MASTER CLINICAL RESEARCH AGREEMENT

This Agreement is entered into as of this 1st day of May, 1996, by and between

The University of Texas Health Sciences Center at San Antonio, The University of Texas Health Science Center at Houston, The University of Texas - M.D. Anderson Cancer Center, The University of Texas Southwestern Medical Center at Dallas, and The University of Texas Medical Branch at Galveston, (each an "Institution") each with an office and place of business as set forth on Exhibit 1 hereto and each a component of The University of Texas System located at 201 West 7th Street, Austin, Texas 78701

and

Hoffmann-La Roche Inc., a New Jersey corporation with its office and place of business at 340 Kingsland Street, Nutley, New Jersey 07110 (the "Sponsor").

WHEREAS, Institution possesses certain expertise in the field of pharmaceutical clinical and related research and evaluation of such research; and

WHEREAS, Sponsor is interested in engaging Institution in order to obtain the benefit of such expertise with respect to research and development projects being conducted by Sponsor into the clinical development, effectiveness and efficiency of various pharmaceutical compounds or products being developed by Sponsor;

Therefore, in consideration of the premises and undertakings set forth herein, Institution and Sponsor agree as follows:

1. **Clinical Study Protocol Riders**

(A) Whenever Sponsor wishes Institution to perform clinical research on an identified pharmaceutical compound (the "Compound"), Sponsor will provide a copy of the study protocol to Institution and Sponsor and Institution shall agree on (a) a budget setting forth the cost for all the activities described in the study protocol and the payments terms (the "Budget"), (b) a designated Principal Investigator, and (c) a study schedule for the clinical study to be performed pursuant to the study protocol. (the study protocol and these other items are collectively referred to as the "Study").

(B) For each Study in which Institution shall participate, a Clinical Study Protocol Rider, in the form attached hereto as Attachment A, shall (a) be prepared by Sponsor, (b) have attached to it as Exhibit 2 thereto a copy of the subject Study protocol (the "Protocol") and (c) be executed by both Sponsor and Institution. Each Clinical Study Protocol Rider shall be subject to the terms of this Agreement and are incorporated herein and upon execution by both Sponsor and Institution become an integral part of this Agreement by this reference.

2. **Scope of Work**

For each Study conducted under the terms of this Agreement:

(A) Sponsor shall use its best efforts to supply Institution with sufficient clinical supplies of the Compound which is the subject of the clinical study necessary to perform the services required hereunder.

(B) Institution shall perform those research activities and tests with the Compound as described in the Protocol for the subject Study. Sponsor may, from time-to-time, in its sole discretion modify the Study and/or the Protocol.

(C) Institution shall comply with all the terms and requirements of the Study and Protocol, and shall not make any changes thereto, nor deviate therefrom, without the prior written consent of Sponsor.

(D) If any terms of this Agreement are in conflict with any terms of the Study or Budget, the terms of this Agreement shall govern.

3. **Payment**

Payments by Sponsor to Institution shall be in accordance with the Budget set forth on each respective Clinical Study Protocol Rider and shall constitute full payment for each Study and Sponsor shall have no other payment obligations hereunder.

4. **Principal Investigator**

The Principal Investigator for each Study shall be agreed between the Sponsor and Institution designated on the Clinical Study Protocol Rider. The Principal Investigator shall be responsible for performing the Study and the direct supervision of any individual performing portions of the Study. In the event the Principal Investigator becomes unable to perform any of the activities in the Study or complete the Study for any reason, Sponsor and Institution may mutually agree to a substituted Principal Investigator, in which event this Agreement shall continue in full force and effect. Institution shall use its best efforts to identify and obtain a substitute Principal Investigator acceptable to Sponsor. If Sponsor and

Institution cannot agree on a substitute Principal Investigator, Sponsor may immediately terminate this Agreement in accordance with Sections 10(B) and 10(C).

5. **Confidentiality**

(A) During the term of this Agreement, Institution may obtain certain Confidential Information, as defined in Section 5(B), either from Sponsor or from performing the Study.

(B) "Confidential Information" shall mean (i) any and all information, data, know-how, whether written or oral, technical or non-technical, as well as tangible materials, including without limitation samples, models, drawings, or diagrams which Institution receives from Sponsor; and (ii) case reports and any other data or information resulting from the Study which is not published as provided in Section 6.

(C) With respect to Phase II Studies, for a period of six (6) years after completion or termination of the Study, or, with respect to Phase III Studies or other Studies for a period of four (4) years after completion or termination of the Study, Institution agrees (i) to use the Confidential Information only in connection with its performance of this Agreement; (ii) to treat the Confidential Information as it would its own proprietary and confidential information; (iii) to disclose the Confidential Information only to employees or agents of the Institution that agree to be bound by these confidentiality obligations and who need to know such Confidential Information because they are assisting with the Study; and (iv) to take all reasonable precautions to prevent the disclosure of the Confidential Information to any third-party without the prior written consent of Sponsor.

(D) Institution shall be relieved of all obligations under this Section regarding Confidential Information which: (i) was known to Institution prior to receipt hereunder as set forth in written records; or (ii) at the time of disclosure to Institution was generally available to the public, or which after disclosure hereunder, becomes generally available to the public, through no fault of the Institution; or (iii) is hereafter made available to Institution from any third-party having a right to do so; or (iv) is needed for purposes of treating a patient that participated in the Study; or (v) is required by law or regulation to be disclosed.

6. **Publications**

(A) (1) If the Study has been designed as a single-center Study, Institution shall have the right, consistent with academic standards, to publish or present the results of its work performed pursuant to the Study, provided that any proposed publication or

presentation (collectively, "Proposed Publication") is first reviewed by Sponsor and in accordance with Section 6(B).

(2) If the Study has been designed as a multicenter Study, Institution acknowledges that, due to the limited patient population in its treatment group, the data generated from its individual participation in the Study and evaluation of its individual results, may not be sufficient from which to draw any meaningful scientific conclusions. For these reasons, except as provided below, Institution agrees not to individually publish or present the results it obtains from Institution's participation in the multicenter Study. Institution may, however, upon written notice to Sponsor participate in a joint, multicenter publication of the Study results with other third party principal investigators and/or institutions, provided that the Proposed Publication is first reviewed by Sponsor in accordance with Section 6 (B). In the event that the multicenter publication has not been completed within two (2) years from the date of the completion or termination of the Study, then notwithstanding the foregoing, with Sponsor's prior written approval Institution may individually publish a Proposed Publication regarding its individual results from the Study, provided that the Proposed Publication is first reviewed by Sponsor in accordance with Section 6(B).

(B) Sponsor shall complete its review within sixty (60) days after receipt of any Proposed Publication (individual or multicenter) from Institution. If Sponsor believes that any Proposed Publication contains any information relating to patentable items, the disclosure of such Proposed Publication to any third party shall be delayed for up to ninety (90) days to permit the filing of a patent application. Should Sponsor request such a delay, then upon the written request of Institution, Sponsor shall use its best efforts consistent with reasonable business and scientific practice to do all things which it believes would expedite the filing of such patent application. However, if at the end of such ninety (90) day period, despite the use of diligent efforts on the part of Sponsor, additional time in necessary or required in order to complete the filing of a patent application, Sponsor may request, and Institution shall grant, an extension of the period of time within which to file the patent application not to exceed an additional ninety (90) days. If Sponsor believes that any Proposed Publication contains any Confidential Information, Sponsor shall so notify Institution, and Institution shall remove all references to such Confidential Information.

(C) Notwithstanding the foregoing, neither Sponsor nor Institution shall issue a press release that references or that uses either party's name or trademarks without the express written consent of the other party. Institution shall not issue a press release that references the Study or its results without the express written consent of the Sponsor.

7. **Promotional Activities**

Neither party shall use the other party's or its affiliates names or trademarks for publicity or advertising purposes, except with the prior written consent of the other party.

8. **Patent Rights**

(A) The Compound and all other materials supplied by Sponsor hereunder shall only be used by Institution for the Study as specified in the Protocol.

(B) Institution shall promptly disclose only to Sponsor any discovery or invention resulting from performance of this Agreement.

(C) The entire right, title and interest in and to any invention or discovery or know-how conceived and reduced to practice resulting directly from performance of this Agreement in accordance with the Protocol provided by Sponsor shall be owned by Sponsor. Sponsor shall have the sole and exclusive right to obtain, at its option, patent protection in the United States and foreign countries on any such invention. At the written request of Sponsor, Institution shall assign to Sponsor any and all right, title and interest in and to any such invention or discovery upon payment of patent costs, if any, incurred by Institution. Institution shall also render all reasonable assistance to Sponsor in the filing and prosecution of U.S. and foreign counterpart patent applications. Further prosecution costs, if any, shall thereafter be borne by Sponsor. The allocation of rights set forth in this Section 8(C) is only appropriate for a Study wherein the Sponsor provides the protocol and other circumstances may require a different allocation of rights.

(D) Institution shall ensure that all individuals working on the Study, including the Principal Investigator, have assigned to Institution their rights to any invention resulting from performance of this Agreement.

9. **Term**

This Agreement shall become effective when it has been executed by duly authorized representatives of both parties and shall continue in force until it is terminated in accordance with Section 10.

10. **Termination**

(A) Termination of this Agreement.

(1) Either party may terminate this Agreement if the other party breaches any of its obligations or provisions of this Agreement, provided however, that the defaulting

party shall be given not less than thirty (30) days' prior written notice of such default and the opportunity to cure the default during such period.

(2) Either party may terminate this Agreement for cause or convenience upon ninety (90) days' written notice.

(3) In the event this Agreement is terminated, by either party, pursuant to Section 10(A)(2), then Sponsor, in its sole discretion, may specify in writing which activities and Studies must be completed by Institution and the effective date of termination shall be extended only with respect to those activities and Studies specified by Sponsor until they are completed.

(B) Termination of A Study.

(1) Sponsor may terminate a Study being performed under the terms of this Agreement or Institution's participation in such Study, immediately, (a) in the event the Institution does not enroll the specified minimum evaluable patients per calendar quarter, or (b) for safety reasons relating to the use of the Compound, or (c) in the event Sponsor terminates its development program relative to the Compound or the indication for the Compound specified in the Protocol, or (d) if the FDA requests that the Study be terminated.

(2) Upon receipt of notice of termination of a Study from Sponsor, Institution shall immediately stop entering patients into the Study and, to the extent medically permissible, cease administering the Compound and conducting procedures on patients already entered into the Study.

(3) Institution shall use all reasonable efforts, upon the request of Sponsor, to (i) complete reports for all patients that have been entered into the Study as of the termination date of this Agreement and/or (ii) write a final report for that portion of the Study that has been completed as of the termination date.

(4) Upon termination of a Study, Sponsor's sole obligation shall be to pay Institution a pro-rated amount, in accordance with Section 3, for actual work performed pursuant to the Study. In the event Sponsor has overpaid Institution for work actually performed up to the date of the termination of the Study, Institution shall refund to Sponsor, as soon as reasonably practicable but in no event later than 90 days after termination, any amounts already paid by Sponsor to Institution that are in excess of what Institution is due under this Agreement for the Study which has been terminated.

(C) Termination of this Agreement or any individual Study being performed under the terms of this Agreement shall not affect any rights or remedies of either party at law or in equity.

11. **Scientific Communications**

All medical and scientific communications directed to the Institution, whether or not containing Confidential Information, shall be addressed to the Principal Investigator for each Study identified on the Clinical Study Protocol Rider. All medical and scientific communications directed to Sponsor shall be addressed to Clinical Leader for each Study identified on the Clinical Study Protocol Rider.

12. **Supply of Compound**

(A) Sponsor shall use its best efforts to provide, free of charge, necessary amounts of the each Compound required for any Study being performed hereunder.

(B) Institution shall not charge any patient enrolled in the Study, or any third party payor, for the Compound, nor shall Institution include the cost of such drug in any cost report to third party payors.

13. **Indemnification**

(A) Sponsor shall indemnify and hold harmless Institution, The University of Texas System and its Regents, Principal Investigator and their employees and agents (hereinafter "Indemnitees") from and against losses, damages, costs, claims, suits and expenses, including the cost and expense of handling and defending such claims and suits, that are directly attributable to Institution's testing of the Compound pursuant to the Study or that result from the use by Sponsor of the results of the Study; provided that Indemnitees have complied with (i) all the terms of this Agreement and the Study; (ii) all dosage and other specifications, directions and recommendations furnished in writing by Sponsor for the use and administration of the Compound; and (iii) all FDA and other applicable laws, rules and regulations.

(B) The indemnity set forth in Section 13(A) is expressly conditioned on Institution: (i) promptly notifying Sponsor of any such claim or suit; (ii) having maintained records relating to the testing of the Compound as required by this Agreement and by law; (iii) making such records available to Sponsor; (iv) in all other respects, subject to any statutory duties of the Texas Attorney General, cooperating fully with Sponsor in defending against such claim or suit; and (v) in the event of suit, attending hearings and trials and assisting in securing and giving evidence, and obtaining the attendance of necessary and proper witnesses. Sponsor shall reimburse Institution for all reasonable expenses incurred by Institution at Sponsor's request in connection with item B(v) above.

(C) The indemnity set forth in Section 13(A) shall not cover any negligence, malpractice or other wrongful acts on the part of the Indemnitees.

(D) Sponsor may, at its sole discretion, and at its own expense, and only subject to any applicable statutory duties of the Texas Attorney General, carry out the sole management and defense of such claims or suits, and shall provide attorneys of its sole choosing to defend against any such claims or suits.

(E) The parties understand and agree that the indemnification provided herein is not intended as, nor is it, a substitute for full and complete malpractice and other forms of liability insurance, and Institution shall obtain any insurance coverage necessary and proper for conducting clinical and investigational studies.

14. **Debarment Certification, Principal Investigator's Certification**

(A) Institution hereby certifies that it has not been debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §335a(a) and (b). In the event that during the term of this Agreement, Institution (i) becomes debarred, or (ii) receives notice of an action or threat of an action with respect to its debarment, Institution shall notify Sponsor immediately.

(B) In the event that Institution becomes debarred this agreement shall automatically terminate, without any further action or notice by either party. In the event that Sponsor receives notice from Institution or otherwise becomes aware that a debarment action has been brought against Institution or that Institution is threatened with a debarment action as set forth in clause (ii) above, then Sponsor shall have the right to terminate this Agreement immediately.

(C) Institution hereby certifies that it has not and will not use in any capacity the services of any individual, corporation, partnership or association which has been debarred under 21 U.S.C. §335a(a) or (b). In the event that Institution becomes aware of the debarment or threatened debarment of any individual, corporation, partnership or association providing services to Institution which directly or indirectly relate to activities under this Agreement, Institution shall notify Sponsor immediately. Upon the receipt of such notice by Sponsor or if Sponsor otherwise becomes aware of such debarment or threatened debarment, Sponsor shall have the right to terminate this Agreement immediately.

(D) Each designated Principal Investigator for a Study shall execute a Principal Investigator's Certification attached as Exhibit 1 to the Clinical Study Protocol Rider.

15. **Access**

Institution agrees to allow Sponsor, its employees, agents and authorized employees of the FDA access to the Institution, its personnel and their records for the purpose of determining compliance with the terms of this Agreement and compliance with FDA and other applicable laws, rules and regulations.

16. **Ownership of Documents**

All documents, protocols, data, know-how, methods, operations, formulas, Confidential Information, and materials of any kind provided to Institution pursuant to this Agreement are and shall remain Sponsor's property. The Completed Case Reports and other results of the Study, if any, shall also be owned by Sponsor. Copies of any or all documents referenced herein shall be returned to Sponsor or its designee upon Sponsor's request.

17. **Compliance with Law**

Institution shall conduct the Study in accordance with all rules and regulations promulgated by the FDA, and all other applicable federal, state and local laws, rules and regulations.

18. **Assignment**

This Agreement may not be assigned by Institution without the prior written consent of Sponsor.

19. **Independent Contractors**

For purposes of this Agreement, neither the Institution nor the Principal Investigator shall be deemed an agent or employee of Sponsor, and neither has authority to take action on Sponsor's behalf or bind Sponsor. Rather, Institution and Principal Investigator shall be deemed independent contractors of Sponsor.

20. **No Waiver**

Either party's failure to require the other party to comply with any provision of this Agreement shall not be deemed a waiver of such provision or any other provision of this Agreement.

21. **Force Majeure**

Neither party shall be liable for the failure to perform its obligations under this Agreement if such failure is occasioned by a contingency beyond such party's reasonable control, including, but not limited to, strikes or other labor disturbances, lockouts, riots, wars, fires,

floods or storms. A party claiming a right to excused performance under this Section shall immediately notify the other party in writing of the extent of its inability to perform, which notice shall specify the occurrence beyond its reasonable control that prevents such performance.

22. **Notices**

Whenever any notice is to be given hereunder to the Institution, it shall be in writing and sent by certified return receipt mail to the addresses of each respective Institution as set forth on Exhibit 1 hereto. Notices sent to Sponsor shall be addressed to Clinical Leader identified on the Clinical Study Protocol Rider, with a copy to the "Corporate Secretary," at the address as set forth first above. Notices to the Principal Investigator shall be sent to Institution. Any notice given hereunder shall be deemed effective three (3) days after being mailed.

23. **Entire Agreement**

This Agreement represents the entire understanding of the parties with respect to the subject matter hereof. Except for the Protocol which will be attached to each Clinical Study Protocol Rider, which may be modified in accordance with Section 2(B), any modification, amendment or supplement to this Agreement or Exhibits and/or Attachments attached hereto shall be in a writing signed by an authorized representative of both parties.

24. **Survival of Provisions**

Sections 5, 6, 7, 8, 13, 15, 16, and 17 hereof shall survive termination or expiration of this Agreement.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date written first above.

HOFFMANN-LA ROCHE INC.

By: Judith L. Siegel
Judith L. Siegel
Vice President & Director,
U. S. Clinical Operations

Date: June 14 1996

he University of Texas Health Science Center at San Antonio

By: _____
R.B. Price
Executive Vice President for
Administrative & Business Affairs

Date: _____

Apprv'd as to Form
LAW DEPT.
By

The University of Texas Health Science Center at Houston

By: _____
David E. Kusnerik
Contract Administrator

Date: 5/21/96

The University of Texas M.D. Anderson Cancer Center

By: _____
Donna S. Gilberg, CPA
Manager, Sponsored Programs

Date: 5/23/96

The University of Texas Southwestern Medical Center at Dallas

By: _____
Peter H. Fitzgerald
Exec. Vice President for
Business Affairs

Date: 5/17/96

The University of Texas Medical Branch at Galveston

By: _____
George M. Bernier, Jr. M.D.
Vice President for Academic Affairs
and Dean of Medicine

Date: 5/28/96

22278

Exhibit 1

Addresses for Notices to the Institutions

Ms. Donna Gilberg
Manager, Sponsored Programs
The University of Texas
M.D. Anderson Cancer Center
1515 Holcombe Blvd., Box 202
Houston, Texas 77030

Mr. David Kusnerik
Contract Administrator
The University of Texas Health Science Center at Houston
P.O. Box 20036
Houston, Texas 77225

Ms. Marci Padia
The University of Texas Medical Center Branch at Galveston
Research Administrative Services
Galveston, Texas 77550-2774

Mr. Earl A. Siebold
Director, Grants Management
The University of Texas Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7862

Ms. Janice Hinds
Director, Grants Management
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Blvd.
Dallas, Texas 75235-9105

Attachment A

University of Texas System
Clinical Study Protocol Rider

This Clinical Study Protocol Rider is issued pursuant to the Master Clinical Research Agreement, dated as of May 1, 1996, between **The University of Texas Health Sciences Center at San Antonio, The University of Texas Health Science Center at Houston, The University of Texas-M.D. Anderson Cancer Center, The University of Texas Southwestern Medical Center at Dallas, and The University of Texas Medical Branch at Galveston**, (each an "Institution") each a component of The University of Texas System located at 201 West 7th Street, Austin, Texas 78701, and **Hoffmann-La Roche Inc.**, a New Jersey corporation, with its principal office and place of business at 340 Kingsland Street, Nutley, New Jersey 07110 (the "Sponsor") and incorporates all of the terms and conditions therein (the "Agreement").

Any capitalized terms not otherwise defined herein shall have the same meaning ascribed to them in the Agreement.

Protocol Title and Number:

_____

_____

_____

_____(the "Study").

A copy of the Protocol is attached hereto as Exhibit 2 and incorporated herein by this reference.

Principal Investigator(s) Name: _____

Principal Investigator(s) Address: _____

_____

_____

_____(the "Site")

Phone: _____

Facsimile: _____

A copy of the Principal Investigator's Certification is attached hereto as Exhibit 1 and is incorporated herein by this reference.

Study Schedule:

1. Study Initiation and Completion.

   (a) All contractual and regulatory documentation must be completed, executed and received by the Sponsor no later than _____.

   (b) The Study shall be initiated no later than _____ ("Initiation Date") and shall be completed no later than _____ ("Completion Date").

2. Enrollment.

   (a) It is anticipated that the Principal Investigator(s) may enroll _____ patients into the Study (the "Site Maximum"). Patient enrollment shall be completed on or before _____. Enrollment of each patient over the Site Maximum requires the agreement of the Sponsor. No payments shall be made for patients enrolled over the Site Maximum without the agreement of the Sponsor.

   (b) Notwithstanding whether the Site Maximum has been reached, the Principal Investigator(s) agrees to immediately cease enrolling patients upon notice from the Sponsor that, in the sole discretion of the Company either (1) the Sponsor's target enrollment for the Study has been achieved; or (2) the rate of enrollment at the Site has fallen below an acceptable rate, which is defined as _____ evaluable patients per calendar quarter.

3. Study Documentation.

   (a) A "Completed Case Report Form" ("CRF") shall mean a case report (i) that has been completed by the Principal Investigator in accordance with all Food and Drug Administration ("FDA") and Study requirements, (ii) for a patient who properly qualified, participated in and completed the Study in accordance with all Study requirements, and (iii) which the Sponsor determines can be used in all analyses of the Study results.

   (b) CRF's must be satisfactorily completed within _____ days of completion of the patient's participation in the Study and receipt of patient's test results, if any, but in no event later than the Completion Date for the Study.

   (c) Any requests by or on behalf of the Sponsor for verification, clarification or correction of data on CRF's must be responded to and returned to the Sponsor within ten (10) business days of receipt.

Study Budget, Payment Recipient and Mailing Address

1. Institution shall provide Sponsor with _____ CRFs, as defined above, at a cost of $_____ per report for a total amount of $_____. Details of this per patient budget are attached hereto as Schedule 1 and incorporated herein by this reference.

2. Payment by Sponsor for the CRFs shall be made as follows:

   $_____ within 60 days after the execution of this Agreement or shipment of the Compound by Sponsor to Institution, whichever is later;

   $_____ within 60 days after Sponsor receives, to its satisfaction, _____ CRFs and an accompanying invoice; and

   $_____ within 60 days after Sponsor receives, to its satisfaction, an additional _____ CRFs, a final report in accordance with the Study, and an accompanying invoice.

*(**Note:** Specific Payment terms may vary dependent upon the nature of the Study and the work being performed under the Protocol. The above is merely an example of a payment schedule.)*

3. Payment for patients enrolled over the Site Maximum with Sponsor's agreement shall be made in accordance with the above.

4. Payment as set forth in this Clinical Study Protocol Rider shall constitute full payment for the Study and Sponsor shall have no other payment obligations hereunder.

5. The name and address of the payee for all payments due to Institution hereunder is:

   _____
   _____
   _____
   _____

   Tax ID Number of the payee: _____

6. Site mailing address for correspondence (if different from mailing address for payments).

   _____
   _____
   _____
   _____

This Clinical Study Protocol Rider is entered into and made effective as of _____.

Accepted and Agreed to by:

(Institution Site Name)	**Hoffmann-La Roche Inc.**
_____	_____
Signature of Responsible Officer	Signature
_____	_____
Typed Name and Title	Typed Name and Title
_____	_____
Date	Date

Exhibit 1 to Clinical Study Protocol Rider

PRINCIPAL INVESTIGATOR'S CERTIFICATION

I acknowledge that I have read this Clinical Study Protocol Rider and am aware of the terms and conditions of the Agreement referred to therein and I agree to and will comply with all the terms and conditions of each, both as an individual and as an employee of Institution. In particular, I represent and warrant that I shall not use any information, data, case report forms and any other similar data and information arising from or relating to the Study for any purpose other than an academic or scientific publication or for internal Institution scientific, patient treatment and educational non-commercial purposes.

I represent that my entering into and participating in this Study shall not conflict with or be a breach of any other agreement to which I am a party or am bound.

I represent and warrant that the Institution or entity identified above is the appropriate entity to receive payment(s) for this Study.

I certify that I have not been disqualified by the federal Food and Drug Administration or otherwise disqualified from serving as a Principal Investigator.

I certify that I have not been debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §335a(a) and (b). In the event that I, (i) become debarred; or (ii) receive notice of an action or threat of an action with respect to my debarment, during the term of this Study, I agree to immediately notify Hoffmann-La Roche ("Roche") and Institution. I also agree that in the event that I become debarred, I shall immediately cease all activities relating to this Agreement.

I understand that in the event Roche receives notice or otherwise becomes aware that (i) I have been debarred, (ii) a debarment action has been brought against me, or (iii) I have been threatened with a debarment action, Roche shall have the right, at its sole discretion, to (i) terminate immediately my participation in the Study, or (ii) agree with Institution to a substitute Principal Investigator who will assume full responsibility and perform all the remaining activities under this Study.

PRINCIPAL INVESTIGATOR

_____

Print Name

_____

Signature Date: _____

PDA-NU-996749

FIRST AMENDMENT TO MASTER CLINICAL RESEARCH AGREEMENT

This first amendment ("First Amendment") effective as of August 24, 1998 by and between The University of Texas Health Sciences Center at San Antonio, The University of Texas Health Science Center at Houston, The University of Texas – M.D. Anderson Cancer Center, The University of Texas Southwestern Medical Center at Dallas, and The University of Texas Medical Branch at Galveston (each an "Institution") each with an office and place of business as set forth on Exhibit 1 hereto and each a component of The University of Texas System located at 201 West 7th Street, Austin, Texas 78701 and Hoffmann-La Roche Inc. ("Roche") hereby amends the Master Clinical Research Agreement dated (May 1, 1996) by and between Institution and Roche ("Master Agreement").

WHEREAS, Institution and Roche entered into the Master Agreement to encompass clinical trial research to be performed at Institution and sponsored by Roche; and

WHEREAS, Institution and Roche desire to amend Exhibit 1, Addresses for Notices to the Institutions, to the Master Agreement as set forth herein;

NOW, THEREFORE, in consideration of the mutual promises contained herein and other good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, the parties hereto promise and agree as follows:

1. All capitalized terms not defined herein have the same meaning as those in the Master Agreement.

2. Exhibit 1 of the above Master Agreement is deleted in its entirety and replaced by the following:

Ms. Donna Gilberg
Manager, Grants and Contracts Accounting
The University of Texas
M.D. Anderson Cancer Center
1515 Holcombe Blvd., Box 202
Houston, Texas 77030

Mr. David Kusnerik
Contract Administrator
The University of Texas Health
Science Center at Houston
P.O. Box 20036
Houston, Texas 77225

Ms. Marci Padia
The University of Texas Medical Center
Branch at Galveston
Research Administrative Services
Galveston, Texas 77550-2774

Ms. Jane Youngers
Director, Grants Management
The University of Texas Health
Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7862

Perrie M. Adams, Ph.D.
Associate Dean for Research
The University of Texas Southwestern
Medical Center at Dallas
5323 Harry Hines Blvd.
Dallas, Texas 75235-9016

3. Any and all provisions of the Master Agreement not expressly modified hereby shall remain in full force and effect.

Institution: Univ. of Texas

IN WITNESS WHEREOF, the undersigned duly authorized representatives of the parties have executed this First Amendment as of the date written first above.

The University of Texas Health Science Center at San Antonio

By:_____

R. B. Price
Executive Vice President for Administrative & Business Affairs

Date:_____

Hoffmann-La Roche Inc.

By: Judith Siegel

Judith L. Siegel, Ph.D.
Vice President & Head U.S. Clinical Operations

Date: 12-3-99
11/11/99

The University of Texas Health Science Center at Houston

By:_____

David E. Kusnerik
Contract Administrator

Date:_____

The University of Texas – M.D. Anderson Cancer Center

By:_____

Donna S. Gilberg, CPA
Manager, Sponsored Programs

Date:_____

The University of Texas Southwestern Medical Center at Dallas

By: Perrie M. Adams

~~**Peter H. Fitzgerald**~~
~~**Exec. Vice President for Business Affairs**~~

Perrie M. Adams, Ph.D.
Associate Dean for Research

Date:_____

The University of Texas Medical Branch at Galveston

By:_____

George M. Bernier, Jr. M.D.
Vice President for Academic Affairs and Dean of Medicine

Date:_____

Institution: Univ. of Texas

IN WITNESS WHEREOF, the undersigned duly authorized representatives of the parties have executed this First Amendment as of the date written first above.

The University of Texas Health Science Center at San Antonio

By:_____

R. B. Price
Executive Vice President for Administrative & Business Affairs

Date:_____

Hoffmann-La Roche Inc.

By: Siegel

Judith L. Siegel, Ph.D.
Vice President & Head U.S. Clinical Operations

Date: 12-3-99 & 11/11/99

The University of Texas Health Science Center at Houston

By:_____

David E. Kusnerik
Contract Administrator

Date:_____

The University of Texas – M.D. Anderson Cancer Center

By:_____

Leonard A. Zwelling, M.D., M.B.A.
Associate Vice President for Research Administration

Date: 2-24-00

The University of Texas Southwestern Medical Center at Dallas

By:_____

Peter H. Fitzgerald
Exec. Vice President for Business Affairs

Date:_____

The University of Texas Medical Branch at Galveston

By:_____

George M. Bernier, Jr. M.D.
Vice President for Academic Affairs and Dean of Medicine

Date:_____

Institution: Univ. of Texas

IN WITNESS WHEREOF, the undersigned duly authorized representatives of the parties have executed this First Amendment as of the date written first above.

The University of Texas Health Science Center at San Antonio

By:_____

R. B. Price
Executive Vice President for Administrative & Business Affairs

Date:_____

The University of Texas Health Science Center at Houston

By: David E. Kusnerik

David E. Kusnerik
Contract Administrator

Date: 9/10/98

The University of Texas – M.D. Anderson Cancer Center

By:_____

Donna S. Gilberg, CPA
Manager, Sponsored Programs

Date:_____

The University of Texas Southwestern Medical Center at Dallas

By:_____

Peter H. Fitzgerald
Exec. Vice President for Business Affairs

Date:_____

The University of Texas Medical Branch at Galveston

By:_____

George M. Bernier, Jr. M.D.
Vice President for Academic Affairs and Dean of Medicine

Date:_____

Hoffmann-La Roche Inc.

By: Judith L. Siegel

Judith L. Siegel, Ph.D.
Vice President & Head
U.S. Clinical Operations

Date: 12-3-98
8y 11/11/98

Institution: Univ. of Texas

IN WITNESS WHEREOF, the undersigned duly authorized representatives of the parties have executed this First Amendment as of the date written first above.

The University of Texas Health Science Center at San Antonio

By: _____
Jane A. Youngers, Director
Office of Grants Management

Date: 4 Oct 99

Hoffmann-La Roche Inc.

By: _____
Judith L. Siegel, Ph.D.
Vice President & Head
U.S. Clinical Operations

Date: 12-3-99
or 11/11/99

The University of Texas Health Science Center at Houston

By: _____
David E. Kusnerik
Contract Administrator

Date: _____

The University of Texas – M.D. Anderson Cancer Center

By: _____
Donna S. Gilberg, CPA
Manager, Sponsored Programs

Date: _____

The University of Texas Southwestern Medical Center at Dallas

By: _____
~~Peter H. Fitzgerald~~
~~Exec. Vice President for Business Affairs~~
Perrie M. Adams, Ph.D.
Associate Dean for Research

Date: _____

The University of Texas Medical Branch at Galveston

By: _____
George M. Bernier, Jr. M.D.
Vice President for Academic Affairs and Dean of Medicine

Date: _____

Institution: Univ. of Texas

IN WITNESS WHEREOF, the undersigned duly authorized representatives of the parties have executed this First Amendment as of the date written first above.

The University of Texas Health Science Center at San Antonio

By:_____
R. B. Price
Executive Vice President for Administrative & Business Affairs

Date:_____

The University of Texas Health Science Center at Houston

By:_____
David E. Kusnerik
Contract Administrator

Date:_____

The University of Texas – M.D. Anderson Cancer Center

By:_____
Donna S. Gilberg, CPA
Manager, Sponsored Programs

Date:_____

The University of Texas Southwestern Medical Center at Dallas

By:_____
Peter H. Fitzgerald
Exec. Vice President for Business Affairs

Date:_____

The University of Texas Medical Branch at Galveston

By:_____
George M. Bernier, Jr. M.D.
Vice President for Academic Affairs and Dean of Medicine

Date: 9/4/98

Hoffmann-La Roche Inc.

By:_____
Judith L. Siegel, Ph.D.
Vice President & Head
U.S. Clinical Operations

Date: 12-3-99
87 11/11/99

Institution: Univ. of Texas