



Department of Energy

Oak Ridge Operations

P. O. Box E

Oak Ridge, Tennessee 37831

707089

FEB 25 1985

Dr. William E. Felling
Executive Director
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831

Dear Dr. Felling:

NIFEDIPINE STUDY FOR PFIZER PHARMACEUTICALS (DOE NO. ERD 85-464)

Enclosed is a signed original and one copy of the subject agreement which ORAU has entered into with Pfizer Pharmaceuticals to conduct a study on the effectiveness of Nifedipine in lowering blood pressure in humans with high blood pressure. Please make note on future agreements, subagreements, etc., regarding this agreement to reference DOE No. ERD 85-464. This is for DOE control purposes only.

DOE concurs that this work is of programmatic interest to us and that ORAU should bill Pfizer for the actual costs incurred (less depreciation and DOE added factor). Also, as stated in your letter of February 11, 1985, DOE would appreciate your sending us the purchase order between ORAU and UT Memorial Research Center and Hospital for our approval.

Sincerely,

William R. Bibb
William R. Bibb, Director
Energy Programs and Support Division

ER-112:Spradlen

Enclosure:
Agreement (original & 1 copy)

cc w/encl:
W. P. Snyder, CC-10, ORO ←

*Unn. Agr. Pfizer
ORAU &
Pharmaceuticals*

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REPOSITORY Oak Ridge Operations
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AGREEMENT BETWEEN
OAK RIDGE ASSOCIATED UNIVERSITIES
AND
PFIZER PHARMACEUTICAL CORPORATION

This agreement entered into this 15th day of February, 1985
by and between Oak Ridge Associated Universities, Inc. (ORAU) acting under
agreement No. DE-AC05-76OR00033 with the United States Department of Energy,
(DOE) and Pfizer Pharmaceuticals, a division of Pfizer, Inc. (Pfizer).

WITNESSETH THAT:

WHEREAS Pfizer wants a drug known as nifedipine tested to determine its
ability to lower blood pressure in humans, and has requested ORAU to conduct
certain tests described herein;

WHEREAS ORAU is negotiating with the University of Tennessee Memorial Research
Center and Hospital (Hospital) to provide services and facilities needed by
ORAU in the conduct of such tests, and

WHEREAS ORAU is willing to conduct such test if it is successful in concluding
an agreement with the Hospital,

NOW THEREFORE, the parties agree as follows:

1. The obligations of ORAU are expressly conditioned on its entering into
an agreement with the Hospital in which to conduct the test described below on
the drug nifedipine.

2. ORAU agrees to conduct a test substantially in accordance with the
protocol titled "A Fourteen Week Double Blind Placebo - Controlled Study

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Comparing Long-Acting Nifedipine and Hydrochlorothiazide in Essential Hypertension" (dated May 7, 1984) which is attached (Attachment No. 1.) hereto and incorporated herein. Any alteration in or amendment to the protocol must be approved in writing by ORAU and Pfizer prior to such alteration or amendment becoming effective.

3. Pfizer agrees to pay ORAU for the cost incurred by ORAU in carrying out the tests with reimbursement to be on the same basis that DOE reimburses ORAU for work performed under the DOE-ORAU agreement. In particular, Pfizer will be billed for the cost elements as indicated in the "Budget" attached (Attachment No. 2 dated February 1, 1985) hereto and made a part of this Agreement.

It is understood that the maximum charge to Pfizer for this work will not exceed \$61,261.00 unless amended by the parties hereto. However, it is also understood that when expenditures and commitments for this work are equal to the stated maximum charge, ORAU will cease the work, finalize the report and submit the final bill to Pfizer, unless Pfizer authorizes in writing an increase in the maximum charge.

ORAU has determined that the results of this work will be of programmatic benefit to the work ORAU is performing for DOE. DOE has concurred in this finding and has agreed that ORAU not be required to bill Pfizer a depreciation charge on DOE facilities (normally about 5%) nor the DOE added factor of 15%.

Payments shall be made as follows:

~~A. Within 15 days of the date of this agreement, Pfizer will pay ORAU 30% of the total estimated cost as reflected in the document titled "Budget" attached hereto and incorporated~~

*See Attachment 2
- pay unit
- schedule.
KHS*

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herein.

B. Within 15 days of receipt of a notice by ORAU that the work is essentially 30% completed, as reflected in a status report submitted with the notice, Pfizer will pay ORAU an additional 30% of the total estimated cost. The status report will consist of:

1. Legible (either handwritten or typed) case records representing all forms provided to the investigator by Pfizer for completion on each patient.

2. Recording on case report forms of all tests, studies and information highlighted in the protocol as being significant tests, studies or other information for purposes of such protocol.

3. Statement on compliance with other aspects of the clinical protocol dealing with individual patients.

C. Within 15 days of receipt of a notice by ORAU that the work is essentially 60% completed, as reflected in a status report submitted with the notice, Pfizer will pay ORAU an additional 30% of the total estimated cost.

D. Final payment of actual cost within thirty (30) days of receipt of the final invoice and status report.

4. The parties agree that each retains all liability for the acts or omissions of its employees, agents, and officers except that Pfizer agrees to pay the costs, including that of treatment of injury to patients injured in or as a result of their participation in this study, and all liability resulting from or connected with its products.

5. In the agreement which ORAU will attempt to obtain with the Hospital in which to conduct this work, ORAU will seek to have that institution agree to retain all liability for its employees, officers, and agents and all liability resulting from or connected with its products. Obtaining such an agreement is

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a condition precedent for the present agreement. Case records on each participant in this study will be generated by the Hospital in which the patients will be examined, etc. These records will include, among other things, the data desired by Pfizer on the results of the drugs on the individual patients. These records are to remain the property of the Hospital; however, Pfizer will be furnished a case report on each patient.

6. Pfizer hereby grants ORAU the right to publish reports, technical or scientific papers or other publications arising from or related to this work or its results provided that such publication does not identify individual patients. Pfizer will be furnished a copy of any manuscript to be submitted for publication and have three months in which to provide any comments-suggestions on the manuscript.

7. This agreement may be terminated by either party thirty (30) days after receipt of a notice to terminate. In such case, ORAU will be paid its cost of performance through the termination date.

8. It is understood and agreed that this agreement is entered into by ORAU for and on behalf of the Government; that title to all supplies furnished hereunder by the Seller shall pass directly from the Seller to the Government, as purchaser, at the point of delivery; that ORAU is authorized to, and will make payment hereunder from Government funds advanced and agreed to be advanced to it by the DOE, and not from its own assets, and administer this Order in other respects for the DOE, unless otherwise specifically provided for herein; that administration of this Order may be transferred from ORAU to the DOE or its designee, and in case of such transfer and notice thereof to the Seller, ORAU shall have no further responsibilities hereunder; and that nothing herein shall preclude liability of the Government for any payment properly due hereunder, if for any reason such payment is not made by ORAU from such

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Government funds.

9. Pfizer will supply ORAU with all drugs necessary to carry out this agreement. The drugs are to be provided to the Hospital at the following address:

The University of Tennessee
Department of Family Medicine
Memorial Research Center and Hospital
1924 Alcoa Highway
Knoxville, TN. 37920

For: Dr. James E. Crook
c/o Dr. George Shacklett

Pfizer warrants that such drugs will be free from all defects.

10. No member of, or delegate to, Congress or resident Commissioner shall be admitted to any share or part of this Agreement or any benefit that may arise therefrom; but this provision shall not be construed to extend to this Agreement if made with a corporation for its general benefit.

11. Pfizer warrants that no person or selling agency has been employed or retained to solicit or secure this agreement upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by Pfizer for securing business. For breach or violation of this warranty, ORAU or DOE shall have the right to annul this Agreement without liability.

12. It is expressly agreed by the parties hereto that this Agreement supercedes any and all previous agreement or agreements and constitutes the entire and only agreement between the parties relative to this Work; that there are no other agreements, understandings, or covenants between the parties hereto of any kind, nature, or description, expressed or implied, which have not been set forth herein.

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13. Pfizer agrees that the only use it will make of the name Oak Ridge Associated Universities or ORAU will be as the author of reports formally submitted by ORAU in accordance with Article 14.

14. ORAU agrees to deliver two copies of a report summarizing the results of the study.

15. Any invention first conceived or reduced to practice under this Agreement will be subject to the patent provisions of the DOE/ORAU Agreement No. DE-AC05-76OR00033.

16. Neither the Government, the DOE, ORAU, nor persons acting on their behalf makes any warranty express or implied (1) with respect to the accuracy, completeness or usefulness of any information furnished hereunder, (2) that the use of any such information may not infringe privately owned rights, (3) that the services, materials, or information furnished hereunder will not result in injury or damage when used for any purpose, (4) that the services, materials, or information furnished hereunder will accomplish the intended results or are safe for any purpose including the intended purpose, (5) that materials accepted for analysis or other service will not be destroyed, lost or otherwise altered in physical or chemical properties, (6) nor shall any implied warranty of merchantability or fitness for a particular purpose apply. Neither the Government, the DOE, ORAU, nor persons acting on their behalf will be responsible, irrespective of causes, for failure to perform the services or furnish the materials or information hereunder at any particular time or in any specific manner.

17. This agreement is of no force or effect until approved by the Department of Energy.

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IN WITNESS WHEREOF, the parties have executed this agreement as of the day and year first above written.

OAK RIDGE ASSOCIATED UNIVERSITIES, INC.

BY William E. Felling
TITLE Exec. Dir.
DATE 12/14/84

PFIZER PHARMACEUTICAL CORPORATION

BY Howard R. Steinberg, M.D.
TITLE Sr. Assoc. Med. Director
DATE 4/1/85

APPROVED BY U. S. DEPARTMENT OF ENERGY

BY James E. Nichols
WILLIAM R. BIBB, DIRECTOR
TITLE ENERGY PROGRAMS & SUPPORT DIVISION
DATE 2/25/85

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Attachment No 1

A FOURTEEN WEEK DOUBLE BLIND
PLACEBO-CONTROLLED STUDY COMPARING
LONG-ACTING NIFEDIPINE TO HYDROCHLOROTHIAZIDE
IN ESSENTIAL HYPERTENSION

CSA0057/004

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Revised 5/7/84

NIFEDIPINE

I. PRINCIPAL INVESTIGATOR:

II. INTRODUCTION:

Procardia^R (nifedipine) is a slow channel calcium blocker that has been studied extensively in the United States and throughout the world for treatment of numerous cardiovascular disease states and is currently marketed in approximately 50 countries. It was approved by the FDA for the treatment of vasospastic and refractory chronic stable angina pectoris in 1982. Nifedipine's anti-hypertensive effect has been documented in several publications. (Editorial, Archives of Internal Medicine, Vol. 141, No. 7, P. 843, June 1981; Thibonnier, M. et. al., European Journal of Clinical Pharmacology, Vol. 17, pp. 161-164, 1980; Guintoli, F., et. al., Current Therapeutic Research, Vol. 30, No. 4, October 1981; Pedersen, O.L., et. al., Journal of Cardiovascular Pharmacology, Vol. 2, pp. 357-366, 1980; Mueller, H.S., et. al., Pharmacotherapy, Vol. 1, pp. 78-94, 1981; Beer, N., et. al., Chest, Vol. 79, No. 5, pp. 571-574, May 1981). Nifedipine's mechanism of action is related to its vasodilatory effect achieved through the blockade of calcium ion influx into the smooth muscle cells of the vasculature. The antihypertensive effect of nifedipine is rapid in onset and persists for 8 to 12 hours. In published reports it has been shown to be effective in the treatment of hypertension secondary to multiple etiologies. Furthermore, since nifedipine is not a beta blocker, it may be a more effective and versatile anti-hypertensive agent in patients with left-ventricular failure, bronchospasm, or conduction abnormalities. Thus, nifedipine may be a valuable therapeutic agent in the treatment of hypertension.

III. OBJECTIVE:

To determine the therapeutic efficacy of the long-acting tablet formulation of nifedipine compared to hydrochlorothiazide (HCTZ) and to placebo in the management of mild essential hypertension in outpatients.

IV. LENGTH OF STUDY:

Each patient will be studied for a maximum of 14 weeks, consisting of a one week tapering off current medications, a three week placebo baseline, a two week titration phase and an eight week efficacy phase.

V. NUMBER OF SUBJECTS:

30 patients will complete the study at each site. This study is being conducted at multiple sites.

VI. INFORMED CONSENT:

The risks and benefits of participating in the study will be explained to each potential subject prior to entering into the study. Written informed consent is also required prior to study entry. Pfizer will provide a sample informed consent form. The final form must be approved by Pfizer; it must contain at least all the elements in the sample form in language readily understood by the subjects. The receipt of informed consent will be recorded in each subject's case record. The signed consent form will be retained by the investigator.

VII. INSTITUTIONAL REVIEW:

Prior to shipment of study medication, the investigator will provide Pfizer with written documentation that the study protocol and informed consent forms have been approved by the appropriate institutional review committee. Additionally, the DHHS assurance number or the names and occupations of committee members will be provided.

VIII. CRITERIA FOR PATIENT INCLUSION:

- A. Adults with mild hypertension aged 21 or older
- B. Males, or females who are beyond childbearing potential (postmenopausal or surgically sterilized)
- C. Hypertension as defined by an average of two diastolic blood pressures in the range of 95-105 mm Hg (off all antihypertensive medication) in the sitting position, documented on two separate occasions during the placebo run-in. ~~(at the end of weeks 2 and 3, see Sec X. 2.)~~
- D. Hypertension which is not caused by the following conditions:
 1. Hyperaldosteronism
 2. Pheochromocytoma
 3. Renal artery stenosis
 4. Coarctation of the aorta
 5. Cushing's disease or syndrome

IX. EXCLUSION CRITERIA:

- A. Women of childbearing potential
- B. Concomitant therapy with agents that are not being prescribed as antihypertensive therapy but that have antihypertensive effects or with agents that cause systemic vasodilation such as the use of long acting nitrates, beta blockers, or calcium channel blockers
- C. Therapy with another investigational drug within the previous month
- D. Angina pectoris or intermittent claudication
- E. Concurrent serious disease
- F. Presence of cardiac decompensation as evidenced by the presence of clinical heart failure, left ventricular hypertrophy on electrocardiogram, serious arrhythmia, or greater than second degree heart block
- G. Presence of liver disease or hepatic dysfunction as evidenced by history or by the presence of abnormal liver function tests
- H. Presence of renal decompensation as evidenced by a serum creatinine of greater than 2.0 mg/dl and/or blood urea of 50 mg/100 ml or above
- I. Presence of orthostatic hypotension due to autonomic dysfunction and unrelated to medication or dehydration
- J. Myocardial infarction or cerebrovascular accident within the previous six months
- K. Evidence of end organ (ophthalmic-Grade III or IV, renal or cardiac) damage
- L. Significant psychiatric disorder
- M. Known previous intolerance to nifedipine
- N. Blood donation during the study period or one month preceding entrance into the study
- O. Gross obesity
- P. Chronic diarrhea (including a history of ulcerative colitis or regional enteritis)
- Q. History of documented diverticulitis, partial or complete gastrectomy or small bowel resection

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X. EXPERIMENTAL PROTOCOL:

A. General Design

The study is designed as a double-blind, parallel trial with three treatment groups: placebo, HCTZ, nifedipine long acting tablet formulation. Patients may either be presently treated with antihypertensive therapy or on no therapy but requiring it. For patients currently being treated with antihypertensive medication, it is divided into four phases:

Phase I. During the first week of the study, patients will be tapered off all their antihypertensive medication.

Phase II. A three week single-blind, placebo baseline period will follow during which patient compliance will be evaluated and blood pressures will be recorded. Patients on no previous therapy will enter the study at this phase.

Phase III. A two week titration phase to reach optimal dose.

Phase IV. An eight week efficacy phase of placebo vs. nifedipine vs. HCTZ will follow during weeks 6 through 13.

B. Elimination of Variable Factors

1. Diet - Patients will be instructed to maintain their current dietary habits, including sodium intake, and not to deviate from this regimen for the duration of the trial.

2. Blood Pressure Determinations - Blood pressure determinations will be made using the same sphygmomanometer and the patient's same arm throughout the course of the study. Four/six blood pressure readings will constitute each determination as follows:

a. Sitting BP and heart rate will be taken after the patient has been in a sitting position for three minutes, and repeated 2 minutes later.

b. Standing BP and heart rate will be taken after the patient has been in a fully erect position for three minutes, and repeated 2 minutes later.

If the difference between the two sitting or the two standing diastolic readings is greater than 10 mm Hg, a third measurement will be taken.

All blood pressures should be recorded in the case report form.

The diastolic determination will be the point at which there is cessation of sound (Korotkoff Phase V).

The same investigator or study nurse will monitor blood pressure measurements in individual patients at each visit throughout the study. The appropriate size cuff will be used in all patients. For all return visits, patients will be evaluated approximately 24 hours after their last dose of study medication (i.e., just prior to the morning dose).

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C. Phase I - Tapering Phase (Week -1)

1. On day 1 of Phase I patients will have the following evaluations:
 - a. Complete history and physical examination
 - b. Weight
 - c. Sitting and standing blood pressure (as described in Sec. X.B.2.), heart rate
 - d. CBC with differential and platelet count
 - e. SMA-18 or -20
 - f. Urinalysis
 - g. Standard 12-lead ECG
 - h. Chest X-ray - PA and lateral

Patients will be tapered off all their antihypertensive medication over one week. (Each investigator will determine the manner of tapering depending on the patient's current regimen.)

2. The patients will return at the end of week-1, at which time the evaluations listed below will be performed.
 - a. Sitting and standing blood pressure (as described in Sec. X.B.2), heart rate
 - b. Adverse experiences evaluation.

D. Phase II - Placebo Baseline Phase (Weeks 1, 2 and 3)

Patients not on previous antihypertensive treatment will enter the study at this point and will have the evaluations described under Section C.1. All patients will be given placebo tablets and instructed to take one of each tablet (one is a placebo of the diuretic and one is a placebo of nifedipine tablet) each day immediately following breakfast for the following seven days. At the end of the first week of the placebo baseline period, the patients will return and receive additional tablets and the same instructions. On the day of their return visit at the end of weeks 2 and 3, the patients will be instructed not to take the tablet at home but to take it in the clinic/office after blood pressure and heart rate measurements are taken. The following evaluations will be performed at the end of weeks 2 and 3:

1. Sitting and standing blood pressure as described in (Sec. X. B.2.), heart rate
2. Adverse experience evaluation
3. Patient drug compliance
4. Blood chemistry (SMA-18 or -20) (end of week 3 only)
5. Urinalysis (end of week 3 only)
6. Weight (end of week 3 only)
7. Physical examination (end of week 3 only)

E. Criteria to Advancement to Phase III

At the end of week 3 the patient will be evaluated to determine if the following criteria are met in order for the patient to advance.

1. Blood Pressure Stabilization: The patient's average sitting diastolic blood pressure as recorded both at the end of week 2 and at the end of week 3 must be within the 95 - 105 mm Hg. range.
2. Compliance in placebo run in (Phase II) between 80-110%.

If these criteria are not met, the patient will be dropped from the study.

F. Phase III - Dose Titration Phase (Weeks 4 and 5)

1. Entry

Patients meeting all criteria for entry into this phase will be assigned a study number and receive their initial medication using a computer-generated randomization code. Patients not meeting all entry criteria will receive a study number from a different set beginning with 101.

2. Design

Patients meeting entrance criteria will be assigned to receive placebo, 30 mg nifedipine tablets or 25 mg of hydrochlorothiazide. (To preserve blindness, "double-dummy" placebo will be used.) At the end of week 3, the patients will receive these study drugs. They will all be instructed to take one of each tablets each day immediately after breakfast starting the following morning (first day of Phase III). At the end of week 4 the patients will return for an evaluation of the following:

- a. Sitting and standing blood pressure (as described in Sec. X.B.2.), heart rate
- b. Adverse experience evaluation
- c. Drug compliance by pill count

If patients have had no significant adverse experiences on the study medications and their average diastolic blood pressures are 90 mm Hg or greater, they will receive the higher dose of each medication (a 60 mg nifedipine tablet, or a 50 mg HCTZ tablet or the appropriate placebo) for one week. If the average diastolic blood pressure is less than 90 mm Hg, then they will remain on their present dose for one week.

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At the end of week 5 the patients will return for an evaluation of the following:

- a. Sitting and standing blood pressure and heart rate (see Sec. X.B.2.).
- b. Adverse experience evaluation
- c. Drug compliance by pill count

If the patients taking the lower dose of medication have had no adverse experiences and their diastolic blood pressures are 90 mm Hg or greater, they will receive the higher dose of medication (a 60 mg nifedipine tablet or a 50 mg HCTZ tablet or the "higher" placebo) for the completion of the study. Patients already receiving the higher dose of study medications who have had no adverse experiences will remain on this dose for the completion of the study. Those patients whose blood pressure is less than 90 mm Hg will remain on their present dose.

G. Phase IV - Eight Week Efficacy Phase (Weeks 6-13)

The patients will return at the end of weeks 7, 9 and 13 at which time evaluations will be performed:

- a. Standing and sitting blood pressure and heart rate (as described in Sec.X.B.2.), heart rate.
- b. Adverse experience and drug compliance will be evaluated.
- c. SMA-18 or 20
- d. Week 13 only
 - 1) physical examination
 - 2) weight
 - 3) CBC with differential platelet count
 - 4) urinalysis
 - 5) Standard 12-lead ECG

A repeat chest x-ray will be done only if it is medically indicated.

If during the efficacy portion of Phase IV the patient's drug compliance falls to less than 80% or exceeds 110%, the patient will be permitted to continue in the study for 1 week. At the end of the week the patient will return for a visit to evaluate whether compliance is improved. If compliance is not improved to greater than 80% or less than 110%, the patient must be discontinued for poor compliance.

If adverse experiences are encountered and the patient wishes to continue in the study, the investigator has the option of continuing therapy at the same dosage level to see if adverse symptomatology resolves in the course of the following week. If adverse reactions occur in patients taking the higher dose of study medication, the dosage may be decreased to the lower dose. During the efficacy phase, the dose may not be increased.

XI. MEDICATION:

A. Randomization

Medication will be dispensed as placebo which is identically matching to the nifedipine tablets, placebo identically matching to the HCTZ tablets, 30 mg and 60 mg nifedipine tablets, and 25 mg and 50 mg HCTZ tablets in individually coded blister cards prepared for each patient. A double-blind label will be attached to each card. Part of this label will be removed and attached to the patient's case record form so that if necessary the investigator will know what medication the patient is taking.

Patients will be assigned to treatment regimens in balanced blocks by a computer-generated random number.

B. Concurrent Medication

Concurrent medications to be excluded are listed under Section IX, B.

C. Storage and Accounting of Study Medication

The investigator must store all study medication in a secure area. Medication will be dispensed under the direct supervision of the investigating physician. The "tear-off" portion of the medication label will be attached to the case record. All study medications will be accounted for on the study medication inventory sheet. All unused study medication, including all used and unused blister cards, will be returned to Pfizer.

XII. DISCONTINUATION OF PATIENTS FROM THE STUDY:

Patients may be discontinued if any of the following occur:

- A. Intolerable or severe adverse experiences related to significant blood pressure reduction,
- B. Other significant drug related adverse experiences,
- C. Reduction of blood pressure to levels the investigator believes is detrimental to patient safety, or elevation of the average diastolic blood pressure to a level greater than 105 mm Hg,
- D. Inadequate blood pressure reduction by week 9
- E. Any reason which, in the investigator's opinion, will jeopardize the patient's care in the trial (eg., severe intercurrent illness),

At the time of discontinuation, the clinical summary must be completed. In addition, the tests outlined in Section X.F., 1-3 should be completed. Appropriate alternate therapy may then be initiated.

XIII.

SAFETY:

All patients will have a complete history, physical examination, and laboratory evaluation before entering the trial. This complete testing will be repeated at the end of the efficacy phase of study drug therapy. Laboratory abnormalities will be commented on and/or repeated until they return to baseline values or normalize.

The incidence and severity of all observed or volunteered adverse experiences will be recorded by the investigator at each examination during all phases of the study.

If patients drop out of the study, the reasons for this must be thoroughly explained and documented in the clinical summary report.

If the attending physician judges that optimal care would be jeopardized by continuing a patient in the trial, that patient should be removed from the study.

If the investigator withdraws patients from the study due to serious adverse experiences, significant laboratory abnormalities, or for any reason, the circumstances and data will be clearly documented on the case report forms. The investigator will supply documentation of the medical follow-up of patients dropped due to severe, unanticipated or drug-related adverse experiences.

The investigator agrees to institute procedures to ensure his availability to the patient and/or the patient's regular physician should significant untoward reactions or problems occur during the study and to make these procedures known to those individuals at the time of entrance into the study.

Serious adverse experiences and deaths should be reported to the medical monitor Caren Heller, M.D., (212) 573-3265 (days) or (212) 573-7936 (nights and weekends) within 24 hours.

XIV.

RECORDS:

A set of individual case report forms which have been approved by both the sponsor and the investigators will be kept for each patient. Data recorded will include complete history and physical examinations, laboratory data, chest X-ray and all the clinical parameters specified above.

All report forms will be kept up to date and will be submitted to the sponsor at regular intervals. The sponsor will review the data at intervals during the study.

XV.

APPROVAL

I, _____ M.D., agree to conduct this study according to the above protocol and to make no additions and/or changes thereto without the consent of the sponsor.

Principal Investigator:
CSA0057/004

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Date

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BUDGET

A Fourteen Week Double-Blind
Placebo-Controlled Study of Long Acting
Nifedipine in Essential Hypertension

| | | | | | |
|-------------------------------|-------|-----|-------|---|---------|
| Initial visit-patient history | | 1 x | \$270 | = | \$270 |
| Clinic visits | | 8 x | \$ 60 | = | \$480 |
| Physical exam | | 3 x | \$100 | = | \$300 |
| Chest x-ray | | 1 x | \$ 60 | = | \$ 60 |
| Laboratory work | 5 SMA | 3 x | | } | = \$210 |
| (CBC, SMA-12, urinalysis) | 3 CBC | | | | |
| | 3 UA | | | | |
| Electrocardiogram | | 2 x | | | |

SUBTOTAL PER PATIENT = \$1,320 x 30 Patients = \$39,600.00

ADMINISTRATIVE COSTS _____

54.7% OVERHEAD EXPENSES 21,661.00

TOTAL PROJECTED BUDGET FOR 30 PATIENTS = \$61,261.00

PAYMENT SCHEDULE

A. Pfizer will pay ORAU initially 12% of the total estimated cost as reflected in the document titled "Budget" attached hereto and incorporated herein. This payment shall be made at or before the initiation of the study.

B. Pfizer will pay an additional 22% of the total estimated cost upon the completion of $\frac{1}{4}$ of the designated work, an additional 22% upon the completion of $\frac{1}{2}$ the designated work, an additional 22% upon the completion of $\frac{3}{4}$ of the designated work, and the final 22% upon completion of the study. The designated work will consist of:

1.) Legible (either handwritten or typed) case records representing all forms provided to the investigator by Pfizer for completion on each patient.

2.) Recording on case report forms of all tests, studies and information highlighted in the protocol as being significant tests, studies or other information for purposes of such protocol.

3.) Statement on compliance with other aspects of the clinical protocol dealing with individual patients.

HRS

ATTACHMENT I
TO
PURCHASE ORDER NO.

In order for Dr. Crook to carry out the testing of nifedipine and its ability to lower blood pressure in humans, a fourteen week double blind placebo-controlled study will be conducted. Dr. Crook is to involve thirty patients in this study and is expected to have 10-15 patients active at any one time. These patients will be selected from patients identified under UT's Family Practice Program. The actual contact with the patients by Dr. Crook will be in the Family Practice Unit (Unit) at the UT Hospital. The Unit will arrange for and provide the following:

1. Identification and referral of suggested patients for the program. The Unit will use its computer data base to select patients as likely participants in the program. Dr. Crook will make the final selection of the 30 patients and any alternates. The charge for this service is \$_____.

2. The Unit will make available an examining room with standard examining room equipment. A nurse shall be present when any female patients are being examined by Dr. Crook. It is estimated that Dr. Crook will see four (4) patients per hour, 4-8 patients per day; once a week.

The charge for these services will be (a) \$_____ per hour for the use of the room and (b) \$_____ per hour for nursing services.

3. The Unit will furnish a secure space to store the drugs used by Dr. Crook in these studies. Dr. Crook will be responsible for the inventorying, dispensing, and record keeping of said drugs. The charge for this service shall be \$_____.

4. The Unit will furnish clerical assistance such as arranging appointments, pulling patient files, filing new material from this study in patient files, refiling files, etc.

The charge for this service shall be \$_____ per hour.

5. The Unit will arrange to draw blood from patients identified by Dr. Crook and obtain SMA-18.

The charge for this service shall be \$_____ for each sample drawn and analyzed.

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6. The Unit will arrange to draw blood from patients identified by Dr. Crook and obtain analysis for CBC with differential and platelet count.

The charge for this service will be \$ _____ for each sample drawn and analyzed.

7. The Unit will arrange to secure urine samples from patients identified by Dr. Crook and obtain analysis for routine and microscopic.

The charge for this service shall be \$ _____ for each sample obtained and analyzed.

8. The Unit will arrange for a PA and lateral chest X-ray for each patient identified by Dr. Crook and arrange for the X-ray to be read by a radiologist.

The charge for this service will be \$ _____ for each X-ray and reading.

9. The Unit will arrange for EKG's for each patient identified by Dr. Crook and arrange for the EKGs to be read by a cardiologist.

The charge for this service will be \$ _____ for each EKG and reading.

The results of the blood and urine tests, as well as the results of EKGs and X-rays, are to be furnished to Dr. Crook as soon as they are available.

It is agreed and understood that the above listed charges are the Seller's standard charge for the described services.

A copy of all data generated on each patient will be made and provided to Pfizer at the conclusion of the experiment. The data regarding each of the patients will be included in his/her hospital record.