INVESTIGATOR AGREEMENT

Project/Protocol:	Paroxetine 29060/329
Protocol Date:	August 20, 1993
Investigator Name:	Neil Ryan M.D. Boris Birmaher M.D.
Telephone Number:	(412) 624-1231
Study Site Address:	Western Psychaitric Institute and Clinic University of Pittsburgh School of Medicine 3811 O'Hara Street Pittsburg, PA 15213

the University of Pittsburgh, by and through its faculty and employees,

WHEREAS, SmithKline Beecham Pharmaceuticals, a division of SmithKline Beecham Corporation (the "Company") and Neil Ryan M.D. & Boris Birmaher, M.D. (the "Principal Investigator(s)") have agreed that the Company will sponsor a study to be conducted by the Principal Investigator(s) of the drug identified in the protocol named herein; and the Principal Investigator(s) has the personnel and facilities to undertake the study; NOW, THEREFORE, the parties agree as follows:

INITIALS

1. Scope of Work:

The Principal Investigator(s) shall conduct the study of Paroxetine (the "Study Drug") described in the protocol 29060/329 entitled "A Multi-Center, Double-Blind, Placebo-Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression", dated August 20, 1993, (the "Protocol") which is hereby incorporated into this Agreement by reference. The Principal Investigator(s) shall exercise due care in conducting the study in compliance with all applicable Food and Drug Administration ("FDA") regulations, as reflected on FDA Form 1572, and in accordance with the Protocol, without changes, except as agreed to and approved in writing by the Company and, where required, the Principal Investigator(s)'s research Institutional Review Board ("IRB").

2. Period of Performance:

This study shall be conducted under the following schedule, with such scheduling changes as may, from time to time, be mutually agreed upon by the parties:

Study Initiation:	Approximately on or before: ~~November 1, 1993~~ January 1, 1994
Patient Enrollment Complete:	Approximately on or before: March 1, 1997
Study Completion:	Approximately on or before: November 1, 1997

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3. Payment:

Payment of costs associated with the Protocol shall be as follows:

(a) Itemized Per Patient Budget: Payment for Qualified Subjects/Patients enrolled into the study will be based on a per patient budget attached hereto and incorporated herein which shall include up to 50 patients. "Qualified Subjects/Patients" are defined as evaluable subjects/patients who have satisfied all protocol requirements, including compliance with dosing regimen and visit schedule, and can be included in the statistical analysis for the study.

Payments are subject to the following terms:

(i) A payment will not be made for any subject/patient who is not qualified to participate in the Protocol based on the inclusion and exclusion criteria contained in the Protocol. Questions pertaining to a subject/patient's eligibility must be addressed to and resolved by the Company Medical Monitor identified in the Protocol prior to that subject/patient's entry into the study.

(ii) Payment will not be made for any subject/patient who is not evaluable due to failure to comply with the Protocol.

(iii) Payments for Qualified Subjects/Patients dropped from the Protocol will be based on actual costs as defined in the budget, provided that complete documentation is submitted.

(iv) Payments for Qualified Subjects/Patients enrolled in the study over the maximum number, provided the Company agrees to include such additional subjects/patients, shall be made in accordance with the schedule set forth in (c), below.

(b) Payment Schedule: The schedule of payment is as follows:

10% 5% of the total grant will be paid upon initiation of the study
20% of the per patient budget will be paid, as each group of three (3) patients complete the week four (4) visits
20% of the per patient budget will be paid, as each group of three (3) patients complete the month two (2) visits
20% of the per patient budget will be paid, as each group of three (3) patients complete the month four (4) visits
20% of the per patient budget will be paid, as each group of three (3) patients complete the month six (6) visits
10% 15% of the grant will be upon completion of the study and when all case report forms have been submitted and reviewed by SmithKline Beecham. This payment will be used to make adjustments for discontinued patients.

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(c) Payment for Subject/Patients Over Maximum Enrollment

Provided that the Company agrees to include such subjects/patients, payment for Qualified Subjects/Patients shall be made as follows:

20% of the per patient budget upon enrollment and then follow schedule described in section 3(b)

(d) Payment of Advertising

Advertising costs will be invoiced on Actual Costs. These costs are not to exceed $1,000 per year.

4. Confidentiality and Publication:

All unpublished information given to the Principal Investigator(s) by the Company in connection with this Agreement or the conduct of the Protocol is confidential and/or proprietary to the Company and shall not be published or disclosed to a third-party without the prior written consent of the Company. This paragraph shall not apply to information which:

(a) at the time of receipt by the Principal Investigator is in the public domain; or

(b) after its receipt by the Principal Investigator is made public by a third party, unless such publication was improper; or

(c) was in the possession of the Principal Investigator before receipt from the Company and was developed independently or acquired directly or indirectly from a source wholly independent of the Company; or

(d) is the subject of a valid subpoena or is otherwise required by law to be disclosed, provided that prompt notice is given to the Company of the requirement of such disclosure.

The obligations of this paragraph pertaining to confidentiality shall survive the termination of the Agreement.

The Principal Investigator(s) shall have the right to publish and/or disclose publicly information and/or data arising from the Protocol, provided, however, that the text of any such publication and/or public disclosure shall be submitted to the Company to review for confidential or proprietary information and for comment at least thirty (30) days prior to submission for publication or other disclosure and further provided that, at the Company's request, such submission shall be deferred for a further period not exceeding one hundred ~~eighty~~ (180) days to enable the Company to protect its rights in such confidential or proprietary information. fifty (150)

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5. Inventions & Discoveries:

All patentable inventions and discoveries made or conceived in the course of or as a result of the Study shall be solely owned by the Company. Whenever requested to do so by Sponsor, Institution will at Sponsor's expense, execute any and all documents or other instruments and give testimony which Sponsor shall deem necessary to apply for and obtain patent(s) in any country or to otherwise protect Sponsor's interest therein. These obligations shall continue beyond the termination of this Agreement and shall be binding upon Institution's assigns, administrators and other legal representatives.

6. Indemnification:

and University of Pittsburgh Medical Center and affiliates

Except as set forth below, the Company agrees to defend, indemnify and hold harmless the Principal Investigator(s) and/or University, its trustees, officers, agents and employees from any liability, loss, damage and expense, including attorneys' fees and costs, in connection with any claim or lawsuit, regardless of merit, brought against the Principal Investigator(s) for personal injuries (including death) or property damage allegedly arising from the Protocol. The Company shall have the exclusive right to manage claims and control litigation, including compromise or settlement. The Company's obligations under this paragraph 6 shall survive the termination of this Investigator Agreement.

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Notwithstanding the foregoing, the Company shall have no obligations pursuant to this Agreement to defend or indemnify the Principal Investigator(s) from liability, loss, damage or expense arising from: (1) the negligence or willful misconduct of the Principal Investigator(s) (2) the Principal Investigator(s)'s failure to adhere to the terms of the Protocol or the Company's written instructions with respect to the Protocol; or (3) the Principal Investigator(s)'s failure to comply with state or federal regulations, including FDA regulations. In addition, the Company shall have no obligations under this Article unless the Principal Investigator(s) (1) gives the Company prompt notice of any claim or lawsuit for which it seeks to be indemnified under this Agreement; and (2) cooperates fully with the Company and its agents in defense of the claim or lawsuit.

In addition to the foregoing obligations, the Company will be responsible for medical expenses not covered by other insurance or government programs, which are incurred by any Qualified Subject/Patient in the Protocol and which arise from his or her direct participation in the Protocol, unless a diagnostic work-up establishes that the condition giving rise to such expenses was unrelated to the Protocol, in which event the Company's responsibility shall be limited to medical expenses reasonably incurred in connection with the diagnostic work-up. Review and approval from the Medical Monitor is required in advance of such expenditures.

7. Insurance:

The Company shall, through its self-insurance program, provide comprehensive general liability insurance in amounts not less than $2,000,000.00 per incident and $5,000,000.00 annual aggregate. Such insurance shall provide (1) product liability coverage and (2) broad form contractual liability coverage. Upon written request, the Company shall provide the Principal Investigator with written evidence of its self-insurance program.

8. Termination:

The Company reserves the right to terminate this Investigator Agreement in part or in whole at any time by giving thirty (30) days written notice to the Principal Investigator(s). The thirty (30) day notice shall not apply if the Company, in its sole opinion, deems that the safety of the patients will be compromised by the delay.

Notwithstanding the above, either party may immediately terminate this Investigator Agreement by written notice of breach by the other. Breach shall be defined as a failure to comply with any provision of the Investigator Agreement and the documents incorporated herein.

In the event this Investigator Agreement is terminated, the Company shall reimburse the University for all patient costs, compensable under paragraph 3, incurred to the effective date of termination. If the amount the Company has previously paid to the University exceeds the amount that is actually earned, the University shall reimburse the balance to the Company after he/she receives written notice of the final accounting.

MWC INITIALS

9. Independent Contractor:

The University's relationship to the Company in the performance of this Investigator Agreement is that of an independent contractor.

10. Changes:

This Investigator Agreement may be amended only by the further written agreement between authorized representatives of the parties.

11. Order of Precedence:

In any conflict between the terms of this Investigator Agreement and the documents incorporated herein the terms of this Investigator Agreement shall take precedence.

12. Applicable Law:

This Investigator Agreement shall be construed, interpreted and enforced under the laws of the Commonwealth of Pennsylvania.

13. Assignment:

The Principal Investigator(s) may not assign this Investigator Agreement without the prior written approval of the Company.

ACCEPTED AND AGREED TO:

SmithKline Beecham Pharmaceuticals

Essie N Earle
By

Aug 31 1993
Date

If the terms of this Investigator Agreement are acceptable to you, please sign below, indicate to whom checks should be made payable, and provide the following information:

ACCEPTED AND AGREED TO:

Principal Investigator(s):

Signature
Neal Ryan, M.D.
Typed Name
Date: 12/13/93
Month/Day/Year

Signature
Typed Name
Month/Day/Year

Checks Payable to: University of Pittsburgh
Must be consistent with Federal Form W-9
Federal Tax I.D. Number: 25-0965591
or
Social Security Number

Mail to: The University of Pittsburgh
Comptroller's Office/Research Accounting
Lock Box 371220
Pittsburgh, PA 15251-7220
Attn: William G. Laird

Telephone: (412) 624-7400 Attn: Kim Carter

If you are a clinical investigator associated with a Veterans Administration hospital and/or a Medical School/University hospital and the proposed study will be conducted under the auspices of and in either or both of these institutions, you must obtain the institution's Chief Operating or Financial Officer's signature(s) or sign below indicating that such approval is not required.

Veterans Administration Hospital

Not Applicable:
Signature

Date

Medical School/University Hospital

Not Applicable:
Signature

Date

Chief Operating or Financial Officer:

Signature
Michael Crouch
Typed Name
Director, Office of Research
Title

Institution: University of Pittsburgh
Typed Name

Date: 12,14,93
Month/Day/Year

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GUIDELINES FOR PATIENT INFORMED CONSENT

Basic Elements:

The following eight (8) elements must be contained in the informed consent:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed and identification of any procedures which are experimental.

2. A description of any reasonably foreseeable risks or discomforts to the patient.

3. A description of any benefits to the patient or to others which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.

5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and, that notes the possibility that the Food and Drug Administration and a representative of SmithKline Beecham may inspect the records.

6. For research involving a more than minimal risk, 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.

7. An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights, and whom to contact in the event of a research-related injury to the patient.

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

Additional Elements

When appropriate one or more of the following elements of information **shall** also be provided to each patient.

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus, if the patient is or may become pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the patient's participation may be terminated by the investigator without regard to the patient's consent.

3. Any additional costs to the patient that may result from participation in the research.

4. The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.

5. A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient.

6. The approximate number of patients involved in the study.

7. All information concerning payment of a stipend, including the amount and schedule of payment, must be set forth in the informed consent form.

You should note that the informed consent requirements in these regulations are not intended to preempt any applicable Federal, State or Local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State or Local law.

The documentation of informed consent must contain the following elements:

A. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the patient or the patient's legally authorized representative. A copy shall be given to the person signing the form.

B. Except as provided in 21 CFR 56.109(c), the consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent required above. This form may be read to the patient or the patient's legally authorized representative, but, in any event, the investigator shall give either the patient or the representative adequate opportunity to read it before it is signed.

2. A "Short Form" written consent document stating that the elements of informed consent required above have been presented orally to the patient's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the patient or the representative. Only the short form itself is to be signed by the patient or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the patient or the representative in addition to a copy of the short form.

Finally, the exception for the necessity of documenting informed consent which is referred to in 21 CFR 56.109(c) involves the following conditions:

C. An IRB shall require documentation of informed consent in accordance with 21 CFR 50.27 except that the IRB may, for some or all patients, waive the requirement that the patient or the patient's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to patients and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide patients with a written statement regarding the research.