an increasing leukocytosis. Leukocytosis associated with multiple doses may produce serious obstacles to further development and study.

As a reasonable next step, we recommend a study that establishes 1) the minimal multiple dose level that will produce leukocytosis and 2) the pattern of leukocytosis (i.e. sustained, increasing, or return toward normal) with multiple doses of the drug.

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EXPLANATION FOR POTENTIAL SUBJECTS
ADDENDUM TO EXPERIMENT NO. 13

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

GENTLEMEN:

The study for which you have applied involves taking by mouth the antimalarial drug WR 172,435·CH_3SO_3H or a placebo containing no active drug. WR 172,435·CH_3SO_3H has previously undergone safety and tolerance testing at this facility.

Animal studies suggest that WR 172,435·CH_3SO_3H 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 Department, sponsors of this study, and the Food and Drug Administration have approved WR 172,435·CH_3SO_3H for clinical testing in human subjects.

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

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

Transient lightheadedness or gastrointestinal symptoms occurred occasionally in subjects administered either placebo or drug at the lower dose levels. Temporary mild gastrointestinal symptoms were the only symptoms attributed to drug and occurred in 1 of 2 subjects receiving 800 mg and 2 of 4 subjects receiving 1000 mg WR 172,435·CH_3SO_3H. Leukocytosis without change in the differential count occurred in 9 study subjects. Seven of these received WR 172,435·CH_3SO_3H. Three of 4 subjects receiving 1000 mg had leukocytosis 24 hours post dosing which returned to normal by 48 hours: leukocytosis in these subjects was observed on day 2 with a return to normal leukocyte counts on day 3. The data suggest a dose effect, but the small number of observations are inadequate for definite conclusions.

Leukocytes are white blood cells of which there are two major series according to origin. One series is produced primarily by the bone marrow and the other primarily by the lymph glands. In our previous study there was a transient increase in the total number of leukocytes reported without a change in the proportion of one series as compared with the other. Since the two series are produced by different organ systems susceptible to different stimuli, there is a question as to whether the increase was real or due to technical error.

The purpose of the study for which you are being considered is to determine if the transient increase in leukocytes reported is real or a laboratory error.

The study method used in this study is called a double-blind design. Four subjects will be admitted to the research unit at a time. Two will receive drug and two 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 will be broken and you will be told if you received the drug. The amount of drug given is 1000 mg orally. The study plan is presented schematically below.

SCHEMATIC STUDY PLAN - SINGLE ORAL DOSE ADMINISTRATION
WR 172,435·CH_3SO_3H

Study Day	0*	1*	2*	3	4	7	14
Dose		X					
Physical Examination	X		X				X
Interview	X	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				X
Laboratory Tests+	X		X	X		X	X
Hematologic Studies++	X	X	X	X	X	X	X

*Controlled Environment - You will remain in the study unit from morning Day 0 to morning Day 3.

+Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2, 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 on day 0, on day 1 prior to and immediately after dosing, and at 4, 8, 12, 24, 48, 72 hours, and at 6 and 13 days after dosing.

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·CH_3SO_3H 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 duraton.

The Human Use Committee is also looking after your safety. It insures 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 Washington Hospital Center. After members of the investigating team and Human Use Committee 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 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 your consent at any time without prejudice.

_____
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: Effect on the Total and Differential Leukocyte Counts Following a Single Oral 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 Dr. _____, and are set forth in the document titled "EXPLANATION FOR POTENTIAL SUBJECTS, Addendum to Experiment No. 13: WR 172,435·CH_3SO_3H: Short Term Dosage, Safety and Tolerance: Effect on the Total and Differential Leukocyte Counts Following a Single Oral Dose," 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 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	

ADDENDUM TO EXPERIMENT NO. 13: WR 172,435·CH_3SO_3H: SHORT TERM DOSAGE, SAFETY AND TOLERANCE: EFFECT ON THE TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING ORAL ADMINISTRATION

TABLE I: Symptoms Possibly Drug Related

GROUP	CODE NO.	DRUG/ PLACEBO	Abdominal Discomfort		Loose Stools		Emesis		Lightheadedness		Headache		Other	
			Onset*	Duration+	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration	Other	Duration
I	372	D	?	2.0					?	2.0				
	373	P	NONE											
	374	P	NONE											
	375	D	4.0 "gassy feeling"	5.0	4.0	<0.5	9.0	0.2						
II	376	P	NONE											
	377	D			9.0 3 semi-formed to loose stools	.30					6.0 dull, generalized	7.0	2.25 urinary 10.0 chilliness	5.0 frequency 2.0
	378	P	NONE											
	379	D	1.0 abdominal cramps, recurrent nausea	23	1.25 3 loose stools	12.5					14.0 mild	2.0 frontal		
III	380	D	6.5	7.5	6.5 4 loose stools cramping	1.5							9.0 lethargy	5.0
	381	D	9.0 cramping	6.0 & flatus									(-)2.0 mental	27 "fuzziness"
	382	P	NONE											
	383	P	NONE											

* :Approximate onset hours after dosing
\+ :Approximate duration hours after onset
0:0 hours:minutes

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

H = High -- Not Done
L = Low

Group	Code Number	Drug/ Placebo	Abnormal Test	SCR	0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normal Values
				Study Day												
I	372	Drug	Glucose	102	82						72	88		130-H	93	66-114mg/dl
			Alka Phos	76	96H						90	88		83	85	26-94 u/l
			Hct	47.0	51.1H	50.3H	49.3 48.9	47.1 46.5	49.8 49.7	49.1 48.8	47.7 48.2	45.9 46.6	45.1 45.5	45.9 44.2	49.1 48.3	40-50 Vol.%
			Hgb	16.5	17.4H	17.1H	17H 17H	16.2 15.8	17.2H 17.2H	16.7 16.7	16.6 16.5	16.2 16.3	15.8 15.8	15.5 15.6	16.1 16.4	13.3-16.7GMS%
			RBC	5.38	5.73H	5.62	5.60 5.53	5.31 5.27	5.65 5.64	5.48 5.55	5.43 5.39	5.30 5.33	5.18 5.22	5.22 5.05	5.43 5.45	mill/ 4.3-5.7cu.mm.
			Platelets (000)	268	364	325	351	375	364	480	362	300	297	295	328	thous/ 102-426 cc.
			Retic Ct.		1.5	2.3H	1.6H	--	—	.9 1.0	1.8H	2.3H	2.8H 2.4H	2.0H	1.8H	0.5-1.5%
			WBC	7.2	7.4	8.7	7.5 7.6	8.8 9.1	13.5H 13.3H	16.5H 16.0H	11.7H 11.4H	6.8 7.1	5.2 5.2	7.2 7.1	6.0 6.1	thous/ 3.1-9.5cu mm
			Lymph	32	27	28	20 33	21 28	14L 15L	14L 14L	16L 14L	21 25	20 23	28 29	22 23	19-59%
			Seg	62	67	61	64 57	70 63	79 75	83H 84H	77 75	68 61	69 62	64 61	75 73	36-80%
			ATL	0	0	2H	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 %
			Mono	4	5	4	10 11H	7 7	6 8	2 2	6 8	10 13H	10 11H	5 7	1 2	0-10
	373	Placebo	SGPT	31	42						56H	65H		38	31	0-47 u/l
			Retic Ct	--	1.1	0.9	1.5	0.8	2.0H	2.6H	1.3	1.0	1.3	0.7	2.4H	0.5-1.5 %
			WBC	6.1	5.4 5.3	6.2 6.3	6.1 6.2	6.8 6.5	8.7 9.0	9.3 9.2	7.0 7.2	9.7H 9.6H	8.0 8.2	7.6 7.8	6.2 6.2	thous/ 3.1-9.5 cu mm
			Lymph	33	40 34	44 46	26 30	32 35	35 38	54 54	58 54	24 24	17L 16L	36 33	44 42	19-59 %
			ATL	0	0 0	2H 3H	2H 0	0 0	0 0	0 0	0 0	0 0	2H 2H	0 0	0 0	0 %

H = High — Not Done
L = Low

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

Group	Code Number	Drug/ Placebo	Abnormal Test	Study Day SCR	PTD	5"	4°	8°	12°	24°	48°	72°			Normal Values
					0	1				2	3	4	7	14	
I	374	Placebo	BUN	20	20					24-H	26-H		23-H	12	9-21 mg/dl
			Potassium	3.3L	3.8					3.9	3.9		4.6	4.0	3.6-5.2 mEq/L
			Uric Acid	5.8	6.9					6.1	6.1		8.2-H	6.1	4-8 mg/dl
			T.Protein	7.2	6.7					6.6	6.2L		6.4	6.9	6.4-8.0 g/dl
			Calcium	9.6	9.4					9.6	9.5		8.9L	9.4	9.0-10.9mg/dl
			Retic Ct	--	0.9	1.7H	1.8H	--	--	1.0 1.1	1.6H	1.1	2.1H	1.0	0.8	0.5-1.5 %
			Lymph	23	24	29	33 28	32 39	26 36	35 36	33 38	27 26	32 33	34 28	18L 25	19-59%
			Eosin	3	4	4	4 4	5 2	1 0	2 1	4 4	2 0	0 0	1 2	6H 5	0-5 %
			ATL	0	2H	2H	0 0	0 0	0 0	0 0	0 0	0 0	3H 3H	0 0	0 0	0 %
			Mono	9	5	7	11H 10	8 8	5 6	6 7	5 5	8 6	4 6	8 8	7 12H	0-10
	375	Drug	Chloride	103	99						96L	96L		99	100	98-110 mEq/L
			CO_2	29	29						32H	31		31	31	23-31 mEq/L
			LDH	158	192						197	248H		175	221	73-233 u/l
			Retic Ct	--	0.1L	0.6	0.2L	--	--	0.7 0.6	1.6H	1.1	0.7 0.7	1.2	0.3L	0.5-1.5 %
			WBC	5.0	4.9	4.7	5.2 5.3	5.5 5.6	8.0 8.3	10.8H 11.4H	7.7 7.6	5.4 5.4	4.9 5.1	4.2 4.2	4.8 4.8	thous/ 3.1-9.5cu mm
			Lymph	22	26	34	36 39	38 39	21 23	15H 14H	19 22	23 31	35 31	28 25	20 25	19-59 %
			Seg	66	65	52	50 48	52 52	72 70	82H 85H	74 76	65 57	53 56	58 65	68 65	36-80 %
			Eosin	3	4	5	3 6H	6H 5	2 2	0 0	4 1	3 2	3 4	1 2	5 3	0-5%
			Mono	8	5	8	10 7	3 4	5 4	3 0	3 0	9 10	8 8	13H 7	5 5	0-10 %

H = High — Not Done

L = Low

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

Group	Code Number	Drug/ Placebo	Abnormal Test	SCR	Study Day 0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	8	14	Normal Values
II	376	Placebo	T.Protein		6.4						6.1L	6.5		6.2L	6.3L	6.4-8.0 g/dl
			Globulin		1.5L						1.50L	1.70L		1.7L	1.6L	1.8-3.4 g/dl
			T.Bili		0.9						0.4	0.4		1.5H	1.3	0.0-1.3 mg/dl
			Glucose		95						95	88		70	61L	66-114 mg/dl
			U/A Prot		N						TrH	--		N	N	N
			Retic Ct		1.6H	1.4	2.0H	0.4L	2.2H	2.4H	1.8H	1.5	1.7H	2.7H	2.1H	0-1.5 %
			Eosin		2	5	3	1	3	5	0	0	2	2	0	
					2	7H	5	2	3	4	1	2	1	3	6H	0-5 %
			Mono		2	2	5	2	6	5	5	2	6	5	3	
					1	4	11H	2	2	2	4	3	0	7	6	0-10 %
-17-	377	Drug	Glucose	90	84						64L	83		Day 7 103	87	66-114 mg/dl
			Sodium	136	141						140	141		140	140	137-151 mEq/L
			T.Prot	6.5	6.0L						6.5	6.3L		6.3L	6.5	6.4-8.0 g/dl
			Hct			39.9L	38.6L	38.7L	42.3	43.4	39.6L	42.8	42.5	41.0	41.7	
				42.0	39.3L	39.0L	38.3L	38.3L	42.1	43.8	40.5	42.8	42.9	41.6	41.3	40-50 Vol %
			Hgb			13.3	13.0L	13.0L	14.5	14.8	13.7	14.2	14.5	13.8	14.0	
				14.4	13.2L	13.3	13.0L	13.0L	14.6	14.8	13.6	14.3	14.5	13.9	13.9	13.3-16.7GMS%
			Retic Ct		1.4	1.6H	0.8	1.2	1.6H	2.2H	1.3	2.0H	1.0	0.8	1.8H	0.5-1.5 %
			WBC		4.0	5.9	4.8	5.8	8.6	14.4H	10.0H	7.6	6.2	6.5	7.0	thous/
				5.3	4.0	5.7	4.7	5.9	8.6	14.8H	10.0H	7.7	6.3	6.1	7.2	3.1-9.5cu mm
			Lymph		42	44	36	44	28	13L	19	22	36	29	25	
				29	46	43	34	41	25	11L	25	28	28	25	28	19-59 %
			Seg		46	46	53	47	63	79	75	66	55	61	62	
				60	44	46	59	51	62	82H	71	67	59	67	63	36-80 %
			ATL		0	0	0	0	0	0	0	0	3H	0	0	
				0	0	2H	0	0	0	0	2H	0	2H	0	0	0 %
			Mono		10	8	9	7	7	6	4	9	3	8	13H	
				8	10	8	7	8	9	6	2	5	8	6	7	0-10 %

H = High — Not Done

L = Low

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

Group	Code Number	Drug/ Placebo	Abnormal Test	Study Day SCR	0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normal Values
II	379	Drug	UA-Prot	N	N						Tr-H			N	N	N
			Retic Ct	—	1.4	0L	0.5	1.3	1.4	1.8H	1.1	1.1	0.8	1.4	1.0	0.5-1.5 %
			WBC	7.5	6.5 6.5	6.1 6.2	6.3 6.5	7.4 7.3	9.1 9.3	14.3H 14.7H	10.7H 10.6H	6.7 6.6	6.8 6.9	7.2 7.3	6.1 5.9	thous/ 3.1-9.5cu mm
			Lymph	31	34 39	40 40	40 44	44 41	32 29	20 15L	21 23	39 30	43 39	43 38	49 41	19-59 %
			Eosin	3	4 3	5 4	6H 5	5 2	0 1	0 0	2 3	1 2	5 7H	4 1	0 2	0-5 %
	378	Placebo	SGPT	25	27						40	50H		43	39	0-47 u/L
			Glucose	79	82						73	79		97	128H	66-114 mg/dl
			Potassium	4.0	4.5						4.5	4.3		4.1	3.5L	3.6-5.2 mEq/L
			Sodium	135L	136L						138	139		138	140	137-151 mEq/L
			Calcium	9.2	9.6						9.6	9.6		8.9L	9.6	9.0-10.9mg/dl
			Hct	46.9	45.2	50.4H 49.9	48.0 48.7	48.5 48.5	43.8 44.1	47.0 46.5	47.4 47.5	48.2 48.3	44.1 43.9	44.1 44.4	46.4 45.9	40-50 %
			Hgb	15.7	15.1	16.9H 16.9H	16.0 15.9	16.0 16.1	14.7 14.7	15.5 15.6	15.8 15.9	15.8 15.9	14.6 14.8	14.1 14.4	15.1 15.1	13.3-16.7GMS%
			RBC	5.84H	5.57	6.28H 6.23H	5.86H 5.90H	5.96H 6.00H	5.41 5.41	5.80H 5.77H	5.82H 5.87H	5.87H 5.93H	4.94 5.07	5.37 5.44	5.64 5.64	mill/ 4.3-5.7 cu mm
			MCV	80L	82	81L 81L	83 83	82 82	82 82	82 81L	82 82	83 82	90 87	83 82	83 82	cu 82-98 microns
			MCH	26.9L	26.5L	26.3L 26.5L	26.6L 26.3L	26.3L 26.2L	26.6L 26.7L	26.3L 26.5L	26.5L 26.5L	26.2L 26.1L	28.9 28.4	25.6L 25.8L	26.2L 26.0L	micromicro 27-33 GM
			Retic Ct	—	1.2	1.4	1.0	1.0	1.8H	0.7	0.6	0.0L	0.8	0.6	1.0	0.5-1.5 %
			Lymph	25	48 51	64H 60H	64H 58	69H 68H	57 57	72H 70H	58 62H	56 62H	30 28	47 55	36 37	19-59 %
			Seg	69	40 41	26L 32L	31L 34L	26L 26L	34L 38	21L 26L	38 32L	39 32L	60 61	43 37	51 50	36-80 %
			Eosin	0	6H 0	2 1	0 3	0 2	3 3	3 1	0 0	1 0	2 1	2 0	1 1	0-5 %
			ATL	0	0 0	3H 2H	2H 0	0 0	0 0	0 0	2H 3H	2H 2H	0 0	0 0	0 0	0 %

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

H = High — Not Done
L = Low

Group	Code Number	Drug/ Placebo	Abnormal Test	SCR	0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	15	Normal Values
III	380	Drug	CO_2	29	29						32H	30		29	28	23-31 mEq/L
			T.Protein	5.9L	6.0L						6.1L	5.8L		5.9L	6.9	6.4-8.0 g/dl
			Globulin	1.7L	1.8						1.7L	1.6L		1.5L	2.1	1.8-3.4 g/dl
			Calcium	8.8L	8.9L						9.1	8.6L		9.0	9.2	9.0-10.9 mg/dl
			Potassium	3.6	3.7						3.9	3.7		3.5L	4.5	3.6-5.2 mEq/L
			Retic Ct		0.9	0.9	0.9	1.2	2.1H	2.6H	1.1.	1.3	0.7	0.8	1.3	0.5-1.5 %
			WBC		5.3	6.2	5.5	6.8	12.9H	13.5H	6.1	5.6	5.0	5.8	6.4	thous/
				6.5	5.1	6.2	5.4	6.6	12.8H	14.0H	5.9	5.6	5.2	5.6	6.3	3.1-9.5 cu mm
			Lymph		31	32	30	22	12L	7L	32	28	37	42	22	
				34	33	27	33	27	14L	12L	34	43	38	42	27	19-59 %
			Seg		57	62	64	68	80	86H	60	58	52	50	67	
				56	56	68	64	62	78	82H	55	53	50	47	65	36-80 %
III	381	Drug	Glucose	90	93						62L	82		NS	85	66-114 mg/dl
			Uric Acid	7.9	8.1H						7.2	7.6		NS	8.5H	4-8 mg/dl
			T.Protein	6.1L	6.4						6.1L	6.2L		NS	6.1L	6.4-8.0 g/dl
			Globulin	1.8	1.8						1.7L	1.6L		NS	1.7L	1.8-3.4 g/dl
			LDH	126	200						282H	179		NS	142	73-233 u/l
			Retic Ct		0.6	0.5	0.4L	1.5	1.8H	1.9H 1.7H	1.1	0.4L	NS	NS	0.7	0.5-1.5 %
			WBC		7.7	7.5	7.4	8.2	11.8H	13.8H	9.1	7.0			7.1	thous/
				8.0	7.6	7.4	7.4	8.4	11.6H	13.9H	9.2	7.1	NS	NS	7.2	3.1-9.5 cu mm
			Lymph		28	28	23	24	18L	18L	24	22			27	
				18L	26	23	28	24	22	17L	20	21	NS	NS	23	19-59 %
			Mono		1	11H	5	7	5	7	2	5			10	
				11H	5	13H	9	5	5	10	8	9	NS	NS	8	0-10 %

NS = No Show

H = High -- Not Done

L = Low

ABNORMALITIES TABLE - ADDENDUM TO EXPERIMENT # 13

Group	Code Number	Drug/ Placebo	Abnormal Test	Study Day SCR	0	PTD 1	5"	4°	8°	12°	24° 2	4 ° 3	72° 4	7	15	Normal Values
III	382	Placebo	Potassium	3.9	4.2						3.8	3.6		3.4L	3.7	3.6-5.2 mEq/L
			CO_2	29	32H						32H	30		28	32H	23-31 mEq/L
			Phosphate	2.2L	2.2L						3.3	3.4		2.3L	2.8	2.5-4.5 mg/dl
			Alka Phos	101H	95H						100H	93		77	89	26-94 u/l
			Chloride	101	104						99	97L		101	100	98-110 mEq/L
			T.Bili	0.9	1.3						0.9	1.0		1.3	1.5H	0.0-1.3 mg/dl
			Retic Ct	--	0.3L	1.4	0.9	0.6	2.4H	2.0H	1.5	0.8	1.9H	1.6H	2.1H	0.5-1.5 %
			Lymph	37	30 36	28 34	25 15L	17L 21	19 17L	26 21	34 35	26 30	25 18L	22 26	20 18L	19-59 %
			ATL	0	0 0	2H 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 %
			Mono	3	5 7	2 3	9 13H	5 3	8 4	5 6	3 4	5 4	4 4	10 11H	1 1	0-10 %
III	383	Placebo	T.Protein	7.0	6.8						7.0	6.6		6.3L	6.7	6.4-8.0 g/dl
			Phosphate	3.4	2.3L						3.0	3.4		2.9	2.6	2.5-4.5 mg/dl
			Hgb	15.4	14.5 14.6	14.9 14.9	17.4H 17.4H	14.9 15.1	14.0 14.0	14.3 14.3	15.5 15.5	15.2 15.1	14.8 14.9	14.0 14.0	14.4 14.7	13.3-16.7GMS%
			RBC	5.23	4.99 5.08	5.25 5.22	6.02H 6.05H	5.08 5.18	4.80 4.84	4.93 4.95	5.41 5.42	5.17 5.16	5.06 5.04	4.82 4.89	4.84 4.92	mill/ 4.30-5.7 cumm
			Hct	44.4	43.7 44.3	45.3 45.6	51.9H 52.7H	45.1 45.6	41.6 41.3	43.0 43.2	46.3 46.6	44.7 44.6	43.5 43.3	42.7 42.8	41.6 42.9	40-50 Vol %
			Retic Ct	--	1.2	0.6	1.2	1.4	1.9H	1.8H	1.3	1.5	1.4	2.8H	1.2	0.5-1.5 %
			Lymph	25	17L 18L	22 27	14L 13L	18L 17L	24 22	32 27	24 21	31 25	25 35	16L 20	20 33	19-59 %
			Seg	63	75 72	63 61	84H 84H	76 77	72 70	59 62	60 61	65 70	62 56	71 73	63 55	36-80 %
			Eosin	4	4 2	4 3	0 0	1 2	2 4	0 2	3 5	0 4	3 4	1 0	8H 5	0-5 %
			ATL	0	0 0	0 0	0 0	0 0	0 0	0 0	2H 0	0 0	0 0	0 0	0 0	0 %
			Mono	4	4 7	10 9	2 2	4 4	3 4	4 9	8 10	4 1	9 5	12H 8	9 7	0-10 %

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 10-16-79 Code: 372
Dose Per Kg. 14.60mg/kg Time Dosed: 1425 Group: I
Drug Height: 163.83 cm Weight: 68.49 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	7.5	8.8	13.5	16.5	11.7	6.8	5.2
SAMPLE 2	7.6	9.1	13.3	16.0	11.4	7.1	5.2
% SEGS							
SAMPLE 1	64	70	79	83	77	68	69
SAMPLE 2	57	63	75	84	55	61	62
% LYMPHS							
SAMPLE 1	20	21	14	14	16	21	20
SAMPLE 2	32	28	15	14	14	25	23

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 10-23-79 Code: 373
Dose Per Kg. 0 mg/kg Time Dosed: 0945 Group: I
Placebo Height: 172.72 cm Weight: 60.10 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	6.1	6.8	8.7	9.3	7.0	9.7	8.0
SAMPLE 2	6.2	6.5	9.0	9.2	7.2	9.6	8.2
% SEGS							
SAMPLE 1	60	57	56	36	39	66	72
SAMPLE 2	63	54	55	37	39	69	74
% LYMPHS							
SAMPLE 1	26	32	35	54	58	24	17
SAMPLE 2	30	35	38	54	54	24	16

ADDENDUM TO EXPERIMENT NO.#13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 10-16-79 Code: 374
Dose Per Kg. 0 mg/kg Time Dosed 1430 Group: I
Placebo Height: 165.10 cm Weight: 64.64 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	7.0	7.6	7.8	7.9	6.3	6.9	6.5
SAMPLE 2	7.1	7.6	7.7	7.8	6.2	6.7	6.4
% SEGS							
SAMPLE 1	50	54	67	57	58	62	61
SAMPLE 2	57	51	58	55	53	68	57
% LYMPHS							
SAMPLE 1	33	32	26	35	33	27	32
SAMPLE 2	28	39	36	36	38	26	33

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435 CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 10-16-79 Code: 375
Dose Per Kg. 12.56mg/kg Time Dosed: 1430 Group: I
Drug Height: 180.98 cm Weight: 79.61 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	5.2	5.5	8.0	10.8	7.7	5.4	4.9
SAMPLE 2	5.3	5.6	8.3	11.4	7.6	5.4	5.1
% SEGS							
SAMPLE 1	50	52	72	82	74	67	53
SAMPLE 2	48	52	70	85	76	57	56
% LYMPHS							
SAMPLE 1	36	38	21	15	19	23	35
SAMPLE 2	39	39	23	14	22	31	31

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 11-6-79 Code: 376
Dose Per Kg. 0 mg/kg Time Dosed: 0800 Group: II
Placebo Height: 180.34 cm Weight: 71.21 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	5.7	5.7	5.9	6.6	7.1	7.1	6.3
SAMPLE 2	5.9	5.6	6.0	6.6	7.1	7.1	6.6
% SEGS							
SAMPLE 1	50	67	59	54	49	47	60
SAMPLE 2	45	68	62	60	49	51	65
% LYMPHS							
SAMPLE 1	41	33	32	36	44	47	30
SAMPLE 2	37	28	33	34	46	51	29

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 10-23-79 Code: 377
Dose Per Kg. 13.48mg/kg Time Dosed: 0945 Group: II
Drug Height: 178.44 cm Weight: 74.16 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	4.8	5.8	8.6	14.4	10.0	7.6	6.2
SAMPLE 2	4.7	5.9	8.6	14.8	10.0	7.7	6.3
% SEGS							
SAMPLE 1	53	47	63	79	75	66	55
SAMPLE 2	59	51	62	82	71	67	59
% LYMPHS							
SAMPLE 1	36	44	28	13	19	22	36
SAMPLE 2	34	41	25	11	25	28	28

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 10-23-79 Code: 378
Dose Per Kg. 0 mg/kg Time Dosed: 0945 Group: II
Placebo Height: 177.80 cm Weight: 77.11 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	4.4	6.5	6.2	7.3	5.5	5.3	7.4
SAMPLE 2	4.5	6.2	6.1	7.1	5.4	5.5	7.5
% SEGS							
SAMPLE 1	31	26	34	21	38	32	60
SAMPLE 2	34	26	38	26	32	39	61
% LYMPHS							
SAMPLE 1	64	69	57	72	58	56	30
SAMPLE 2	58	68	57	70	62	62	28

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 11-6-79 Code: 379
Dose Per Kg. 16.96 mg/kg Time Dosed: 0800 Group: II
Drug Height: 165.10 cm Weight: 58.97 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	6.3	7.4	9.1	14.3	10.7	6.7	6.8
SAMPLE 2	6.5	7.3	9.3	14.7	10.6	6.6	6.9
% SEGS							
SAMPLE 1	47	51	61	70	68	52	44
SAMPLE 2	52	56	65	77	65	56	47
% LYMPHS							
SAMPLE 1	40	44	32	20	21	39	43
SAMPLE 2	44	31	29	15	23	30	39

ADDENDUM TO EXPERIMENT NO. #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 10-30-79 Code: 380
Dose Per Kg. 12.60mg/kg Time Dosed: 0800 Group: III
Drug Height: 184.15 cm Weight: 79.38 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	5.5	6.8	12.9	13.5	6.1	5.6	5.0
SAMPLE 2	5.4	6.6	12.8	14.0	5.9	5.6	5.2
% SEGS							
SAMPLE 1	64	68	80	86	60	58	52
SAMPLE 2	64	62	78	82	55	53	50
% LYMPHS							
SAMPLE 1	30	22	12	7	32	28	37
SAMPLE 2	33	27	14	12	34	43	38

ADDENDUM TO EXPERIMENT NO.#13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 1000 mg Dosing Date 10-30-79 Code: 381
Dose Per Kg. 16.83mg/kg Time Dosed: 0800 Group: III
Drug Height: 165.10 cm Weight: 59.42 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	7.4	8.2	11.8	13.8	9.1	7.0	--
SAMPLE 2	7.4	8.4	11.6	13.9	9.2	7.1	--
% SEGS							
SAMPLE 1	68	68	75	75	73	67	--
SAMPLE 2	58	68	72	72	68	69	--
% LYMPHS							
SAMPLE 1	23	24	18	18	24	22	--
SAMPLE 2	28	24	22	17	20	21	--

ADDENDUM TO EXPERIMENT NO.#13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 10-30-79 Code: 382
Dose Per Kg. 0 mg/kg Time Dosed: 0800 Group: III
Placebo Height: 177.17 cm Weight: 66.23 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	5.9	5.8	6.3	6.5	5.1	5.6	4.7
SAMPLE 2	5.5	5.8	6.0	6.2	4.9	5.6	4.6
% SEGS							
SAMPLE 1	65	77	73	68	61	67	70
SAMPLE 2	71	74	79	73	60	66	78
% LYMPHS							
SAMPLE 1	25	17	19	26	34	26	25
SAMPLE 2	15	21	17	21	35	30	18

ADDENDUM TO EXPERIMENT NO.#13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435-CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

INDIVIDUAL SUBJECT DUPLICATE WHITE BLOOD CELL COUNT VALUES

Total Dose: 0 mg Dosing Date 10-30-79 Code: 383
Dose Per Kg. 0 mg/kg Time Dosed: 0800 Group: III
Placebo Height: 180.34 cm Weight: 78.93 kg

STUDY DAY	1				2	3	4
HRS.P.D.	5 min	4	8	12	24	48	72
WBC							
SAMPLE 1	4.3	6.6	6.0	6.1	5.9	6.6	5.9
SAMPLE 2	4.3	6.6	6.2	6.1	5.9	6.8	5.9
% SEGS							
SAMPLE 1	84	76	72	59	60	65	62
SAMPLE 2	84	77	70	62	61	70	56
% LYMPHS							
SAMPLE 1	14	18	24	32	24	31	25
SAMPLE 2	13	17	22	27	21	25	35

PHOTOTOXICITY TESTS RESULTS

Subject Code	Placebo-P Drug-D	PTD* Effect	PD* Effect
# 372	D	NONE	NONE
# 373	P	NONE	NONE
# 374	P	NONE	NONE
# 375	D	NONE	NONE
# 376	P	NONE	NONE
# 377	D	NONE	NONE
# 378	P	NONE	NONE
# 379	D	NONE	NONE
# 380	D	NONE	NONE
# 381	D	NONE	NONE
# 382	P	NONE	NONE
# 383	P	NONE	NONE

PTD - Prior to Dosing
PD - Post Dosing

ELECTROCARDIOGRAM RESULTS

Subject Code	Placebo-P Drug-D	Screen ECG	Rhythm Strips
# 372	D	Normal	No Change
# 373	P	Normal	No Change
# 374	P	Normal	No Change
# 375	D	Normal	No Change
# 376	P	Normal	No Change
# 377	D	Normal	No Change
# 378	P	Normal	No Change
# 379	D	Normal	No Change
# 380	D	Normal	No Change
# 381	D	Normal	No Change
# 382	P	Normal	No Change
# 383	P	Normal	No Change

ADDENDUM TO EXPERIMENT NUMBER 13

PARTICIPANT SUMMARY

Group I	Subject's Name	
#372	Deleted *	Drug
#373		Placebo
#374		Placebo
#375		Drug

Group II		
#376	Deleted *	Placebo
#377		Drug
#378		Placebo
#379		Drug

Group III:		
#380	Deleted *	Drug
#381		Drug
#382		Placebo
#383		Placebo

The Drug was provided in individual vials for each subject by the Walter Reed Army Institute of Research, identified by drug name (WR 172,435·CH_3SO_3H), amount(1000 mg) and group number (I, II or III). Codes identifying drug or placebo were provided separately in a sealed envelope.

* Names on record, available for legitimate need.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10-16-79 | CODE: 372

DOSE PER Kg: 14.60 mg | TIME DOSED: 1425 | GROUP: I

DRUG | HEIGHT: 163.83 cm | WEIGHT: 68.4932 kg

SIGNIFICANT ABNORMALITIES (Secondary to study participation):

DATE: 1979	10-3	10-15	10-16	10-17	10-18	10-19	10-22	10-29
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC				X				
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

A lightheadedness and abdominal discomfort with onset at time of drug administration and persisting for approximately 2 hours. Physical findings were unchanged throughout the study.

Abnormalities Comment:

Leukocytosis with increased neutrophils starting eight hours post dosing, peaking at twelve hours with pre-dose values at forty-eight hours. Other deviations minimal, inconsistent and not considered significant.

Conclusion:

Abdominal discomfort considered possibly related. Neutrophils are considered drug related.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg
DOSE PER Kg: 14.60 mg/kg
DRUG
DOSING DATE: 10-16-79
TIME DOSED: 1425
HEIGHT: 163.83 cm
CODE: 372
GROUP: I
WEIGHT: 68.4932 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normals
Glucose	102	82						72	88		130H	93	66-144 mg/dl
Alka Phos	76	96H						90	88		83	85	26-94 u/l
Hct	47.0	51.1H	50.3H	49.3 48.9	47.1 46.5	49.8 49.7	49.1 48.8	47.7 48.2	45.9 46.6	45.1 45.5	45.9 44.2	49.1 48.3	40-50 Vol %
Hgb	16.5	17.4H	17.1H	17H 17H	16.2 15.8	17.2H 17.2H	16.7 16.7	16.6 16.5	16.2 16.3	15.8 15.8	15.5 15.6	16.1 16.4	13.3-16.7GMS%
RBC	5.38	5.73H	5.62	5.60 5.53	5.31 5.27	5.65 5.64	5.48 5.55	5.43 5.39	5.30 5.33	5.18 5.22	5.22 5.05	5.43 5.45	mill/ 4.3-5.7 cumm
Platelets (000)	268	364	325	351	375	364	480H	362	300	297	295	328	thous/ 102-426 cc
Retic Ct	--	1.5	2.3H	1.6H	--	--	.9 1.0	1.8H	2.3H	2.8H 2.4H	2.0H	1.8H	0.5-1.5 %
WBC	7.2	7.4	8.7	7.5 7.6	8.8 9.1	13.5H 13.3H	16.5H 16.0H	11.7H 11.4H	6.8 7.1	5.2 5.2	7.2 7.1	6.0 6.1	thous/ 3.1-9.5cc mm
Lymph	32	27	28	20 33	21 28	14L 15L	14L 14L	16L 14L	21 25	20 23	28 29	22 23	19-59 %
Seg	62	67	61	64 57	70 63	79 75	83H 84H	77 75	68 61	69 62	64 61	75 73	36-80 %
ATL	0	0	2H	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 %
Mono	4	5	4	10 11H	7 7	6 8	2 2	6 8	10 13H	10 11H	5 7	1 2	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 10-23-79 | CODE: 373

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0945 | GROUP: I

PLACEBO | HEIGHT: 172.72 cm | WEIGHT: 60.1016 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-3	10-22	10-23	10-24	10-25	10-26	10-29	11-5
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Subject remained asymptomatic and physical examination unchanged during entire study.

Abnormalities Comment:

Laboratory deviations were minor and inconsistent and not considered significant.

Conclusion:

No adverse effect from placebo administration.

INDIVIDUAL SUBJECT FINAL SUMMARY

H = High
L = Low
-- Not Done

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg
DOSE PER Kg: 0 mg/kg
PLACEBO

DOSING DATE: 10-23-79
TIME DOSED: 0945
HEIGHT: 172.72 cm

CODE: 373
GROUP: I
WEIGHT: 60.1016 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°	7	14	Normals
								2	3	4			
SGPT	31	42						56H	65H		38	31	0-47 u/l
Retic Ct	--	1.1	0.9	1.5	0.8	2.0H	2.6H	1.3	1.0	1.3	0.7	2.4H	0.5-1.5 %
		5.4	6.2	6.1	6.8	8.7	9.3	7.0	9.7H	8.0	7.6	6.2	thous/
WBC	6.1	5.3	6.3	6.2	6.5	9.0	9.2	7.2	9.6H	8.2	7.8	6.2	3.1-9.5cu mm
		40	44	26	32	35	54	58	24	17L	36	44	
Lymph	33	34	46	30	35	38	54	54	24	16L	33	42	19-59 %
		0	2H	2H	0	0	0	0	0	2H	0	0	
ATL	0	0	3H	0	0	0	0	0	0	2H	0	0	0 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 10/16/79 | CODE: 374

DOSE PER Kg: 0 mg/kg | TIME DOSED: 1430 | GROUP: I

PLACEBO | HEIGHT: 165.10 cm | WEIGHT: 64.6376 k

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979		10-15	10-16	10-17	10-18	10-19	10-22	10-29
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Subject remained asymptomatic during entire study.

Abnormalities Comment:

Laboratory deviations were minor and inconsistent and not considered significant.

Conclusions:

No adverse effect from placebo administration.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg
DOSE PER Kg: 0 mg/kg
PLACEBO

DOSING DATE: 10-16-79
TIME DOSED: 1430
HEIGHT: 165.10 cm

CODE: 374
GROUP: I
WEIGHT: 64.6376 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normals
BUN	20	20						24H	26H		23H	12	9-21 mg/dl
Uric Acid	5.8	6.9						6.1	6.1		8.2H	6.1	4-8 mg/dl
T. Protein	7.2	6.7						6.6	6.2L		6.4	6.9	6.4-8.0 g/dl
Calcium	9.6	9.4						9.6	9.5		8.9L	9.4	9.0-10.9mg/dl
Retic Ct	--	0.9	1.7H	1.8H	--	--	1.0 1.1	1.6H	1.1	2.1H	1.0	0.8	0.5-1.5 %
Lymph	23	24	29	33 28	32 39	26 36	35 36	33 38	27 26	32 33	34 28	18L 25	19-59 %
Eosin	3	4	4	4 4	5 2	1 0	2 1	4 4	2 0	0 0	1 2	6H 5	0-5 %
ATL	0	2H	2H	0 0	0 0	0 0	0 0	0 0	0 0	3H 3H	0 0	0 0	0 %
Mono	9	5	7	11H 10	8 8	5 6	6 7	5 5	8 6	4 6	8 8	7 12H	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg	DOSING DATE: 10/16/79	CODE: 375
DOSE PER Kg: 12.56 mg/kg	TIME DOSED: 1430	GROUP: I
DRUG	HEIGHT: 180.98 cm	WEIGHT: 79.6063 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979								
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC			X					
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Four hours afer dosing subject experienced diarrhea and some "gassy feeling" in stomach, no cramping or pain noted at this time. Experienced some nausea and continued with diarrhea for six hours after ingestion of WR 172,435·CH_3SO_3H. Experienced emesis at bedtime about midnight and stated that he felt much better. Abdominal discomfort and diarrhea over at this time. Physical examination was unchanged throughout study interval.

Abnormalities Comment:

Neutrophils at twelve hours with increase over baseline starting at eight hours and return to baseline values by forty-eight hours. Other abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusion:

Neutrophils, diarrhea, "gassy feelings" and emesis are considered drug related.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg
DOSE PER Kg: 12.56 mg/kg
DRUG
DOSING DATE: 10-16-79
TIME DOSED: 1430
HEIGHT: 180.98 cm
CODE: 375
GROUP: I
WEIGHT: 79.6063 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5''	4°	8°	12°	24°	48°	72°			
								2	3	4	7	14	Normals
Chloride	103	99						96L	96L		99	100	98-110 mEq/L
CO_2	29	29						32H	31		31	31	23-31 mEq/L
LDH	158	192						197	248H		175	221	73-233 u/l
Retic Ct	--	0.1L	0.6	0.2L	--	--	0.7 0.6	1.6H	1.1	0.7 0.7	1.2	0.3L	0.5-1.5 %
WBC	5.0	4.9	4.7	5.2 5.3	5.5 5.6	8.0 8.3	10.8H 11.4H	7.7 7.6	5.4 5.4	4.9 5.1	4.2 4.2	4.8 4.8	thous/ 3.1-9.5cc mm
Lymph	22	26	34	36 39	38 39	21 23	15H 14H	19 22	23 31	35 31	28 25	20 25	19-59 %
Seg	66	65	52	50 48	52 52	72 70	82H 85H	74 76	65 57	53 56	58 65	68 65	30-80 %
Eosin	3	4	5	3 6H	6H 5	2 2	0 0	4 1	3 2	3 4	1 2	5 3	0-5 %
Mono	8	5	8	10 7	3 4	5 4	3 0	3 0	9 10	8 8	13H 7	5 5	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 11/6/79 | CODE: 376

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: II

PLACEBO | HEIGHT: 180.34 cm | WEIGHT: 71.21 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979		11-5	11-6	11-7	11-8	11-9	11-13	11-19
STUDY DAY:	Screen	0	1	2	3	4	8*	14
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

* DAY 7 for Group II fell on a holiday; examinations deferred for 1 day.

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

During the physical examination approximately 36 hours after dosing, the subject complained of sensitivity to the ophthalmoscope light. Examination normal. No other symptoms and no change in Physical Examination during the study interval.

Abnormalities Comment:

Laboratory deviations were minor or inconsistent and not considered significant.

Conclusion:

No adverse effect from placebo administration..

H = High
L = Low

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H. EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 11/6/79 | CODE: 376

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: II

PLACEBO | HEIGHT: 180.34 cm | WEIGHT: 72.21 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°	8	14	Normals
								2	3	4			
T.Protein		6.4						6.1H	6.5		6.2L	6.3L	6.4-8.0 g/dl
Globulin		1.5L						1.50L	1.70L		1.7L	1.6L	1.8-3.4 g/dl
T.Bili		0.9						0.4	0.4		1.5H	1.3	0.0-1.3mg/dl
Glucose		95						95	88		70	61L	66-114 mg/dl
U/A-Prot		N						Tr-H			N	N	N
Retic Ct		1.6H	1.4	2.0H	0.4	2.2H	2.4H	1.8H	1.5	1.7H	2.7H	2.1H	0.5-1.5 %
		2	5	3	1	3	5	0	0	2	2	0	
Eosin		2	7H	5	2	3	4	1	2	1	3	6H	0-5 %
		2	2	5	2	6	5	5	2	6	5	3	
Mono		1	4	11H	2	2	2	4	3	0	7	6	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10/23/79 | CODE: 377

DOSE PER Kg: 13.52 mg/kg | TIME DOSED: 0945 | GROUP: II

DRUG | HEIGHT: 178.44 cm | WEIGHT: 74.1631 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-15	10-22	10-23	10-24	10-25	10-26	10-29	11-5
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC			X					
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Two hours and 15 minutes after drug ingestion and hourly for 5 hours the patient urinated. The urinary volume and appearance were unremarkable and there was no dysuria. Six hours after dosing a mild, generalized headache occurred and persisted unchanged until bedtime 7 hours later. After the evening meal, between 9 and 9 1/2 hours after dosing, the subject passed 3 semi-formed to loose diarrhea stools. This was followed by a sensation of "chilliness" with a temperature of 99°F lasting for 2 hours.

The subjects had mild symptoms of the common cold study days 9 through 14.

Abnormalities Comment:

Neutrophils. Other abnormalities were minimal and inconsistent and not considered of clinical significance.

Conclusion:

Diarrhea and leukocytosis related to ingestion of 1000 mg of WR 172,435·CH_3SO_3H. Chilliness and headache possibly related to drug ingestion.

H = High
L = Low

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10/23/79 | CODE: 377

DOSE PER Kg: 13.52 mg/kg | TIME DOSED: 0945 | GROUP: II

DRUG | HEIGHT: 178.44 cm | WEIGHT: 74.1631 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normals
Glucose	90	84						64L	83		103	87	66-114 mg/dl
T.Protein	6.5	6.0L						6.5	6.3L		6.3L	6.5	6.4-8 g/dl
Hct	42.0	39.3L	39.9L 39.0L	38.6L 38.3L	38.7L 38.3L	42.3 42.1	43.4 43.8	39.6L 40.5	42.8 42.8	42.5 42.9	41.0 41.6	41.7 41.3	40-50 Vol %
Hgb	14.4	13.2L	13.3 13.3	13.0L 13.0L	13.0L 13.0L	14.5 14.6	14.8 14.8	13.7 13.6	14.2 14.3	14.5 14.5	13.8 13.9	14.0 13.9	13.3-16.7GMS%
Retic Ct		1.4	1.6H	0.8	1.2	1.6H	2.2H	1.3	2.0H	1.0	0.8	1.8H	0.5-1.5 %
WBC	5.3	4.0 4.0	5.9 5.7	4.8 4.7	5.8 5.9	8.6 8.6	14.4H 14.8H	10.0H 10.0H	7.6 7.7	6.2 6.3	6.5 6.1	7.0 7.2	thous/ 3.1-9.5cu mm
Lymph	29	42 46	44 43	36 34	44 41	28 25	13L 11L	19 25	22 28	36 28	29 25	25 28	19-59 %
Seg	60	46 44	46 46	53 59	47 51	63 62	79 82H	75 71	66 67	55 59	61 67	62 63	36-80 %
ATL	0	0 0	0 2H	0 0	0 0	0 0	0 0	0 2H	0 0	3H 2H	0 0	0 0	0 %
Mono	8	10 10	8 8	9 7	7 8	7 9	6 6	4 2	9 5	3 8	8 6	13H 7	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 10/23/79 | CODE: 378

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0945 | GROUP: II

PLACEBO | HEIGHT: 177.80 cm | WEIGHT: 77.11 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-15	10-22	10-23	10-24	10-25	10-26	10-29	11-5
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

The subject was asymptomatic during the study and physical findings remained unchanged except for non-specific T wave inversion changes seen on close-out ECG. He was asked to return for a repeat cardiogram, but did not return.

Abnormalities Comment:

Laboratory deviations were minor and inconsistent and not considered significant.

Conclusion:

No adverse effect from placebo administration.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg
DOSE PER Kg: 0 mg/kg
PLACEBO

DOSING DATE: 10/23/79
TIME DOSED: 0945
HEIGHT: 177.80 cm

CODE: 378
GROUP: II
WEIGHT: 77.11 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD 1	5"	4°	8°	12°	24° 2	48° 3	72° 4	7	14	Normals
SGPT	25	27						40	50H		43	39	0-47 u/l
Glucose	79	82						73	79		97	128H	66-114 mg/dl
Potassium	4.0	4.5						4.5	4.3		4.1	3.5L	3.6-5.2mEq/L
Sodium	135L	136L						138	139		138	140	137-151mEq/L
Calcium	9.2	9.6						9.6	9.6		8.9L	9.6	9.0-10.9mg/dl
Hct	46.9	45.2	50.4H 49.9	48.0 48.7	48.5 48.5	43.8 44.1	47.0 46.5	47.4 47.5	48.2 48.3	44.1 43.9	44.1 44.4	46.4 45.9	40-50 %
Hgb	15.7	15.1	16.9H 16.9H	16.0 15.9	16.0 16.1	14.7 14.7	15.5 15.6	15.8 15.9	15.8 15.9	14.6 14.8	14.1 14.4	15.1 15.1	13.3-16.7GMS%
RBC	5.84H	5.57	6.28H 6.23H	5.86H 5.90H	5.96H 6.00H	5.41 5.41	5.80H 5.77H	5.82H 5.87H	5.87H 5.93H	4.94 5.07	5.37 5.44	5.64 5.64	mill/ 4.3-5.7cu mm
MCV	80L	82	81L 81L	83 83	82 82	82 82	82 81L	82 82	83 82	90 87	83 82	83 82	cu 82-98microns
MCH	26.9L	26.5L	26.3L 26.5L	26.6L 26.3L	26.3L 26.2L	26.6L 26.7L	26.3L 26.5L	26.5L 26.5L	26.2L 26.1L	28.9 28.4	25.6L 25.8L	26.2L 26.0L	micro 27-33microGM
Retic Ct	--	1.2	1.4	1.0	1.0	1.8H	0.7	0.6	0.0L	0.8	0.6	1.0	0.5-1.5 %
Lymph	25	48 51	64H 60H	64H 58	69H 68H	57 57	72H 70H	58 62H	56 62H	30 28	47 55	36 37	19-59 %
Seg	69	40 41	26L 32L	31L 34L	26 26	34L 38	21L 26L	38 32L	39 32L	60 61	43 37	51 50	36-80 %
Eosin	0	6H 0	2 1	0 3	0 2	3 3	3 1	0 0	1 0	2 1	2 0	1 1	0-5 %
ATL	0	0 0	3H 2L	2H 0	0 0	0 0	0 0	2H 3H	2H 3H	0 0	0 0	0 0	0 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 11/6/79 | CODE: 379

DOSE PER Kg: 16.96 mg/kg | TIME DOSED: 0800 | GROUP: II

DRUG | HEIGHT: 165.10 cm | WEIGHT: 59.967 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-31	11-5	11-6	11-7	11-8	11-9	11-13	11-19
STUDY DAY:	Screen	0	1	2	3	4	8	14
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC			X					
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

One hour after drug administration the subject complained of abdominal cramping and slight nausea followed by a voluminous loose stool. Abdominal cramps persisted without nausea for twelve hours. He had another voluminous stool eight and a half hours after dosing and a less voluminous stool thirteen and a half hours after ingestion of the drug. Fourteen hours after dosing he experienced a mild frontal headache which lasted about two hours until he went to bed. Twenty-two and one half hours after taking the drug he had vague abdominal discomfort with relief after breakfast. He remained asymptomatic with physical exam unchanged for the remainder of the study.

Abnormalities Comment:

Neutrophils was observed 12 and 14 hours after dosing. Other deviations minimal and inconsistent and not considered significant.

Conclusion:

Gastrointestinal symptoms and leukocytosis related to ingestion of WR 172,435·CH_3SO_3H.

H = High
L = Low

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 11/6/79 | CODE: 379

DOSE PER Kg: 16.96 mg/kg | TIME DOSED: 0800 | GROUP: II

DRUG | HEIGHT: 165.10 cm | WEIGHT: 59.967 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°			
								2	3	4	7	14	Normals
U/A Prot	N	N						Tr-H			N	N	N
Retic Ct		1.4	0L	0.5	1.3	1.4	1.8H	1.1	1.1	0.8	1.4	1.0	0.5-1.5 %
		6.5	6.1	6.3	6.5	9.1	14.3H	10.7H	6.7	6.8	7.2	6.1	thous/
WBC	7.5	6.5	6.2	6.5	7.4	9.3	14.7H	10.6H	6.6	6.9	7.3	5.9	3.1-9.5cu mm
		34	40	40	44	32	20	21	39	43	43	49	
Lymph	31	39	40	44	39	29	15L	23	30	39	38	41	19-59 %
		4	5	6H	5	0	0	2	1	5	4	0	
Eosin	3	3	4	5	2	1	0	3	2	7H	1	2	0-5 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10/30/79 | CODE: 380

DOSE PER Kg: 12.60 mg/kg | TIME DOSED: 0800 | GROUP: III

DRUG | HEIGHT: 184.15 cm | WEIGHT: 79.38 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-23	10-29	10-30	10-31	11-1	11-2	11-5	11-13
STUDY DAY:	Screen	0	1	2	3	4	7	14
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry			X	X			X	X
7. CBC			X					
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Starting six and a half hours after drug administration the subject had the onset of abdominal cramps with the passage of four loose stools during a 90 minute interval. Anorexia and abdominal cramping persisted with lessening degree until fourteen hours after drug administration at which time the subject became asymptomatic. He had lethargy from nine to fourteen hours after dosing with the sensation of increased body temperature. He did have an elevation of 99.4°F 13 hours after dosing, which had returned to normal within two hours.

Abnormalities Comment:

Neutrophils at eight and twelve hours after ingestion of the drug, which had returned to normal at the twenty-fourth hour. Other deviations were minor or inconsistent.

Conclusion:

Gastrointestinal symptoms and leukocytosis due to ingestion of WR 172,435·CH_3SO_3H.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg
DOSE PER Kg: 12.60 mg/kg
DRUG
DOSING DATE: 10/30/79
TIME DOSED: 0800
HEIGHT: 184.15 cm
CODE: 380
GROUP: III
WEIGHT: 79.38 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°	7	14	Normals
Potassium	3.6	3.7						3.9	3.7		3.5L	4.5	3.6-5.2mEq/L
CO_2	29	29						32H	30		29	28	23-31 mEq/L
T.Protein	5.9L	6.0L						6.1L	5.8L		5.9L	6.9	6.4-8.0 g/dl
Globulin	1.7L	1.8						1.7L	1.6L		1.5L	2.1	1.8-3.4 g/dl
Calcium	8.8L	8.9L						9.1	8.6L		9.0	9.2	9.0-10.9mg/dl
Retic Ct	--	0.9	0.9	0.9	1.2	2.1H	2.6H	1.1	1.3	0.7	0.8	1.3	0.5-1.5 %
		5.3	6.2	3.5	6.8	12.9H	13.5H	6.1	5.6	5.0	5.8	6.4	thous/
WBC	6.5	5.1	6.2	5.4	6.6	12.8H	14.0H	5.9	5.6	5.2	5.6	6.3	3.1-9.5cu mm
		31	32	30	22	12L	7L	32	28	37	42	22	
Lymph	34	33	27	33	27	14L	12L	34	43	38	42	27	19-59 %
		57	62	64	68	80	86H	60	58	52	50	67	
Seg	56	56	68	64	62	78	82H	55	53	50	47	65	36-80 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10/30/79 | CODE: 381

DOSE PER Kg: 16.83 mg/kg | TIME DOSED: 0800 | GROUP: III

DRUG | HEIGHT: 165.10 cm | WEIGHT: 59.42 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-22	10-29	10-30	10-31	11-1	11-2	11-5	11-13
STUDY DAY:	Screen	0	1	2	3	4	7	15
1. Symptoms			X					
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry			X	X			X	X
7. CBC			X					
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Forty-five minutes after drug administration the subject had vague, ill defined "mental fuzziness" which recurred to 27 hours later and difficulty concentrating persisting for 6 days. Abdominal cramping and flatulence occurred 9 hours post dosing and persisted for 6 hrs. Temperature recorded as 99.8°F 13 hours post dosing was normal on repeat at 15 hours.

The subject had a history of bleeding gums with minor trauma and one minor episode occurred 6 days after dosing.

Physical examination remained unchanged throughout the study interval.

Abnormalities Comment:

Neutrophils ~~were~~ was reported 8 and 12 hours after ingestion of the drug with return to normal at 24 hours. Other deviations were minimal and not considered significant.

Conclusion:

Gastrointestinal symptoms and leukocytosis drug related. Mental fuzziness and difficulty concentrating possibly drug related.

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 1000 mg | DOSING DATE: 10/30/79 | CODE: 381

DOSE PER Kg: 16.83 mg/kg | TIME DOSED: 0800 | GROUP: III

DRUG | HEIGHT: 165.10 cm | WEIGHT: 59.42 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°	7	15	Normals
								2	3	4			
Glucose	90	93						62L	82		NS*	85	66-114 mg/dl
Uric Acid	7.9	8.1H						7.2	7.6		NS	8.5H	4-8 mg/dl
T.Protein	6.1L	6.4						6.1L	6.2L		NS	6.1L	6.4-8.0 g/dl
Globulin	1.8	1.8						1.7L	1.6L		NS	1.7L	1.8-3.4 g/dl
LDH	126	200						282H	179		NS	142	73-233 u/l
Retic Ct		0.6	0.5	0.4L	1.5	1.8H	1.9H 1.7H	1.1	0.4L	NS	NS	0.7	0.5-1.5 %
WBC	8.0	7.7 7.6	7.5 7.4	7.4 7.4	8.2 8.4	11.8H 11.6H	13.8H 13.9H	9.1 9.2	7.0 7.1	NS	NS	7.1 7.2	thous/ 3.1-9.5cu mm
Lymph	18L	28 26	28 23	23 28	24 24	18L 22	18L 17L	24 20	22 21	NS	NS	27 23	19-59 %
Mono	11H	1 5	11H 13H	5 9	7 5	5 5	7 10	2 8	5 9	NS	NS	10 8	0-10 %

* N.S. = No Show

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 10-30-79 | CODE: 382

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: III

PLACEBO | HEIGHT: 177.17 cm | WEIGHT: 66.23 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-8	10-29	10-30	10-31	11-1	11-2	11-5	11-13
STUDY DAY:	Screen	0	1	2	3	4	7	15
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Subject remained asymptomatic during entire study. Physical examination remained unchanged throughout study interval.

Abnormalities Comment:

Laboratory deviations were minor and inconsistent and not considered significant.

Conclusion:

No adverse effect from placebo administration.

H = High
L = Low
-- Not Done

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg
DOSE PER Kg: 0 mg/kg
PLACEBO
DOSING DATE: 10/30/79
TIME DOSED: 0800
HEIGHT: 177.17 cm
CODE: 382
GROUP: III
WEIGHT: 66.23 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°			
								2	3	4	7	15	Normals
Potassium	3.9	4.2						3.8	3.6		3.4L	3.7	3.6-5.2mEq/L
CO_2	29	32H						32H	30		28	32H	23-31 mEq/L
Phosphate	2.2L	2.2L						3.3	3.4		2.3L	2.8	2.5-4.5mg/dl
Alka Phos	101H	95H						100H	93		77	89	26-94 u/l
T.Bili	0.9	1.3						0.9	1.0		1.3	1.5H	0-1.3 mg/dl
Chloride	101	104						99	97L		101	100	98-110 mEq/L
Retic Ct	--	0.3L	1.4	0.9	0.6	2.4H	2.0H	1.5	0.8	1.9H	1.6H	2.1H	0.5-1.5 %
		30	28	25	17L	19	26	34	26	25	22	20	
Lymph	37	36	34	15L	21	17L	21	35	30	18L	26	18L	19-59 %
		0	2H	0	0	0	0	0	0	0	0	0	
ATL	0	0	0	0	0	0	0	0	0	0	0	0	0 %
		5	2	9	5	8	5	3	5	4	10	1	
Mono	3	7	3	13H	3	4	6	4	4	4	11H	1	0-10 %

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg | DOSING DATE: 10-30-79 | CODE: 383

DOSE PER Kg: 0 mg/kg | TIME DOSED: 0800 | GROUP: III

PLACEBO | HEIGHT: 180.34 cm | WEIGHT: 78.93 kg

SIGNIFICANT ABNORMALITIES (Secondary to Study Participation):

DATE: 1979	10-19	10-29	10-30	10-31	11-1	11-2	11-5	11-13
STUDY DAY:	Screen	0	1	2	3	4	7	15
1. Symptoms								
2. Physical Exam								
3. ECG								
4. Phototoxicity								
5. Urinalysis								
6. Biochemistry								
7. CBC								
8. Platelets								

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

LABORATORY ABNORMALITIES SUMMARY: See Next Page.

Symptoms and Physical Findings:

Subject remained asymptomatic during entire study. Physical examination remained unchanged throughout study interval.

Abnormalities Comment:

Laboratory deviations were minor and inconsistent and not considered significant.

Conclusion:

No adverse effect from placebo administration.

H = High
L = Low
-- Not Done

INDIVIDUAL SUBJECT FINAL SUMMARY

ADDENDUM TO EXPERIMENT #13: SHORT TERM SAFETY AND TOLERANCE TO WR 712, 435·CH_3SO_3H: EFFECT ON TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS FOLLOWING A SINGLE ORAL DOSE. DOSE - 1000 mg.

TOTAL DOSE: 0 mg
DOSE PER Kg: 0 mg/kg
PLACEBO

DOSING DATE: 10/30/79
TIME DOSED: 0800
HEIGHT: 180.34 cm

CODE: 383
GROUP: III
WEIGHT: 78.93 kg

LABORATORY ABNORMALITIES SUMMARY:

	SCR	0	PTD	5"	4°	8°	12°	24°	48°	72°			
								2	3	4	7	15	Normals
T.Protein	7.0	6.8						7.0	6.6		6.3L	6.7	6.4-8.0 g/dl
Phosphate	3.4	2.3L						3.0	3.4		2.9	2.6	2.5-4.5mg/dl
		14.5	14.9	17.4H	14.9	14.0	14.3	15.5	15.2	14.8	14.0	14.4	
Hgb	15.4	14.6	14.9	17.4H	15.1	14.0	14.3	15.5	15.1	14.9	14.0	14.7	13.3-16.7GMS%
	44.4	43.7	45.3	51.9H	45.1	41.6	43.0	46.3	44.7	43.5	42.7	41.6	
Hct		44.3	45.6	52.7H	45.6	41.3	43.2	46.6	44.6	43.3	42.8	42.9	40-50 Vol %
		4.99	5.25	6.02H	5.08	4.80	4.93	5.41	5.17	5.06	4.82	4.84	mill/
RBC	5.23	5.08	5.22	6.05H	5.18	4.84	4.95	5.42	5.16	5.04	4.89	4.92	4.3-5.7cu mm
Retic Ct	--	1.2	0.6	1.2	1.4	1.9H	1.8H	1.3	1.5	1.4	2.8H	1.2	0.5-1.5 %
		17L	22	14L	18L	24	32	24	31	25	16L	20	
Lymph	25	18L	27	13L	17L	22	27	21	25	35	20	33	19-59 %
		75	63	84H	76	72	59	60	65	62	71	63	
Seg	63	72	61	84H	77	70	62	61	70	56	73	55	36-80 %
		4	4	0	1	2	0	3	0	3	1	8H	
Eosin	4	2	3	0	2	4	2	5	4	4	0	5	0-5 %
		0	0	0	0	0	0	2H	0	0	0	0	
ATL	0	0	0	0	0	0	0	0	0	0	0	0	0 %
		4	10	2	4	3	4	8	4	9	12H	9	
Mono	4	7	9	2	4	4	9	10	1	5	8	7	0-10 %

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EXPERIMENT NUMBER 14

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

PROGRESS REPORT

This three part study was begun 11 June 1979.

Part I, involving the oral administration of 750 mg of two preparations - each to two subjects in a group of four, was completed 2 July 1979. This part of the study was performed to obtain preliminary absorption and elimination data from which optimal dosage scheduling and blood sampling times could be established for subsequent parts of the study.

Gastrointestinal symptoms attributable to drug occurred in all subjects. However, no significant changes occurred in biochemical values and no untoward physical findings were noted.

Part II was implemented on 6 August and the clinical phase was completed 22 October 1979. This part of the study followed a classical design aimed at making a highly precise estimate of the comparative bioavailability of two preparations (single dose level, double-blind intra-group cross-over, 3 replications (= groups)).

As expected from Part I, transitory gastrointestinal symptoms occurred in the subjects. Nevertheless, Part II was completed without serious misadventure. The pharmacokinetic data are now being studied to determine the optimal dosing schedule for Part III.

BIO - MED, Inc.

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ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 14

TITLE:	PHARMACOKINETICS OF WR 180,409·H_3PO_4 (A PYRIDINE-METHANOL) FOLLOWING ORAL ADMINISTRATION
PRINCIPAL INVESTIGATOR:	RICHARD C. REBA, M.D.
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PROGRESS REPORT

EXPERIMENT NUMBER 14

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

TABLE OF CONTENTS

TITLE:

Pharmacokinetics of WR 180,409·H_3PO_4 (A Pyridinemethanol) Following Oral Administration

PURPOSE:

The purpose of this study is to derive a working pharmacokinetic model for the absorption and elimination of orally administered doses of WR 180,409·H_3PO_4 in humans. From this model, dosing schedules can be designed to optimize efficacy and minimize toxicity.

BACKGROUND:

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 oral 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 taking 1000 mg and in 3 of the 4 subjects taking 1250 mg. Two subjects took 1500 mg of WR 180,409·H_3PO_4 as a single dose, and both experienced similar symptoms. 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.

RATIONALE:

In order to design further Phase I and Phase II studies with WR 180,409·H_3PO_4, additional information is needed concerning its absorption and elimination. With this information, it will be determined whether or not this compound represents a potential single dose antimalarial. In rats and monkeys, the drug was apparently well absorbed and the elimination half-time of radio-labeled WR 180,409·H_3PO_4 (which is generally considered an over-estimate) was between 3-5 days. There are no data from human studies concerning the pharmacokinetics of this drug from which we might estimate its expected elimination rate. Therefore, the present study will be conducted in three parts. The purpose of the first part, which may be regarded as a pilot study, is to obtain preliminary data from which optimum dosage scheduling and blood sampling times can be computed for subsequent parts of the study. In the second part of the study, two formulations will be compared and more definitive data concerning the relative bioavailability and pharmacokinetics of the drug obtained. In the third part of the study, three different doses of the drug will be administered to the same individuals in order to determine whether or not the pharmacokinetics of the drug is linear with respect to the dose.

METHODS:

Twenty healthy male subjects, aged 21-45 years, weighing from 60-90 kg and within 10% of their ideal body weight, will be employed for the study. They will be recruited from the Washington, D.C. Metropolitan Area. Candidates will be hired by BIO-MED, Inc., as temporary employees for study purposes. Candidates for employment will be screened 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 count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, uric acid, total protein , albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin, and G6PD.

Qualified candidates will be presented with 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 and a member of the Human Use Committee. Each participant will be given the opportunity to ask questions. Following this, the subject information sheet will be read and initialed by those wishing to participate, and the formal consent form signed in the presence of a witness,

investigator, and a member of the Human Use Committee. Subjects will be housed for a period of 4 days, beginning 1 day prior to each drug administration, in a controlled environment on Nursing Unit 5W at the Washington Hospital Center. Thereafter they will be seen for brief daily visits according to the schedule in Table I, II, or III, and as required to obtain blood specimens. The subject will fast from midnight on the day of dosing (day 1), and at 6 a.m. will drink 360 ml of Sustacal (Mead Johnson product), containing a total of 360 calories. The drug will be administered at 8 a.m. Water may be taken ad lib until 2 p.m., at which time the subject may have a light lunch. Beginning at 5 p.m. on the day of drug administration, they may return to the regular diet they select from the hospital menu.

In addition to the above qualifications, no subject having previously received the drug, WR 180,409·H_3PO_4, in Phase I studies may participate in any phase of this pharmacokinetic protocol.

Part I. An initial pilot study will be conducted in which 750 mg of the drug will be administered orally to 4 subjects. Two of these will be given the drug in the form of a 250 mg capsule formulation (Lafayette Lot No. E-521) and 2 will be given the drug in the form of a new 250 mg tablet formulation (INTERx Lot No. D-523). Blood samples will be taken for analysis of the parent compound, WR 180,409·H_3PO_4, as follows: 10 ml of venous blood will be obtained by a staff nurse prior to drug administration. Following drug administration, samples will be obtained at 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 30, 36, 40, 44, 48, 60, and 72 hours, and on study days 5, 7, 8, 14, and 21. This represents a total of 23 samples and a total of 230 ml of blood over a period of 21 days.

Part II. Based upon the peak levels and elimination half-time in the pilot study, a more definitive pharmacokinetic and comparative bioavailability study will then be performed. This study will employ 12 subjects in a balanced two-way crossover design, allowing a comparison of the 2 formulations with correction for residual effects. Half of the subjects will be given the tablet formulation and the other half the capsule formulation at the initiation of the study. The schedule of blood sampling following administration of the drug in this part of the study will be determined by information obtained from the first part 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-time of the drug. Following an interval sufficient to allow the amount of drug present to be

less than 10% of its peak level, each of the subjects will then be given a second dose of the drug with the opposite formulation of that which they received previously. Once again, a total of approximately 36 samples of blood will be obtained over a period equal to 3-7 times the elimination half-life of the drug, as determined in the pilot study. It is anticipated that these subjects will also be given 750 mg on each occasion, though this dose may be modified pending the results of the pilot study. In addition to the blood specimens collected, subjects participating in this part of the study may collect urine specimens for drug assay.

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

Part III. The third part of the study, following the determination of comparative bioavailability, will employ 4 additional subjects. These subjects will each be given single doses of the drug on 3 separate occasions. The drug will be administered in the formulation determined to be most bioavailable from the previous portions of the study. Three different doses will be administered to each individual. It is anticipated that these doses will be 250 mg, 500 mg, and 750 mg, although these may also be modified pending the results of Part II. Two subjects will receive the 3 doses in increasing order, and 2 in decreasing order, with respect to

the dose administered. Each dose will be administered and followed by an interval of 3-7 times the elimination half-time. A total of approximately 20 samples will be obtained following each drug administration, according to a schedule optimized from the previous parts of the study.

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. Urine specimens will be collected in standard plastic collection bags and stored on wet ice during collection. They will then be frozen at -20°C pending transport to WRAIR for drug assay.

Clinical and laboratory evaluation of the subjects during their participation in the study is outlined in the following tables: Table I pertains to the pilot study (Part I), Table II to the comparative bioavailability study (Part II), and Table III to the final phase of the study in which the drug will be administered on 3 occasions to each of 4 volunteers (Part III).

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, Carbon Dioxide, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, 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.

[‡]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 neparin 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).

AD-A139 980 ARMY DRUG DEVELOPMENT PROGRAM PHASE I CLINICAL TESTING 3/3
(U) BIO-MED INC COLLEGE PARK MD J JOHNSON MAR 80
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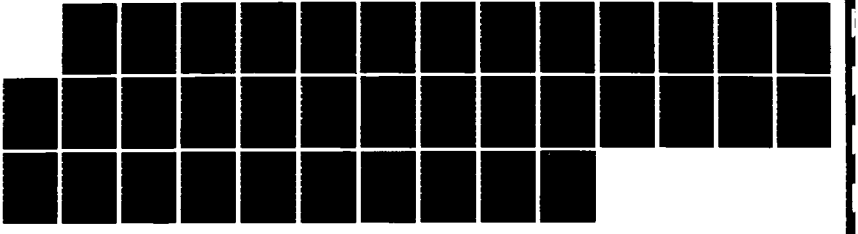

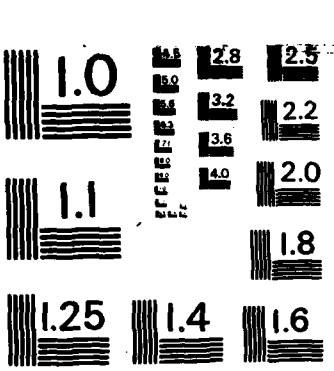

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

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, Carbon Dioxide, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, 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.

TABLE IIA: Schematic Drug Administration and Assay Specimen Collection Schedule

Dose: 750 mg WR 180,409·H_3PO_4
sequence as per protocol pg.4

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

*Day 0 for study interval 2nd drug administration

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, Carbon Dioxide, Uric Acid, T. Protein, Albumin, Globulin, Calcium, Phosphate, Cholesterol, Triglyceride, Alkaline Phosphatase, 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 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.

In the event of an emergency, 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 and the Washington Hospital Center authorities immediately by telephone and by written communication within 24 hours.

All individual 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 obtained for each subject. The following will be recorded on individual forms: blood pressure, pulse, weight, clinical laboratory results, subjective symptoms and physical examination. A cumulative master log will also be kept, which will include laboratory data and the results of a nondirected symptomatology interview. This will provide for ongoing availability of data at all times to the research committee, Washington Hospital Center, and the Army Clinical Monitor. In addition, a specimen schedule form will be kept for each subject and the exact time of drug administration and specimen collections recorded.

DATA ANALYSIS PLAN

Part I

Blood level data from the four individuals in this part of the study will be fit to a nonlinear regression consisting of a sum of exponentials. This will be done using a digital computer program for weighted nonlinear regression analysis. Parameters estimated directly are the absorption constant, elimination half-time, and the presence or absence of a significant lag phase in absorption. In addition, the micro rate constants associated with a compartmental model will be computed. The peak height, integrated area under the time concentration curve, and elimination half-time for the two formulations used in this part of the study will be compared. From this data, optimum sampling times for subsequent parts of the study will be estimated by minimum variance stratification to minimize the error in estimate of the exponents.

Part II

Blood level data from this cross-over study will be analyzed in a manner similar to the data from Part I. However, in this instance each subject will have received both formulations, permitting a comparison of the peak heights, area under the curve, and other parameters of interest by analysis of variance for a cross-over design. A larger number of samples will be obtained in this study, with sampling times optimized for a best estimate of the elimination half-time of the drug. Urine specimens will be assayed for drug content. Percent of the parent compound excreted in the first three days will be calculated and, if feasible, an estimate of drug clearance will also be made.

Part III

Blood concentration-time data will be obtained from each of four subjects following the administration of three different doses of WR 180,409·H_3PO_4 to each subject. This data will once again be analyzed by a weighted nonlinear regression technique with computation of pharmacokinetic parameters as above. Comparison of the area under the time concentration curve for each dose within each subject will allow a determination of the relative linearity of the kinetics of this compound.

Finally, with the above data assembled, a determination will be made concerning the single dose potential of WR 180,409·H_3PO_4 as an antimalarial drug. If it appears that a multiple dose regimen will be required, the dosing schedule may be optimized to achieve satisfactory blood levels for a sufficient period of time based upon the pharmacokinetic parameters derived from this study.

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

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 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 shall be 60-90 kg body weight and within 10% of ideal body weight.

When doubt exists concerning entry 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.

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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	1	0	Prior to Dosing	10
Tuesday	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	9	22 hr	6:00 AM	10
Wednesday	10	28 hr	NOON	10
	11	34 hr	6:00 PM	10
	12	40 hr	MIDNIGHT	10
Day 3	13	48 hr	8:00 AM	10
Thursday	14	56 hr	4:00 PM	10
	15	64 hr	MIDNIGHT	10
Day 4	16	72 hr	8:00 AM	10
Friday				
HOME				
Day 5	17	96 hr	8:00 AM	10
Saturday				
Day 7	18	144 hr	8:00 AM	10
Monday				
Day 9	19	192 hr	8:00 AM	10
Wednesday				
Day 11	20	240 hr	8:00 AM	10
Friday				
Day 14	21	312 hr	8:00 AM	10
Monday				
Day 17	22	384 hr	8:00 AM	10
Thursday				
Day 21*	23	480 hr	8:00 AM	10
Monday				
			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.

+++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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EXPERIMENT NUMBER 15

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

PROGRESS REPORT

A final revision of this protocol was accepted by the Division of Experimental Therapeutics, WRAIR, and BIO-MED, Inc. 18 February 1980.

The protocol was presented to the Institutional Review Board (IRB) of BIO-MED, Inc. 27 February 1980. The protocol was approved by the IRB of BIO-MED, Inc. on 5 March 1980.

Special Assurance for this protocol, and for other studies under the covering contract, was extended by Hqs, USAMRDC by Telephone on 28 March 1980 and by Letter on 3 April 1980.

By 10 April, approximately 150 prospective subjects had been interviewed by telephone, 30 had had complete qualifying examinations, 13 were found fully qualified, and 8 have been enrolled as subjects.

The study was begun on 31 March 1980. By 10 April, four subjects had received 750 mg of drug, or placebo, and were in day 10 of the study without apparent adverse effect. An additional 4 subjects had received 750 mg of drug, or placebo, and were in day 3 of the study without apparent adverse effect.

All programmed clinical records for these subjects are up-to-date. Laboratory studies have been accomplished as scheduled except for subject 400 whose scheduled 7 day blood specimen was obtained on day 8. Specimens for drug assay are in frozen storage at BIO-MED, Inc. Fresh blood specimens for immunologic assay have been delivered to the WRAIR at the scheduled intervals.

This study is scheduled to continue through 26 May 1980, but may be discontinued earlier if clear evidence of drug intolerance appears before the maximum scheduled dose is reached.

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ANTIMALARIAL DRUG PROJECT

EXPERIMENT NUMBER 15

TITLE:	CONTINUATION OF SINGLE DOSE RISING DOSE LEVEL STUDIES WITH ORALLY ADMINISTERED WR 171,669: SHORT TERM SAFETY AND TOLERANCE. PRELIMINARY PHARMACOKINETICS.
PRINCIPAL INVESTIGATOR:	JOHN A. JOHNSON, M.D.
CLINICAL DIRECTOR:	KEVIN G. BARRY, M.D.
ASSOCIATE DIRECTOR:	LESLIE B. ALTSTATT, MD.
CONSULTING AND INSTITUTIONAL REVIEW BOARD MEMBERS:	JUDY HANNAH GEORGE BANNING, JR., M.D. JOSEPH J. D'ERASMO ANGELO J. TROISI JAMES A. DUKE, Ph.D.

JOHN A. JOHNSON, M.D.
PRINCIPAL INVESTIGATOR

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PROGRESS 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

TITLE:

Continuation of Single Dose Rising Dose Level Studies with Orally Administered WR 171,669: Short Term Safety and Tolerance. Preliminary Pharmacokinetics.

PURPOSE:

The prophylactic potential of a new antimalarial drug is dependent upon two important factors: (1) the maximum tolerated single dose, and (2) the biologic half-life of the drug. Since neither of these important determinations have been made for the phenanthrene methanol WR 171,669, the present protocol is designed to provide that information.

BACKGROUND:

In previous Phase I and Phase II studies, WR 171,669 appears to be an important new therapeutic agent against chloroquine-resistant Plasmodium falciparum. Six human volunteers experimentally infected with multi-drug resistant strain of P. falciparum were cured with a dose of 250 mg administered orally every six hours for three days. Additional Phase II studies are in progress. 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 two-by-two, 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, each without adverse effect. Subsequently doses of 1000, 1250, 1500, 1750, and 2000 mg were to have been tested until intolerance occurred. Phototoxicity testing was included in all of the previous Phase I studies and was negative.

In preclinical testing, when administered at doses of 15 mg/kg/day or higher for 28 days to beagle dogs the drug caused weight loss, vomiting and diarrhea, low white blood cell counts and elevations of SGPT and BUN. Organ 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.

RATIONALE:

In light of the recent evidence in animals of moderate phototoxicity (despite negative tests in previous human studies), a thorough evaluation for possible immediate or delayed toxic response to U.V. light should be made. The following design will continue the two-by-two rising single dose tolerance study terminated in 1975 and additionally provides for preliminary pharmacokinetics.

METHODS:

1. Procurement of Subjects and Subject Acceptability Criteria:

   Approximately 28 healthy male subjects, age 18 to 45 years, weighing 60-90 kg and within 10% of ideal body weight, will be employed for the study. They will be recruited from the Washington, D.C. metropolitan area, and hired as temporary employees of BIO-MED, Inc.

   Candidates for employment will be screened to obtain subjects for study. The medical evaluation will include 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 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 or potentially compromise the valldity 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.

When doubt exists concerning entry 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.

Qualified candidates will be presented with 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 and a member of the Institutional Review Board. Each participant will be given the opportunity to ask questions. The consent form will then be read and those wishing to participate will sign it in the presence of a witness, investigator, and member of the Institutional Review Board.

Each participant will then be admitted to the controlled environment of the Clinical Facility in College Park for the period indicated in the study schedule schematic (page 8).

2. Dosing Design:

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

	SUBJECTS	
LEVEL	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 will be coded at WRAIR to maintain the double-blind design. A sealed copy of the code will be provided for the investigator to be used in the event of an emergency.

An interval of 1 week will be required between each dosing level. If serious intolerance is encountered, the study will be discontinued. In the event that equivocal and mild intolerance occurs at a given dose level, that level may be repeated. In addition, if the pharmacokinetic evaluation of the sample data from the first 4 subjects given 750 mg of WR 171,669 indicates a drug half-life of less than 72 hours, the study will also be terminated, since it is therefore unlikely that the drug represents a good potential single weekly dose suppressive prophylactic.

3. Drug Administration and Subject Evaluation:

The design is a simple 2 x 2 double-blind, single rising dose design. Subjects will be 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, will be administered in the form of 250 mg hard gelatin capsules with matching placebos. All drug administration will be done in the presence of a member of the investigating staff.

At 6:00 a.m. on the day of dosing, the subject will drink 360 ml of Sustacal (Mead Johnson product) containing a total of 360 calories. The drug will be administered at 8:00 a.m.. Measured amounts of water may be taken ad lib until noon, at which time the subjects will be permitted to return to their regular diet if they remain symptom free.

Interview, physical examinations, phototoxicity testing and laboratory tests will be conducted as outlined in the study schedule schematic on the following page:

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).

---

4. 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, 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. 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 in 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.

5. 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 Doctors Hospital of Prince George's County authorities and Army Clinical Monitor by telephone and by written communication within 24 hours.

RESULTS AND REPORTING:

Individual worksheets will be maintained for each subject. The following will be recorded on individual work forms: blood pressure, pulse, weight, clinical laboratory results, subjective symptoms, and physical examination. A cumulative master log for the study will also be kept which will include laboratory data and the results of a non-directed symptomatology interview. This will provide for ongoing availability of data at all times to the Clinical Facility in College Park and the Army Research and Development Command.

Upon completion of the study, a report will be submitted detailing the results of the drug administration and all associated clinical and laboratory evaluations. The formal data analysis of blood levels of WR 171,669 obtained in this study will be the responsibility of the Department of Pharmacology at WRAIR and will be reported separately.

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)

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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

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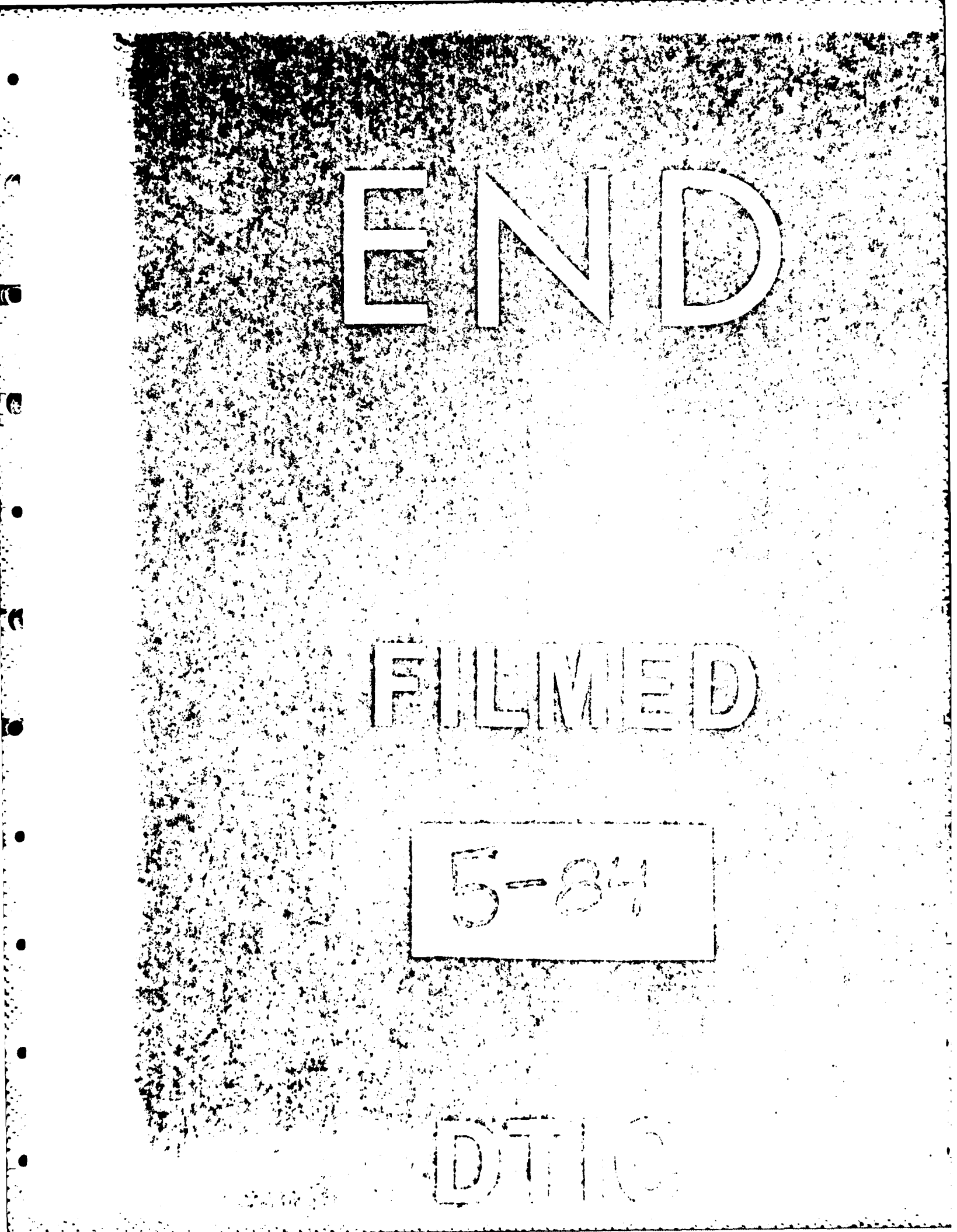
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