THOMPSON MEDICAL COMPANY, INC.
919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 688-4420

1984 MAY 11 P 5

May 10, 1984

Dr. William E. Gilbertson
HFN-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Gilbertson:

In follow-up to our December 2, 1983 discussion of phenylpropanolamine hydrochloride, we enclose herein a draft protocol for a dose escalation clinical study of PPA for discussion purposes at our next meeting.

We have tentative approval of an Investigational Review Board for the project.

We appreciate your kind consideration and cooperation.

Thank you.

Sincerely,

Wm C Waggoner

Wm. C. Waggoner, Ph.D., FAACT
Vice President
Research and Development

WCW:kj
Enclosure

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P 2

I. TITLE:

A Double-Blind Study to Determine the Effects of Escalating Doses of Immediate-Release Phenylpropanolamine Hydrochloride

II. INVESTIGATORS:

George P. Lewis, MD
Robert P. Paone, Pharm. D.

III. SITE OF STUDY:

Clinical Pharmacology Center
Lemuel Shattuck Hospital
170 Morton Street
Boston, MA 02130

IV. INSTITUTIONAL REVIEW BOARD:

Prior to commencement of this study the investigator will receive written approval from a properly constituted Institutional Review Board to initiate this investigation. A copy of this written approval must be reviewed at Thompson Medical Company, Inc. (hereafter, Thompson) prior to delivery of medication to the investigator.

V. BACKGROUND AND RATIONALE:

Phenylpropanolamine hydrochloride (PPA HCl) is a sympathomimetic chemically related to several well-known molecules that have been used clinically for many years. PPA HCl is currently used in the OTC market in the cough/cold and anorectic areas. Current consumption is an estimated 4 to 5 billion doses annually in the United States.

Questions have surfaced regarding the potential effects of PPA HCl and its pharmacological profile in higher than normal doses. As an example, prior unsubstantiated studies have shown blood pressure to increase significantly clinically with oral doses of immediate-release 85 mg. This was also thought to be a more potent dextrorotary form of PPA HCl. The drug, as marketed in the United States consists of a dextro-and levo-rotary mixture, and some studies have shown no clinically significant blood pressure changes or subjective effects with currently recommended (25 mg tid) or 75 mg sustained-release. Another study showed 75 mg immediate-release to have no significant blood pressure effect. Being a sympathomimetic, there is most probably a dose at which clinically significant blood pressure changes and subjective effects are likely to occur. This study will attempt to determine that particular level by giving escalating doses of phenylpropanolamine hydrochloride .

VI. DESIGN:

This study is a double-blind, controlled, random, crossover design of a 26-day duration. The study will be controlled by use of placebo medication, which appears identical to active medication. Subjects will be randomly initially assigned to treatment or control group. Records will be maintained by the sponsor to show the method of randomization and subsequent results.

Volunteers will receive escalating doses of immediate-release PPA HCl

capsules in the following sequence: 25 mg, 50 mg, 75 mg, 100 mg, 125 mg and 150 mg. There will be four days to each dose period. Each of these dose escalation periods will begin and end (day 1 and day 4) with a placebo medication day. On day 2 volunteers will receive either PPA HCl or placebo. On day 3 volunteers will receive the alternative medication from day 2 (eg. PPA HCl or placebo). Day 5 will begin the next dose escalation period, and therefore, volunteers will receive placebo. Only one capsule will be given on each day. Capsules containing immediate-release PPA HCl or placebo will be supplied and coded by the study sponsor.

Dose Schedule at Each Period

| Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|
| Placebo | Drug or Placebo | Drug or Placebo (alternate) | Placebo |

VII. PATIENT DEFINITION:

A. Selection Criteria

Fifteen (15) healthly male volunteers of age 18 and up to and including 45 may enter the study to ensure that ten (10) subjects complete the study. All volunteers will be within 15% of ideal body weight according to the 1983 Metropolitan Height and Weight Tables (Attachment A) and be normotensive as indicated by a supine blood pressure of less than 140/86.

Subjects will be evaluated prior to assignment. Only those subjects judged optimally suited for inclusion will be assigned. Factors to be weighted are those that would insure the subject will maximally cooperate, will attend all scheduled appointments, and will complete the testing period.

Subjects will be individually interviewed and will complete the subject Questionnaire (appended as Exhibit B) prior to evaluation for inclusion in the study. It will be made clear to the subjects that they must remain at the test site for the full 26 days.

Subjects will sign the Informed Consent Form (Exhibit C) before entering the study.

Subjects must have no recent (within one year) history of illicit drug intake.

B. Exclusion Criteria

1. Subjects who require or are currently taking any significant medication other than analgesics on an occasional basis. Specifically excluded are subjects taking any drugs containing monoamine oxidase inhibitors or other medication containing sympathomimetic amines. Subjects, who have any overt endocrine disease, clinical disease, or surgical condition which may interfere with this study's medication are excluded.

2. Subjects who have known renal, hepatic or thyroid disease, diabetes, cardiac disease, hypertension, or glaucoma are excluded

3. Subjects, that are known alcoholics, unless they are participating in an Alcoholics Anonymous or similar reinforcement program, are excluded.

4. Subjects who cannot remain at the test site during the entire study are excluded.

5. Subjects, who are known to be sensitive to phenylpropanolamine hydrochloride or other sympathomimetic amines are excluded.

VIII. TREATMENT DEFINITION:

Study medications to be evaluated are identically appearing capsules containing:

a) phenylpropanolamine HCl, or

b) pharmacologically inert placebo

One capsule will be taken orally by each patient at 9 am daily. Medication is to be ingested each time with 8 ounces of water. Medication will be taken only once a day.

IX. CONCURRENT TREATMENT:

Specifically excluded are drugs containing monoamine oxidase inhibitors, other medications containing sympathomimetic amines, anorectic agents or appetite promotors. No foods containing xanthines (coffee, tea, cola, etc.) are allowed.

If medical need necessitates the use of concomitant medications, the investigator must provide complete information concerning the reason and type of medication given. Administration of all such drugs must be reported in the appropriate section of the case report forms.

X. CLINICAL AND LABORATORY MEASUREMENTS:

Within one week prior to the start of the study, volunteers will undergo a chemical screening, urine drug screen, medical history, and physical examination. Laboratory screening parameters are listed on the appended Exhibit D-1, and D-2 Range of Normal Values. An electro cardiogram will also be obtained. A full schedule of blood pressure will be obtained for with placebo medication for a two-day run in prior to the onset of the first period (Days - 1 & 0). The procedures, medical history excepted, will be repeated at the conclusion of the study.

Patients' blood pressure will be evaluated twice at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 5 hours, 6 hours, 7 hours, and 8 hours. Measurements will continue past eight hours if elevated (above normal) pressure or symptoms are present. Monitoring will continue until symptoms abate or pressure is normal. Data will be recorded on the Clinical Data forms (Exhibits E-1, E-2, E-3, E-4 and E-5). Sitting, standing and supine blood pressure and pulse will be measured each time on the same arm with a mercury sphygomanometer. Systolic pressure is the point at which the initial tapping sound is heard (Korotkoff I). Diastolic Pressure is taken at the point where the sound undergoes maximum change (Korotkoff IV). Both systolic and diastolic pressures are read to the nearest 2 mm mark on the baumanometer scale. Whenever possible, all examinations will be conducted for each subject at essentially the same time of day and by the same examiner.

Time zero is when medication is administered and will be at 9 AM daily. A light breakfast will be given prior to 8 am. Lunch will be given between 12 noon and 2:00 pm, and dinner will be given between 5:00 pm and 7:00 pm. Any given meal will be the same for all subjects.

## XI. CRITERIA FOR SAFETY AND EFFICACY:

### A. Efficacy

Efficacy is not a criterion of this study.

### B. Safety

All adverse experiences are to be entered on the case report forms with regard to severity, onset date, duration frequency, drug relationship, and action taken. Both expected and unexpected untoward experiences should be recorded. The information recorded should be based on the signs or symptoms detected in the examination and clinical interview with the patient. In addition to the information obtained from these sources, the patient should also be asked the following question:

"How have you been feeling?" Signs and symptoms should be recorded in a concise manner using acceptable medical terminology to eliminate vague, ambiguous, or colloquial expressions.

If an unexpected reaction occurs, or if the reaction is excessive, the investigator will let Thompson know immediately. Thompson and the investigator will discuss the reaction and further tests in an attempt to uncover the underlying cause. The subject should be followed carefully until the condition disappears and/or the etiology is identified. Subjects will continue to participate in the study until they refuse to participate as a result of a drug experience or the investigator determines that the subject will be at to great a risk.

Any concomitant illness which the subject develops during the study must be recorded on the appropriate case record form. A concomitant illness is defined as an illness, disorder, or any other pathology for which there is no reason to assume the illness, disorder or pathology is a consequence of the study drug being administered. In other words, the etiology of the concomitant illness could be attributed to the environmental, systemic, or accidental factors that are not associated with the pharmacology of the drug.

## XII. STATISTICAL METHODS:

Data will be analyzed by Thompson or a Thompson consultant. Any additional or supplementary data analyses carried out independently by the investigator should be admitted to Thompson. Comparability of treatment groups based on demographic baseline characteristics of the subject will be determined by an appropriate statistical test. Differences between treatment groups in respect to toxicity observations and measurements will be illustrated by means of tabulations.

Differences between treatment groups in respect to toxicity observations and measurements will be evaluated by appropriate statistical

methods. Subjects that did not complete the study will be considered dropouts and their data will not be included in the final analyses. A genuine effort must be made to determine the reason why a subject fails to return for the necessary visits or is dropped from the study. This information is recorded on the subject report form.

## XIII. ADMINISTRATIVE ASPECTS:

### A. Material Packaging

Phenylpropanolamine HCl and placebo capsules are to be packaged in individual envelopes with each subject requiring 26 envelopes. The following medication will be needed:

400 placebo capsules
20 25mg PPA HCl capsules
20 50mg PPA HCl capsules
20 75mg PPA HCl capsules
20 100mg PPA HCl capsules
20 125mg PPA HCl capsules
20 150mg PPA HCl capsules

An example of the label follows:

Day #_____ Study # 84-013

Subject #_____

Dose: Take contents at 9 AM

THOMPSON MEDICAL COMPANY

Medication will be coded for 20 subjects.

The study codes with the identification of the medication will be contained individually in an envelope for each subject. Should it be necessary if in an emergency to break the code for an individual subject, only that subject's envelope is opened and the remainder remain coded. In an event an envelope is opened, Thompson must be notified by the investigator. All envelopes are returned to Thompson at the conclusion of the study.

All unused medication and empty containers will be returned to Thompson at the end of the study. The containers and medication are inventoried on the Assignment Form (Exhibit F). At the conclusion of the study the investigator will complete the Study Desposition Form (Exhibit G).

### B. Report Forms

The following report forms will be used for this study:

1. Height and Weight Tables (Exhibit A)
2. Subject Questionnaire (Exhibit B)
3. Subject Informed Consent Form (Exhibit C)
4. Range of Normal Values Form (Exhibit D-1, & D-2)

5. Clinical Data Form (Exhibit E-1, E-2, E-3, E-4, & E-5)
6. Assignment Sheet (Exhibit F)
7. Study Disposition Form (Exhibit G)

Study disposition, Clinical Data Forms, Range at Normal Values Forms, Subject Assignment Sheets and Forms will be initially supplied as work sheet. Following the completion of the study, the data and information will be transferred by carbon film typewriter to the final report forms printed as three copies (white, yellow and pink) on NCR paper. Following proofreading of the transfer, the investigator will sign the typewritten form with a black ballpoint pen and retain the pink copy for his/her files. The yellow and white copies of all forms and worksheets are returned to Thompson.

## XIV. SPECIAL INSTRUCTIONS:

### A. Investigator

The investigator will receive in written form all known contraindications, warnings, precautions and adverse reactions associated with administration of the study material. If new information becomes available while the study is in progress the investigator will be advised.

### B. Subject

Written informed consent (Exhibit C) must be obtained from each subject before the subject is entered into the study. No esculpatory language may be included and the primary language of the subject must be used. In seeking and obtaining informed consent, the investigator must provide to each person whose consent is sought or obtain the following information:

1) An explanation of the scope, aims and purposes of the research, the procedures to be followed, and the expected duration of the subject's participation.
2) A description of all reasonably foreseeable risks or discomforts to the subjects.
3) A description of any benefits to the subject or to others that may be reasonably expected from the research.
4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5) An offer to answer any questions a subject may have about the research, subject's rights, or related matters.
6) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
7) A statement indicating that medical records will be made available to Thompson and describing the extent, if any, to which confidentiality or records identifying the subject will be maintained.
8) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

C. Permiss[illegible] to Review Source Subject Reco[illegible]

The investigator agrees that Thompson, its employees or agents, will have the right at reasonable times during the course of this study to audit and review pertinent medical records relating to this clinical trial.

D. Drug Accountability

The principal investigator must maintain a record of the drug received from Thompson and dispensed by him.

The Subject Assignment Sheet will be used by the investigator to record the amount of medication dispensed and returned for each patient.

All study materials will be accounted for, returned to Thompson, and Study Disposition Form signed by the investigator will be completed at the end of the study.

All medication will be stored and dispensed as required by regulations.

E. Confidentiality

It is understood that this investigation will be conducted in accordance with the basic investigator/sponsor contract as drawn up by Thompson.

F. Monitoring and Site Visits

Each study will be monitored by Thompson personnel by site visits and frequent communications (telephone, letter) to insure that the investigation is conducted according to the protocol and to assist in resolving any difficulties encountered while the study is in progress.

G. Study Discontinuation

Thompson reserves the right to discontinue this study for medical or administrative reasons. Should such action be necessary, the investigator will be reimbursed for reasonable expenses that have been incurred or irrevocably committed at the time of discontinuation.

H. Publication

Should preparation of a manuscript for publication of the study results be appropriate, Thompson agrees to assist the investigator, if needed. Any manuscript will be transmitted to the sponsor for information, review, and approval prior to publication.

XV. SIGNATURES

Investigator (Principal) _____ _____ Date

Name: George P. Lewis, MD

Office Phone Number: 617/ 524-3876

Home Phone Number: 617/ 522-4369

Investigator (Associate): _____ _____ Date

Name: Robert P. Paone, Pharm. D.

Office Phone Number: 617/ 524-3876

Home Phone Number: 617/ 848-0007

Thompson Monitor: _____ _____ Date

Name: Wm. C. Waggoner, Ph.D., FAACT

Office Phone Number: 212/ 688-4420

Home Phone Number: 201/ 828-5999


**TO MAKE AN APPROXIMATION OF YOUR FRAME SIZE...**

Extend your arm and bend the forearm upward at a 90 degree angle. Keep fingers straight and turn the inside of your wrist toward your body. If you have a caliper, use it to measure the space between the two prominent bones on *either side* of your elbow. Without a caliper, place thumb and index finger of your other hand on these two bones. Measure the space between your fingers against a ruler or tape measure. Compare it with these tables that list elbow measurements for *medium-framed* men and women. Measurements lower than those listed indicate you have a small frame. Higher measurements indicate a large frame.

| Height in 1" heels | Elbow Breadth |
|---|---|
| **Men** | |
| 5'2"–5'3" | 2½"–2⅞" |
| 5'4"–5'7" | 2⅝"–2⅞" |
| 5'8"–5'11" | 2¾"–3" |
| 6'0"–6'3" | 2¾"–3⅛" |
| 6'4" | 2⅞"–3¼" |
| **Women** | |
| 4'10"–4'11" | 2¼"–2½" |
| 5'0"–5'3" | 2¼"–2½" |
| 5'4"–5'7" | 2⅜"–2⅝" |
| 5'8"–5'11" | 2⅜"–2⅝" |
| 6'0" | 2½"–2¾" |

T22067 (3-83) Printed in U.S.A.

# 1983 Metropolitan Height & Weight Tables

Weights at ages 25-59 based on lowest mortality. Weight in pounds according to frame (in indoor clothing weighing 5 lbs. for men and 3 lbs. for women; shoes with 1" heels).

Metropolitan Insurance Companies

Metropolitan Life Insurance Company
Health and Safety Education Division

## 1983 METROPOLITAN HEIGHT AND WEIGHT TABLES

**MEN**

| Height Feet | Height Inches | Small Frame | Medium Frame | Large Frame |
|---|---|---|---|---|
| 5 | 2 | 128-134 | 131-141 | 138-150 |
| 5 | 3 | 130-136 | 133-143 | 140-153 |
| 5 | 4 | 132-138 | 135-145 | 142-156 |
| 5 | 5 | 134-140 | 137-148 | 144-160 |
| 5 | 6 | 136-142 | 139-151 | 146-164 |
| 5 | 7 | 138-145 | 142-154 | 149-168 |
| 5 | 8 | 140-148 | 145-157 | 152-172 |
| 5 | 9 | 142-151 | 148-160 | 155-176 |
| 5 | 10 | 144-154 | 151-163 | 158-180 |
| 5 | 11 | 146-157 | 154-166 | 161-184 |
| 6 | 0 | 149-160 | 157-170 | 164-188 |
| 6 | 1 | 152-164 | 160-174 | 168-192 |
| 6 | 2 | 155-168 | 164-178 | 172-197 |
| 6 | 3 | 158-172 | 167-182 | 176-202 |
| 6 | 4 | 162-176 | 171-187 | 181-207 |

**WOMEN**

| Height Feet | Height Inches | Small Frame | Medium Frame | Large Frame |
|---|---|---|---|---|
| 4 | 10 | 102-111 | 109-121 | 118-131 |
| 4 | 11 | 103-113 | 111-123 | 120-134 |
| 5 | 0 | 104-115 | 113-126 | 122-137 |
| 5 | 1 | 106-118 | 115-129 | 125-140 |
| 5 | 2 | 108-121 | 118-132 | 128-143 |
| 5 | 3 | 111-124 | 121-135 | 131-147 |
| 5 | 4 | 114-127 | 124-138 | 134-151 |
| 5 | 5 | 117-130 | 127-141 | 137-155 |
| 5 | 6 | 120-133 | 130-144 | 140-159 |
| 5 | 7 | 123-136 | 133-147 | 143-163 |
| 5 | 8 | 126-139 | 136-150 | 146-167 |
| 5 | 9 | 129-142 | 139-153 | 149-170 |
| 5 | 10 | 132-145 | 142-156 | 152-173 |
| 5 | 11 | 135-148 | 145-159 | 155-176 |
| 6 | 0 | 138-151 | 148-162 | 158-179 |



Source of basic data: 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980.

# SUBJECT QUESTIONNAIRE

NAME:_____ HOME PHONE_____ WORK PHONE_____

ADDRESS:_____
(street) (city/town) (state) (zip code)

Sex: M F Date of Birth:_____

Race: Caucasian ____
Negro ____
Amer. Indian ____
Oriental ____
Puerto Rican ____
Other ____

Present Weight:_____ Height:_____

Are you taking any medications? YES NO

If yes, what?_____

Do you have any evidence of lactation, pregnancy, diabetes, glaucoma or cardiac, renal, liver, or endocrine dysfunction? YES NO

If yes, evidence of what?_____

Are you on a regular work schedule? YES NO

If yes, what is your work schedule?_____

Are you allergic to any medications? YES NO

Specify:_____

Are you an alcoholic? YES NO

Could you make the commitment to continue on this study participating at the test site for 26 days and providing us with 100% of the required data, for the entire 26 days of the study, until the study is completed? YES NO

Do you realize that you cannot leave the test site during the entire 26 days? YES NO

Are you a smoker? YES NO

What is your daily smoking consumption?_____

Do you understand that this is a scientific research study and that you must be honest with the records you keep and the information you give us? YES NO

# INFORMED CONSENT AGREEMENT
# DOUBLE-BLIND CLINICAL EVALUATION OF PHENYLPROPANOLAMINE HCl ON BLOOD PRESSURE AND PULSE IN COMPARISON TO A PLACEBO IN NORMAL ADULTS

I, _____, do hereby consent to participate in a study conducted by_____. This study is testing the effectiveness of an over-the-counter ingredient on blood pressure and pulse values in normal persons. Dr. _____has explained orally to me, as described below, and I fully understand the following:

Phenylpropanolamine HCl is a medication which is widely used in over-the-counter preparations for relief of nasal sinus congestion associated with the common cold. It has similar actions to a frequently used oral nasal decongestant. It is also used as a weight loss product.

I will remain at the test site for 26 days, during which I will take up to 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, or 150 mg of phenylpropanolamine HCl about every 4th day. The capsules will be provided to me by the investigator. I will randomly assigned to receive on any day either phenylpropanolamine capsules or placebo. Capsules, the latter of which will have no pharmacological effect. Neither I nor the investigators will know which drug I am receiving. In an emergency, however, this information can be readily obtained, and the investigators will assist in obtaining this information, if necessary. During the 26 days that I am taking capsules, I will have blood pressure and pulse measurements taken before receiving drug and 14 times for at least 8 hours thereafter.

I understand that persons with certain medical conditions, persons receiving certain drugs, and women who are pregnant or lactating should not receive this drug. I am not taking any significant medication other than analgesics (mild pain relievers) on an occasional basis. I am not taking any drugs containing monoamine oxidase inhibitors (a class of anti-depressants) or any other medication containing sympathomimetic amines (such as amphetamines and some other stimulants). I am not aware of having any overt endocrine (glandular) disease, or other clinical disease or surgical condition which the investigators have questioned me about. I am not aware of having any renal, hepatic, or thyroid disease, diabetes, cardiac disease, hypertension, or glaucoma. I do not have a drinking problem. The investigator has questioned me concerning all of these criteria.

I understand that phenylpropanolamine HCl may cause headache, nervousness, hypertension, drowsiness, sleeplessness, or dizziness in some persons. I understand that if I should have any reactions to the medication during this study, I should notify the investigators so that appropriate action may be taken. Should information become available over the course of this study suggesting any other adverse effects of the medication, I understand that I will be notified immediately by the investigators and appropriate action taken.

I understand that the significant possibilities of discomfort and risk which may arise in this study consist primarily of possible side effects from the medication as described above.

Dr. Lewis has agreed to answer any inquires that I may have concerning the procedures and has informed me that I might also contact the Institutional Review Board for Human Research directly. This board administers the agreement with the United States Department of Health and Human Services covering the protection of human subjects.

You should be aware that in the event of physical injury resulting from the research procedures immediate and essential medical treatment is provided. Financial compensation is not available.

I understand that my records of participation in this study are not accessible to the general public and confidentiality will be maintained. Information that may be gained from this study will be used only for research and educational purposes. Information may be published with permission of the principal investigator in medical journals, but my identity will not be revealed. However, identifying information will be available to other authorized personnel.

I also understand that I am free to withdraw my consent and discontinue participation at any time. Discontinuation will in no way jeopardize my ability to receive treatment now or in the future at this institution.

| | |
|---|---|
| Date | Volunteer |
| Date | Investigator |
| Date | Witness |

This project has been approved by the Human Research Review Committee of the Lemuel Shattuck Hospital. If you have any questions or difficulties you may contact the committee through Dr. Joseph Cohen at 522-8400.

(Revised 3/14/84)

Exhibit D-1

# RANGE OF NORMAL VALUES

NOTE TO LABORATORY: SPECIFY UNITS, METHODS, AND RANGES OF NORMAL VALUES USED BY YOUR LABORATORY

| DETERMINATION | UNITS | METHOD | RANGE OF NORMAL VALUES | |
|---|---|---|---|---|
| | | | LOW | HIGH |
| FBS | | | | |
| Uric Acid | | | | |
| BUN | | | | |
| Creatinine | | | | |
| Sodium | | | | |
| Potassium | | | | |
| Chloride | | | | |
| $CO_2$ | | | | |
| Calcium | | | | |
| Phosphorous | | | | |
| Total Protein | | | | |
| Albumin | | | | |
| Globulin | | | | |
| Bilirubin | | | | |
| Alk. Phos. | | | | |
| SGOT | | | | |
| SGPT | | | | |
| LDH | | | | |
| Cholesterol | | | | |
| LDL Cholesterol | | | | |
| Triglyceride | | | | |
| Serum Iron | | | | |
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NAME OF LABORATORY:

ADDRESS OF LABORATORY.

DIRECTOR'S NAME:

INVESTIGATOR NAME:

SIGNATURE:

DATE:

THOMPSON MEDICAL COMPANY, INC.
919 Third Avenue
New York, N.Y. 10022
212/688-4420

To be completed by
Thompson Medical Company
Treatment Code_____

THOMPSON MEDICAL COMPANY, INC.

Clinical Data Form

STUDY NO. _____

SUBJECT NO. _____

| | 0 | ¼ | ½ | 1 |
|---|---|---|---|---|
| WT. TO NEAREST POUND | | | | |
| SYSTOLIC Supine B.P. | | | | |
| DIASTOLIC Supine B.P. | | | | |
| SYSTOLIC Sitting B.P. | | | | |
| DIASTOLIC Sitting B.P. | | | | |
| Systolic Standing B.P. | | | | |
| DIASTOLIC Standing B.P. | | | | |
| PULSE (Supine) | | | | |
| PULSE (Sitting) | | | | |
| PULSE (Standing) | | | | |
| ORAL TEMPERATURE $^{o}F$ | | | | |

To be completed by
Thompson Medical Company
Treatment Code_____

THOMPSON MEDICAL COMPANY, INC.

Clinical Data Form

STUDY NO. _____

SUBJECT NO. _____

| | 1.5 | | 2 | | 2.5 | | 3 | |
|---|---|---|---|---|---|---|---|---|
| WT. TO NEAREST POUND | | | | | | | | |
| SYSTOLIC Supine B.P. | | | | | | | | |
| DIASTOLIC Supine B.P. | | | | | | | | |
| SYSTOLIC Sitting B.P. | | | | | | | | |
| DIASTOLIC Sitting B.P. | | | | | | | | |
| Systolic Standing B.P. | | | | | | | | |
| DIASTOLIC Standing B.P. | | | | | | | | |
| PULSE (Supine) | | | | | | | | |
| PULSE (Sitting) | | | | | | | | |
| PULSE (Standing) | | | | | | | | |
| ORAL TEMPERATURE $^{o}F$ | | | | | | | | |

To be completed by
Thompson Medical Company
Treatment Code_____

THOMPSON MEDICAL COMPANY, INC.

Clinical Data Form

STUDY NO. _____

SUBJECT NO. _____

| | 3.5 | 4 | 5 | 6 |
|---|---|---|---|---|
| WT. TO NEAREST POUND | | | | |
| SYSTOLIC Supine B.P. | | | | |
| DIASTOLIC Supine B.P. | | | | |
| SYSTOLIC Sitting B.P. | | | | |
| DIASTOLIC Sitting B.P. | | | | |
| Systolic Standing B.P. | | | | |
| DIASTOLIC Standing B.P. | | | | |
| PULSE (Supine) | | | | |
| PULSE (Sitting) | | | | |
| PULSE (Standing) | | | | |
| ORAL TEMPERATURE °F | | | | |

Exhibit E-4

To be completed by
Thompson Medical Company
Treatment Code_____

THOMPSON MEDICAL COMPANY, INC.

Clinical Data Form

STUDY NO. _____

SUBJECT NO. _____

| | 7 | | | |
|---|---|---|---|---|
| WT. TO NEAREST POUND | | | | |
| SYSTOLIC Supine B.P. | | | | |
| DIASTOLIC Supine B.P. | | | | |
| SYSTOLIC Sitting B.P. | | | | |
| DIASTOLIC Sitting B.P. | | | | |
| Systolic Standing B.P. | | | | |
| DIASTOLIC Standing B.P. | | | | |
| PULSE (Supine) | | | | |
| PULSE (Sitting) | | | | |
| PULSE (Standing) | | | | |
| ORAL TEMPERATURE $^{o}F$ | | | | |

Did Adverse Reaction Occur? _____ Yes _____ No
If yes, specify under comments data of onset duration, intensity,* whether drug related, action and subject outcome.
Comments: _____

_____

_____

_____

_____

Concomitant Medication (Specify type and Dosage):

_____

_____

_____

Laboratory Follow-up: _____

_____

_____

_____

Investigator Name: _____

Investigator Signature: _____

Date: _____

*Mild = Awareness of sign or symptom but easily tolerated
Moderate = Discomfort enough to cause interference with usual activity
Severe = Incapacitating with inability to work or do usual activity

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 43 | 35 | 1 | 187 | 2 | 25 | 0 | 120/70 | 74 | 120/68 | 72 |
| | | | | | | 0.5 | 110/80 | 72 | 110/78 | 70 |
| | | | | | | 1.0 | 110/78 | 70 | 110/78 | 72 |
| | | | | | | 2.0 | 110/80 | 72 | 110/76 | 72 |
| | | | | | | 4.0 | 114/80 | 72 | 114/80 | 72 |
| | | | | | | 4.5 | 118/82 | 72 | 118/78 | 72 |
| | | | | | | 6.0 | 120/70 | 70 | 120/72 | 70 |
| | | | | | | 8.0 | 120/76 | 72 | 120/76 | 70 |
| | | | | | | 8.5 | 120/72 | 70 | 120/72 | 70 |
| | | | | | | 10.0 | 118/72 | 72 | 118/70 | 70 |
| | | | | | | 12.0 | 122/70 | 72 | 120/68 | 72 |
| 44 | 53 | 0 | 131 | 2 | 0 | 0 | 120/80 | 72 | 120/80 | 70 |
| | | | | | | 0.5 | 120/78 | 72 | 120/78 | 72 |
| | | | | | | 1.0 | 110/76 | 70 | 110/74 | 70 |
| | | | | | | 2.0 | 110/78 | 72 | 110/82 | 70 |
| | | | | | | 4.0 | 112/78 | 72 | 110/78 | 70 |
| | | | | | | 4.5 | 110/76 | 70 | 110/72 | 70 |
| | | | | | | 6.0 | 114/76 | 76 | 112/74 | 74 |
| | | | | | | 8.0 | 116/78 | 74 | 116/76 | 74 |
| | | | | | | 8.5 | 110/74 | 72 | 110/72 | 70 |
| | | | | | | 10.0 | 112/74 | 74 | 112/72 | 72 |
| | | | | | | 12.0 | 118/70 | 72 | 116/70 | 70 |

| | | | | | | | STANDING | | SUPINE | |
|---|---|---|---|---|---|---|---|---|---|---|
| ID | AGE | SEX | WT | CLASS | DOSE | HR | BP | PULSE | BP | PULSE |
| 53 | 32 | 1 | 176 | 2 | 75 | 0 | 130/78 | 66 | 128/78 | 70 |
| | | | | | | 0.5 | 126/78 | 70 | 126/76 | 70 |
| | | | | | | 1.0 | 128/80 | 72 | 126/78 | 72 |
| | | | | | | 2.0 | 126/78 | 70 | 124/76 | 70 |
| | | | | | | 4.0 | 130/78 | 70 | 130/76 | 70 |
| | | | | | | 4.5 | 126/76 | 72 | 124/74 | 70 |
| | | | | | | 6.0 | 128/74 | 70 | 124/70 | 70 |
| | | | | | | 8.0 | 126/74 | 68 | 124/72 | 68 |
| | | | | | | 8.5 | 126/72 | 70 | 126/72 | 70 |
| | | | | | | 10.0 | 129/72 | 68 | 124/72 | 68 |
| | | | | | | 12.0 | 128/74 | 70 | 126/74 | 70 |
| 54 | 34 | 0 | 163 | 2 | 25 | 0 | 100/68 | 60 | 100/68 | 60 |
| | | | | | | 0.5 | 100/70 | 62 | 100/68 | 60 |
| | | | | | | 1.0 | 106/70 | 62 | 104/68 | 62 |
| | | | | | | 2.0 | 108/74 | 64 | 106/72 | 62 |
| | | | | | | 4.0 | 108/74 | 66 | 108/72 | 64 |
| | | | | | | 4.5 | 110/72 | 64 | 108/72 | 62 |
| | | | | | | 6.0 | 104/70 | 62 | 104/70 | 60 |
| | | | | | | 8.0 | 104/70 | 60 | 102/70 | 60 |
| | | | | | | 8.5 | 104/72 | 62 | 102/72 | 62 |
| | | | | | | 10.0 | 104/72 | 64 | 102/72 | 62 |
| | | | | | | 12.0 | 102/70 | 62 | 100/70 | 60 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 59 | 38 | 0 | 130 | 2 | 25 | 0 | 130/86 | 72 | 128/82 | 72 |
| | | | | | | 0.5 | 130/84 | 72 | 128/84 | 72 |
| | | | | | | 1.0 | 132/84 | 70 | 130/82 | 70 |
| | | | | | | 2.0 | 130/84 | 72 | 130/82 | 70 |
| | | | | | | 4.0 | 130/85 | 72 | 130/83 | 70 |
| | | | | | | 4.5 | 127/82 | 70 | 126/82 | 70 |
| | | | | | | 6.0 | 130/82 | 70 | 128/82 | 70 |
| | | | | | | 8.0 | 130/84 | 72 | 129/80 | 72 |
| | | | | | | 8.5 | 130/84 | 70 | 128/83 | 70 |
| | | | | | | 10.0 | 128/82 | 72 | 127/82 | 70 |
| | | | | | | 12.0 | 129/84 | 72 | 128/83 | 72 |
| 60 | 22 | 0 | 184 | 2 | 75 | 0 | 140/82 | 72 | 140/80 | 72 |
| | | | | | | 0.5 | 158/98 | 78 | 158/98 | 78 |
| | | | | | | 1.0 | 154/98 | 78 | 152/98 | 79 |
| | | | | | | 2.0 | 158/98 | 78 | 156/98 | 60 |
| | | | | | | 4.0 | 140/82 | 72 | 139/82 | 72 |
| | | | | | | 4.5 | 142/82 | 70 | 142/82 | 70 |
| | | | | | | 6.0 | 140/82 | 72 | 139/80 | 72 |
| | | | | | | 8.0 | 140/82 | 72 | 138/82 | 72 |
| | | | | | | 8.5 | 140/86 | 74 | 138/84 | 74 |
| | | | | | | 10.0 | 136/84 | 72 | 135/84 | 72 |
| | | | | | | 12.0 | 140/84 | 74 | 138/83 | 74 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 61 | 29 | 1 | 197 | 2 | 25 | 0 | 125/80 | 68 | 124/78 | 66 |
| | | | | | | 0.5 | 128/80 | 66 | 126/78 | 66 |
| | | | | | | 1.0 | 128/82 | 66 | 126/80 | 66 |
| | | | | | | 2.0 | 128/80 | 68 | 127/80 | 68 |
| | | | | | | 4.0 | 130/78 | 68 | 128/78 | 68 |
| | | | | | | 4.5 | 130/80 | 68 | 129/80 | 68 |
| | | | | | | 6.0 | 128/78 | 66 | 127/78 | 66 |
| | | | | | | 8.0 | 126/78 | 66 | 126/78 | 66 |
| | | | | | | 8.5 | 127/80 | 66 | 125/80 | 64 |
| | | | | | | 10.0 | 126/78 | 64 | 124/77 | 64 |
| | | | | | | 12.0 | 128/80 | 66 | 126/79 | 66 |
| 62 | 37 | 0 | 131 | 2 | 75 | 0 | 80/64 | 78 | 80/66 | 78 |
| | | | | | | 0.5 | 82/66 | 78 | 82/66 | 78 |
| | | | | | | 1.0 | 82/64 | 78 | 80/64 | 78 |
| | | | | | | 2.0 | 86/66 | 82 | 84/66 | 82 |
| | | | | | | 4.0 | 86/66 | 80 | 85/65 | 80 |
| | | | | | | 4.5 | 86/64 | 80 | 84/64 | 80 |
| | | | | | | 6.0 | 84/64 | 78 | 82/64 | 78 |
| | | | | | | 8.0 | 84/64 | 78 | 83/63 | 78 |
| | | | | | | 8.5 | 84/64 | 78 | 83/64 | 76 |
| | | | | | | 10.0 | 82/64 | 78 | 82/63 | 76 |
| | | | | | | 12.0 | 84/66 | 80 | 83/64 | 78 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 63 | 31 | 1 | 172 | 2 | 0 | 0 | 130/78 | 84 | 128/78 | 82 |
| | | | | | | 0.5 | 126/74 | 82 | 125/72 | 80 |
| | | | | | | 1.0 | 126/76 | 82 | 124/74 | 82 |
| | | | | | | 2.0 | 128/76 | 84 | 126/76 | 84 |
| | | | | | | 4.0 | 126/76 | 82 | 125/76 | 82 |
| | | | | | | 4.5 | 128/78 | 84 | 127/76 | 82 |
| | | | | | | 6.0 | 126/76 | 82 | 126/76 | 82 |
| | | | | | | 8.0 | 126/74 | 84 | 125/73 | 82 |
| | | | | | | 8.5 | 128/76 | 82 | 127/76 | 82 |
| | | | | | | 10.0 | 128/78 | 82 | 126/78 | 82 |
| | | | | | | 12.0 | 128/77 | 82 | 127/76 | 80 |
| 64 | 29 | 0 | 137 | 2 | 0 | 0 | 118/72 | 68 | 118/72 | 68 |
| | | | | | | 0.5 | 118/74 | 68 | 116/74 | 68 |
| | | | | | | 1.0 | 120/78 | 70 | 118/76 | 68 |
| | | | | | | 2.0 | 118/76 | 68 | 118/76 | 68 |
| | | | | | | 4.0 | 120/78 | 70 | 119/78 | 70 |
| | | | | | | 4.5 | 119/76 | 72 | 118/75 | 72 |
| | | | | | | 6.0 | 120/78 | 70 | 119/78 | 70 |
| | | | | | | 8.0 | 122/80 | 72 | 120/78 | 72 |
| | | | | | | 8.5 | 120/78 | 70 | 120/78 | 70 |
| | | | | | | 10.0 | 120/80 | 70 | 118/80 | 70 |
| | | | | | | 12.0 | 120/80 | 72 | 119/79 | 72 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 67 | 24 | 0 | 180 | 2 | 0 | 0 | 144/84 | 78 | 144/86 | 76 |
| | | | | | | 0.5 | 140/84 | 78 | 140/82 | 78 |
| | | | | | | 1.0 | 142/86 | 78 | 140/84 | 78 |
| | | | | | | 2.0 | 140/86 | 76 | 139/84 | 76 |
| | | | | | | 4.0 | 140/82 | 76 | 140/82 | 76 |
| | | | | | | 4.5 | 142/84 | 78 | 140/82 | 78 |
| | | | | | | 6.0 | 144/86 | 76 | 142/84 | 76 |
| | | | | | | 8.0 | 144/88 | 78 | 141/86 | 78 |
| | | | | | | 8.5 | 144/86 | 78 | 142/86 | 78 |
| | | | | | | 10.0 | 146/88 | 78 | 144/88 | 76 |
| | | | | | | 12.0 | 142/86 | 96 | 140/85 | 76 |
| 68 | 32 | 0 | 175 | 2 | 75 | 0 | 134/90 | 76 | 132/90 | 76 |
| | | | | | | 0.5 | 136/88 | 78 | 134/87 | 78 |
| | | | | | | 1.0 | 134/86 | 76 | 133/86 | 76 |
| | | | | | | 2.0 | 136/88 | 76 | 134/86 | 76 |
| | | | | | | 4.0 | 136/90 | 78 | 135/88 | 78 |
| | | | | | | 4.5 | 136/86 | 76 | 134/86 | 76 |
| | | | | | | 6.0 | 137/85 | 78 | 135/84 | 76 |
| | | | | | | 8.0 | 135/86 | 76 | 133/84 | 74 |
| | | | | | | 8.5 | 136/86 | 78 | 134/86 | 76 |
| | | | | | | 10.0 | 136/88 | 78 | 135/86 | 78 |
| | | | | | | 12.0 | 134/90 | 78 | 132/88 | 76 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 69 | 40 | 1 | 166 | 2 | 25 | 0 | 122/78 | 80 | 124/84 | 84 |
| | | | | | | 0.5 | 126/84 | 80 | 124/82 | 80 |
| | | | | | | 1.0 | 126/84 | 80 | 125/84 | 80 |
| | | | | | | 2.0 | 124/84 | 78 | 122/82 | 78 |
| | | | | | | 4.0 | 124/82 | 80 | 123/82 | 80 |
| | | | | | | 4.5 | 126/86 | 80 | 125/85 | 80 |
| | | | | | | 6.0 | 122/82 | 80 | 122/80 | 80 |
| | | | | | | 8.0 | 124/84 | 78 | 122/82 | 78 |
| | | | | | | 8.5 | 124/82 | 80 | 123/80 | 78 |
| | | | | | | 10.0 | 120/84 | 78 | 120/82 | 78 |
| | | | | | | 12.0 | 124/82 | 80 | 122/80 | 78 |
| 70 | 24 | 0 | 157 | 2 | 25 | 0 | 120/80 | 76 | 120/82 | 76 |
| | | | | | | 0.5 | 122/82 | 78 | 120/80 | 78 |
| | | | | | | 1.0 | 122/82 | 78 | 121/82 | 78 |
| | | | | | | 2.0 | 124/82 | 78 | 122/80 | 76 |
| | | | | | | 4.0 | 126/84 | 80 | 124/82 | 78 |
| | | | | | | 4.5 | 126/84 | 78 | 126/84 | 76 |
| | | | | | | 6.0 | 124/82 | 78 | 122/82 | 78 |
| | | | | | | 8.0 | 126/84 | 80 | 124/84 | 80 |
| | | | | | | 8.5 | 124/82 | 78 | 122/82 | 78 |
| | | | | | | 10.0 | 124/80 | 76 | 123/78 | 76 |
| | | | | | | 12.0 | 122/80 | 78 | 120/78 | 78 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 71 | 30 | 1 | 163 | 2 | 75 | 0 | 118/76 | 70 | 116/76 | 70 |
| | | | | | | 0.5 | 118/80 | 72 | 117/80 | 72 |
| | | | | | | 1.0 | 120/82 | 70 | 119/81 | 70 |
| | | | | | | 2.0 | 120/80 | 72 | 118/79 | 72 |
| | | | | | | 4.0 | 122/78 | 74 | 121/78 | 72 |
| | | | | | | 4.5 | 120/80 | 74 | 118/80 | 74 |
| | | | | | | 6.0 | 122/78 | 72 | 120/78 | 72 |
| | | | | | | 8.0 | 122/78 | 70 | 120/76 | 70 |
| | | | | | | 8.5 | 120/78 | 72 | 119/77 | 72 |
| | | | | | | 10.0 | 122/78 | 74 | 121/78 | 72 |
| | | | | | | 12.0 | 122/78 | 76 | 121/76 | 76 |
| 72 | 21 | 0 | 163 | 2 | 0 | 0 | 108/68 | 70 | 108/68 | 70 |
| | | | | | | 0.5 | 114/74 | 70 | 114/74 | 70 |
| | | | | | | 1.0 | 114/74 | 72 | 112/74 | 72 |
| | | | | | | 2.0 | 112/72 | 70 | 111/72 | 70 |
| | | | | | | 4.0 | 114/72 | 72 | 113/72 | 70 |
| | | | | | | 4.5 | 112/74 | 70 | 110/74 | 70 |
| | | | | | | 6.0 | 112/72 | 70 | 111/71 | 70 |
| | | | | | | 8.0 | 114/74 | 74 | 112/72 | 72 |
| | | | | | | 8.5 | 110/70 | 72 | 109/70 | 72 |
| | | | | | | 10.0 | 112/74 | 70 | 110/74 | 70 |
| | | | | | | 12.0 | 110/76 | 72 | 110/74 | 72 |

| ID | AGE | SEX | WT | WEIGHT CLASS | INIT DOSE | HR | STANDING BP | STANDING PULSE | SUPINE BP | SUPINE PULSE |
|---|---|---|---|---|---|---|---|---|---|---|
| 129 | 28 | 0 | 195 | 3 | 75 | 0 | 134/90 | 70 | 130/90 | 70 |
| | | | | | | 0.5 | 132/90 | 70 | 131/90 | 70 |
| | | | | | | 1.0 | 132/89 | 72 | 130/89 | 72 |
| | | | | | | 2.0 | 132/92 | 72 | 132/90 | 72 |
| | | | | | | 4.0 | 134/92 | 72 | 133/92 | 72 |
| | | | | | | 4.5 | 135/93 | 72 | 134/92 | 72 |
| | | | | | | 6.0 | 137/94 | 74 | 134/92 | 74 |
| | | | | | | 8.0 | 134/92 | 74 | 132/90 | 74 |
| | | | | | | 8.5 | 136/92 | 74 | 135/90 | 74 |
| | | | | | | 10.0 | 136/90 | 72 | 134/89 | 72 |
| | | | | | | 12.0 | 132/88 | 70 | 130/87 | 70 |
| 130 | 60 | 0 | 194 | 3 | 25 | 0 | 154/94 | 80 | 154/92 | 80 |
| | | | | | | 0.5 | 156/92 | 80 | 156/90 | 80 |
| | | | | | | 1.0 | 156/92 | 80 | 155/90 | 80 |
| | | | | | | 2.0 | 154/90 | 80 | 153/89 | 80 |
| | | | | | | 4.0 | 156/92 | 82 | 155/90 | 82 |
| | | | | | | 4.5 | 158/94 | 82 | 156/92 | 82 |
| | | | | | | 6.0 | 160/94 | 80 | 158/93 | 80 |
| | | | | | | 8.0 | 160/94 | 80 | 159/92 | 80 |
| | | | | | | 8.5 | 158/94 | 78 | 158/94 | 78 |
| | | | | | | 10.0 | 160/94 | 82 | 159/94 | 80 |
| | | | | | | 12.0 | 160/93 | 80 | 158/92 | 80 |

# CROSS FILE SHEET

FILE NO: 76N-052N/PR0002

SEE FILE NO: 81N-0022/PR0004