**PUBLIC HEALTH SERVICE**

**COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT**

**FOR NATIONAL CANCER INSTITUTE (NCI), DIVISION OF CANCER TREATMENT AND DIAGNOSIS (DCTD) EXTRAMURAL-PHS CLINICAL RESEARCH**

This Agreement is based on the model Cooperative Research and Development Agreement (“CRADA”) adopted on December 8, 2010 by the U.S. Public Health Service (“PHS”) Technology Transfer Policy Board for use by components of the National Institutes of Health (“NIH”), the Centers for Disease Control and Prevention (“CDC”), and the Food and Drug Administration (“FDA”), which are agencies of the PHS within the Department of Health and Human Services (“HHS”).

This Cover Page identifies the Parties to this CRADA:

The U.S. Department of Health and Human Services, as represented by the

**National Cancer Institute**

herein after referred to as “NCI” an Institute of the

**National Institutes of Health**

 and

**[INSERT Collaborator’s official name]**,

hereinafter referred to as the “Collaborator,”

having offices at **[INSERT Collaborator’s address]**,

created and operating under the laws of **[INSERT State of Incorporation]**.

**COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT**

**FOR EXTRAMURAL-PHS CLINICAL RESEARCH**

**Article 1. Introduction**

This CRADA between NCI and Collaborator will be effective when signed by the Parties, which are identified on both the Cover Page and the Signature Page. The official contacts for the Parties are identified on the Contacts Information Page. Publicly available information regarding this CRADA appears on the Summary Page. The research and development activities that will be undertaken by NCI, NCI’s contractors or grantees, and Collaborator in the course of this CRADA are detailed in the Research Plan, attached as Appendix A. The staffing, funding, and materials contributions of the Parties are attached as Appendix B. An example of typical terms for a MTA for the transfer of Investigational Agent from NCI to NCI Extramural Investigators is attached as Appendix C. For this Agreement, because CTEP and DCTD (defined below) within the NCI are responsible for the Research Plan, NCI, DCTD and CTEP may be used interchangeably in this Agreement when a specific program is responsible for an activity.

**Article 2. Definitions**

The terms listed in this Article will carry the meanings indicated throughout the CRADA. To the extent a definition of a term as provided in this Article is inconsistent with a corresponding definition in the applicable sections of either the United States Code (U.S.C.) or the Code of Federal Regulations (C.F.R.), the definition in the U.S.C. or C.F.R. will control.

“**Active Protocol**” means any Protocol conducted under the CRADA that is actively enrolling Human Subjects in the Protocol, or has Human Subjects in follow-up per the Protocol.

“**Adverse Event**” or “**AE**” means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, as defined under 21 C.F.R § 312.32. See also FDA Good Clinical Practice Guideline (International Conference on Harmonisation (ICH) E6: “Good Clinical Practice: Consolidated Guidance, 62 Federal Register 25, 691 (1997)).

“**Affiliate**” means any corporation or other business entity controlled by, controlling, or under common control with Collaborator at any time during the term of the CRADA. For this purpose, “control” means direct or indirect beneficial ownership of at least fifty percent (50%) of the voting stock or at least fifty percent (50%) interest in the income of the corporation or other business entity.

“**Annual Report**” means the report of progress of an IND-associated investigation that the Sponsor must submit to the FDA within sixty (60) days of the anniversary of the effective date of the IND (pursuant to 21 C.F.R. § 312.33).

“**Background Invention**” means an Invention conceived and first actually reduced to practice before the Effective Date.

“**Biomarker**” means a biological marker that can be used to guide therapeutic administration of a drug including but not limited to: (i) to predict whether or not a patient is likely to be sensitive or resistant to treatment with a certain therapeutic agent; or (ii) to guide any aspect of clinical practice (e.g. dosing, safety, efficacy and response).

**“Biospecimens”** means blood, serum, urine, saliva, other bodily fluid, bone marrow, cells, or tissue samples/specimens collected under a Protocol from Human Subjects. The term “Biospecimen” further includes, without limitation, any tangible material directly or indirectly derived from such Biospecimens collected under the Protocol from Human Subjects, such as genes, gene fragments, gene sequences, proteins, protein fragments, protein sequences, DNA, RNA, and any subcellular structure.

“**Clinical Investigator**” means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Investigational Agent to a subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. For this CRADA, a Clinical Investigator can be an NIH Intramural Investigator or an NCI Extramural Investigator.

“**Clinical Research Site(s)**” means the site(s) at which the Protocol(s) described in the Research Plan will be performed.

“**Collaborator Materials**” means all tangible materials not first produced in the performance of this CRADA that are owned or controlled by Collaborator and used in the performance of the Research Plan. The term “Collaborator Materials” does not include “Investigational Agent” (defined below).

“**Confidential Information**” means confidential scientific, business, financial information, or Identifiable Private Information provided that Confidential Information does not include:

(a) information that is publicly known or that is available from public sources;

(b) information that has been made available by its owner to others without a confidentiality obligation;

(c) information that is already known by the receiving Party, or information that is independently created or compiled by the receiving Party without reference to or use of the provided information; or

(d) information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Investigational Agent.

“**Cooperative Research and Development Agreement**” or “**CRADA**” means an agreement, entered into pursuant to the Federal Technology Transfer Act of 1986, as amended (15 U.S.C. §§ 3710a *et seq*.), and Executive Order 12591 of April 10, 1987.

“**CRADA Collaborator Principal Investigator(s)**” or “**CRADA Collaborator PI(s)**” means the person(s) who will be responsible for the scientific and technical conduct of the Research Plan on behalf of the Collaborator.

“**CRADA Data**” means information developed by or on behalf of the Parties in the performance of the Research Plan, excluding Raw Data. For clarity, CRADA Data includes data generated from Protocol Related Research but excludes data generated from Secondary Research.

“**CRADA Materials**” means all tangible materials first produced in the performance of the Research Plan other than CRADA Data, Collaborator Materials or Investigational Agent. CRADA Materials do not include specimens collected from Human Subjects.

“**CRADA Subject Invention**” means any Invention of either or both Parties, conceived or first actually reduced to practice in the performance of the Research Plan.

**“CTA”** means Clinical Trial Agreement.

**“CTEP”** means the Cancer Therapy Evaluation Program, DCTD, NCI, a program within NCI that plans, assesses and coordinates all aspects of clinical trials including extramural clinical research programs, internal resources, treatment methods and effectiveness, and compilation and exchange of data.

**“CTEP IP Option to Collaborators” or “IP Option”** means the intellectual property option described at: <https://ctep.cancer.gov/branches/rab/intellectual_property_option_to_collaborators.htm>,

also can be found in [The Federal Register, Vol. 76, No. 48, pages 13404-13410 (2011) (https://www.gpo.gov/fdsys/pkg/FR-2011-03-11/pdf/FR-2011-03-11.pdf).](%5C%5C%5C%5Cnciis-p401.nci.nih.gov%5C%5CHome01%5C%5Czhangjia%5C%5C0Model%20Agreements%5C%5CCrada%5C%5C0%20CRADA%20model%20revision%202-16-2017%5C%5CThe%20Federal%20Register%2C%20Vol.%2076%2C%20No.%2048%2C%20pages%2013404-13410%20%282011%29%20%28https%3A%5C%5Cwww.gpo.gov%5C%5Cfdsys%5C%5Cpkg%5C%5CFR-2011-03-11%5C%5Cpdf%5C%5CFR-2011-03-11.pdf%29.)

**“DCTD”** means Division of Cancer Treatment and Diagnosis, NCI.

**“Data Safety Monitoring Board” or “DSMB”** is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DSMB advises the sponsor regarding the continuing safety of Human Subjects and those yet to be recruited to a clinical trial, as well as the continuing validity and scientific merit of the trial. The DSMB is appointed by the Sponsor.

“**Drug Master File**” or “**DMF**” is described in 21 C.F.R. Part 314.420. A DMF is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

**“Drug Approval Form”** is a CTEP form included in a clinical letter of intent (“LOI”) or a clinical concept when CTEP provides the LOI or the concept to the Collaborator for review. The Drug Approval Form is an official correspondence between CTEP and Collaborator regarding the LOI or the concept. Collaborator will check the Drug Approval Form when it approves the LOI or the concept and agrees to supply Investigational Agent for a proposed trial. CTEP will instruct NCI Investigators who summit the LOI or the concept to develop a full clinical Protocol after receiving the approved Drug Approval Form from the Collaborator.

“**Effective Date**” means the date of the last signature of the Parties executing this Agreement.

**“ETCTN”** means theExperimental Therapeutics Clinical Trials Network, a network comprised of 12 lead academic organizations with affiliated participating sites. The ETCTN was created to evaluate promising anticancer therapies using a coordinated, collaborative, and inclusive team-based approach to early phase experimental therapeutic clinical trials. NCI has formed partnerships in the pharmaceutical industry, academic institutions, and individual investigators for the early clinical evaluation of innovative cancer therapies.

**“Funding Agreement”** means a contract, grant, or cooperative agreement entered into between a Federal agency and another party for the performance of experimental, developmental or research work funded in whole or in part by the Federal Government.

“**Government**” means the Government of the United States of America.

“**Human Subject**” means, in accordance with the definition in 45 C.F.R. § 46.102(f), a living individual about whom an investigator conducting research obtains:

(a) data through intervention or interaction with the individual; or

(b) Identifiable Private Information.

“**Identifiable Private Information**” or “**IPI**” about a Human Subject means private information from which the identity of the subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

“**IND**” means an “**Investigational New Drug Application**,” filed in accordance with 21 C.F.R. Part 312 under which clinical investigation of an experimental drug or biologic (Investigational Agent) is performed in Human Subjects in the United States or intended to support a United States licensing action.

“**Institutional Review Board**” or “**IRB**” means, in accordance with 45 C.F.R. Part 46, 21 C.F.R. part 56, and other applicable regulations, an independent body comprising medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of the Human Subjects involved in a study.

“**Invention**” means any invention or discovery that is or may be patentable or otherwise protected under Title 35 of the United States Code, or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 *et seq*.

“**Investigational Agent**” or Investigational New Drug means, in accordance with the definition in 21 C.F.R. § 312.3, a new drug or biological drug that is used in a clinical investigation. For this Agreement, Investigational Agent means xxxxxxxxxxx provided by or on behalf of Collaborator.

“**Investigator’s Brochure**” or **“IB”** means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Investigational Agent, including animal screening, preclinical toxicology, and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the drug.

**“MTA”** means a Material Transfer Agreement.

**“Multi-Party Data”** means data from studies sponsored by NCI pursuant to CTAs or CRADAs, where such data are collected under Protocols and Non-Clinical Studies involving combinations of investigational agents supplied from more than one CTA or CRADA collaborator.

**“NCI Extramural Investigator”** means an investigator who is not an NCI employee and who is supported by NCI Funding Agreements as well as all personnel assisting the investigator in the performance of research under this CRADA.

**“NCI Network”** means the NCI clinical trials network including the ETCTN and the Network Group.

**“NCI Investigator”** includes, for the purpose of this CRADA, any of NIH Intramural Investigator and NCI Extramural Investigator, who conducts clinical trials and/or Non-Clinical Studies.

“**NCI Materials**” means all tangible materials not first produced in the performance of this CRADA that are owned or controlled by NCI and used in the performance of the Research Plan.

**"NCTN"** means the National Clinical Trials Network, a consolidated and integrated program funded by NCI with the overall goal of conducting a spectrum of definitive clinical trials across a broad range of diseases and diverse patient populations, as well as development efforts preliminary to those trials, as part of NCI’s overall clinical research program for adults and children with cancer. The NCTN Program is comprised of four U.S. adult Network Groups, one Canadian adult Network Group, and one pediatric Network Group.

**"Network Group"** means one of the (six) participants in the NCTN. Each Network Group is comprised of investigators who join together to develop and implement protocols. The lead Network Group for each Protocol, through its central operations and statistical center, supports the administrative and regulatory requirements of the clinical research, performs central data collection and analysis, verifies compliance with the relevant Protocol via a quality assurance program and site visit auditing, and publishes the study results.

“**NIH CRADA Extramural Investigator/Officer(s)**” means the NCI staff who are responsible for the conduct and/or management of the CRADA on behalf of the NIH. In the case of this CRADA, the NIH CRADA Extramural Investigator is Dr. XXX and the NIH CRADA Extramural Officer is Dr. Margaret Mooney.

**“NIH Intramural Investigator”** means an investigator who is an NCI or an NIH employee as well as all personnel assisting the investigator in the performance of research under this CRADA.

**“Non-Clinical Studies”** mean exploratory *in vitro*, *in vivo*, and *ex vivo* studies using defined biological models including cell lines, xenograft models, circulating tumor cells, normal tissue, blood and any of its components and shall include ancillary correlative studies, proof-of-mechanism and proof-of-principle assays, development of imaging techniques, and evaluation of target linkage. Non-Clinical Studies may include studies using human materials derived from clinical trials (such as primary, metastatic, or circulating tumor cells, normal tissue, blood, and any of its components). Non-Clinical Studies can be performed by NCI Investigators.

“**Patent**” means any issued United States patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

“**Patent Application**” means an application for patent protection for a CRADA Subject Invention with the United States Patent and Trademark Office (“U.S.P.T.O.”) or the corresponding patent-issuing authority of another nation.

 “**Placebo**” means an inactive substance identical in appearance to the material being tested that is used to distinguish between drug action and suggestive effect of the material under study.

**“PMB”** means the Pharmaceutical Management Branch within CTEP, DCTD, NCI.

“**Protocol**” means the clinical investigation in which a drug is administered or dispensed to, or used involving, one or more human subjects. It describes the objective(s), design, methodology, statistical considerations, and organization of a trial. For the purposes of this CRADA, the term, Protocol, for clinical research involving Human Subjects, includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the study.

**“Protocol Review Committee” (or “PRC”)** means the CTEP/DCTD committee that reviews and approves studies involving NCI investigational agents and/or activities supported by NCI.

“**Protocol Related Research**” or “**PRR**” means research conducted as a part of a Protocol, including Biomarker Studies and correlative studies or research associated with a Protocol that utilizes non-publicly available CRADA Data, de-identified Raw Data, and/or Biospecimens collected from Human Subjects in the conduct of the Protocol. All PRR will be approved by the PRC and Collaborator and will be conducted by NCI Investigators under the CRADA.

“**Raw Data**” means the primary quantitative and empirical data first collected from experiments and clinical trials conducted within the scope of this CRADA. Raw Data includes case report forms.

“**Research Plan**” means the statement in Appendix A of the respective commitments of the Parties. The Research Plan should describe the provisions for sponsoring the IND, clinical and safety monitoring, and data management.

“**Secondary Research**” means research conducted by investigators, not limited to NCI Investigators, using non-publicly available CRADA Data, de-identified Raw Data and/or Biospecimens collected from Human Subjects enrolled in the Protocol(s) under the CRADA. For clarity, Secondary Research is not Protocol Related Research as defined above, and occurs (i) for randomized phase 2 and phase 3 trials, after the DSMB data release and first presentation of the study results; and (ii) for early phase trials and non-randomized trials, after the completion of accrual and treatment of Human Subjects and first presentation of study results. For both (i) and (ii) under this paragraph, if no other presentation of study results has occurred, submission of a study results report to clinicaltrials.gov will constitute a presentation.

“**Sponsor**” means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Investigational Agents, and is sometimes referred to as the IND holder.

“**Steering Committee**” means the team whose composition and responsibilities with regard to the research performed under this CRADA are described in Article 3.12.

“**Summary Data**” means any extract or summary of the Raw Data, generated either by or, on behalf of, NCI or by, or on behalf of, Collaborator. Summary Data may include extracts or summaries that incorporate IPI.

**Article 3. Cooperative Research and Development**

3.1 **Performance of CRADA Activities.** Theactivities to be carried out under this CRADA will be performed by the Parties identified on the Cover Page as well as by NCI Investigators as described in the Research Plan. The NIH CRADA Extramural Investigator/Officer(s) and CRADA Collaborator PI(s) will be responsible for coordinating the scientific and technical conduct of this project on behalf of their employers.

3.2 **Research Plan**. The Parties recognize that the Research Plan describes the collaborative activities they will undertake and that interim research goals set forth in the Research Plan are good faith guidelines. Should events occur that require modification of these goals, then by mutual agreement the Parties can modify them through an amendment, according to Paragraph 13.6.

3.3 **Use and Disposition of Collaborator Materials and NCI Materials**. The Parties agree to use Collaborator Materials and NCI Materials only in accordance with the Research Plan and Protocol(s), not to transfer these materials to third parties except in accordance with the Research Plan and Protocol(s) or as approved by the owning or providing Party, and, upon expiration or termination of the CRADA, to dispose of these materials as directed by the owning or providing Party.

3.4 **Third-Party Rights in Collaborator’s CRADA Subject Inventions**. If Collaborator has received (or will receive) support of any kind from a third party in exchange for rights in any of Collaborator’s CRADA Subject Inventions, Collaborator agrees to ensure that its obligations to the third party are both consistent with Articles 6 through 8 and subordinate to Article 7 of this CRADA.

3.5 **Disclosures to NCI**. Prior to execution of this CRADA, Collaborator agrees to disclose to NCI all instances in which outstanding royalties are due under a PHS license agreement and in which Collaborator had a PHS license terminated in accordance with 37 C.F.R. § 404.10. These disclosures will be treated as Confidential Information upon request by Collaborator in accordance with the definition in Article 2 and Paragraphs 8.3 and 8.4.

3.6 **Clinical Investigator Responsibilities**. The Clinical Investigator will be required to submit, or to arrange for submission of, each Protocol associated with this CRADA to all appropriate IRBs, and for ensuring that the IRBs are notified of the role of Collaborator in the research. In addition to the Protocol all associated documents, including informational documents and advertisements, must be reviewed and approved by the appropriate IRB(s) before starting the research at each Clinical Research Site. The research will be done in strict accordance with the Protocol(s) and no substantive changes in a finalized Protocol will be made unless mutually agreed upon, in writing, by the Parties. Research will not commence (or will continue unchanged, if already in progress) until each substantive change to a Protocol, including those required by either the FDA or the IRB, has been integrated in a way acceptable to the Parties, submitted to the FDA (if applicable) and approved by the appropriate IRBs.

3.7 **Investigational New Drug Applications**.

3.7.1 DCTD, NCI, as indicated in the Research Plan, will prepare and submit any required IND(s) and all Clinical Investigators participating in DCTD-sponsored clinical trials must have completed registration documents on file (e.g. 1572 forms, Supplemental Data Form and Financial Disclosure Form) with CTEP.

3.7.2 Collaborator agrees to provide DCTD background data and information necessary to support the DCTD IND(s). Collaborator further agrees to provide a letter of cross-reference to all pertinent regulatory filings including IND(s) and/or DMF(s) sponsored by Collaborator. Collaborator’s employees will be reasonably available to respond to inquiries from the FDA regarding information and data contained in a Collaborator’s IND, DMF, other filings, or other information and data provided to DCTD by the Collaborator pursuant to this Article 3. If DCTD has provided information or data to assist Collaborator in an IND filing, DCTD will provide a letter of cross reference to its IND and respond to inquiries related to information provided by DCTD, as applicable.

3.7.3 If Collaborator supplies Confidential Information to DCTD in support of an IND filed by DCTD, this information will be protected in accordance with the corresponding confidentiality provisions of Article 8.

3.7.4 Collaborator may sponsor its own clinical trials and hold its own IND(s) for studies performed outside the scope of this CRADA. These studies, however, should not adversely affect the ability to accomplish the goal of the Research Plan, for example, by competing for the same study population. All data from those clinical trials are proprietary to Collaborator for purposes of this CRADA. Collaborator will permit DCTD to review and use such data for regulatory purposes for DCTD-sponsored clinical trials that are under the CRADA.

3.7.5 In the event that Canadian institutions are participating on DCTD-sponsored clinical trials, Collaborator will assist in the submission of the regulatory documents to the Canadian Health Products and Food Branch to allow for such participation. This may include a letter of cross-reference to an existing Clinical Trials Application or a DMF, including supporting documentation on the production of the Investigational Agent. The forms and procedures for preparing Canadian Clinical Trials Application are available at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/index-eng.php>.

3.7.6 In the event that other international Clinical Research Sites are participating on the NCI-sponsored protocols, NCI will provide copies, with Collaborator’s approval, of the Investigational Agent Investigator's Brochure (IB) and Certificates of Analysis to the international Clinical Research Sites to support the regulatory filings. Collaborator will assist the international Clinical Research Sites with the submission of other necessary regulatory documents to allow for such participation. The international Clinical Research Sites will work directly with the Collaborator to obtain the necessary regulatory documents.

3.8 **Investigational Agent Information and Supply**.

3.8.1 Collaborator agrees to provide DCTD without charge and on a schedule that will ensure adequate and timely performance of the research, a sufficient quantity of formulated and acceptably labeled, clinical-grade Investigational Agent (and, as required by the Protocol(s), Placebo) to complete the clinical trial(s) agreed to and approved under this CRADA. Investigational Agent should be suitable for shipment to all countries and sites participating in DCTD-sponsored clinical trials. DCTD does not maintain country-specific Investigational Agent supplies. Collaborator will provide a Certificate of Analysis to DCTD for each lot of the Investigational Agent provided. It is understood that DCTD shall take responsibility for and reasonable steps to maintain appropriate records and assure appropriate supply, handling, storage, distribution and usage of these materials in accordance with the terms of this Agreement, the Protocol(s) and any applicable laws and regulations relating thereto.

3.8.2 Collaborator agrees to supply sufficient inventory to ensure adequate and timely supply of Investigational Agent for mutually agreed upon Protocol(s). DCTD will provide updated forecasts of amounts of Investigational Agent anticipated for ongoing and anticipated studies. Collaborator further agrees to provide draft Investigational Agent labels to the NCI Pharmaceutical Management Branch (PMB) for review and agrees to reasonable labeling revisions to comply with DCTD label guidelines. NCI NSC (National Service Center) numbers will be required to be on the label of Investigational Agent for all DCTD-sponsored clinical trials.

3.8.3 Collaborator agrees to provide without charge Investigational Agent or unformulated analytical grade Investigational Agent or metabolites, if available, to DCTD to supply to NCI Investigators for the development of mutually agreed upon Non-Clinical Studies such as analytical assays and ancillary correlative studies conducted in conjunction with DCTD-sponsored Protocols. These studies will be approved by the PRC and conducted according to mutually approved clinical Protocols.

3.8.4 Collaborator agrees to allow Investigational Agent to be distributed to NIH Intramural Investigators and NCI Extramural Investigators for mutually agreeable Non-Clinical Studies designed to enhance the basic understanding and development of Investigational Agent. These may include, but are not limited to, non-clinical studies designed to support clinical trials in pediatric patients; non-clinical combination studies to provide data in support of a clinical trial and other pertinent requests. Each Non-Clinical Study will be proposed by the NIH Intramural Investigators and NCI Extramural Investigators and must be approved by both the NCI and Collaborator. A copy of the signed MTA for the NIH Intramural Investigator for the Non-Clinical Study will be attached to the CRADA. The Non-Clinical Study conducted by the NIH Intramural Investigator is deemed to be included under the scope of this CRADA Research Plan. All NCI Extramural Investigators will sign MTAs substantially in the form attached hereto as Appendix C that acknowledge the proprietary nature of the Investigational Agent to Collaborator and include intellectual property and publication provisions.

3.8.6 Collaborator agrees to provide to the PMB the IB for Investigational Agent and all subsequent revisions/editions. In addition to being filed to the CTEP IND, the IB will be on file in the PMB and will be distributed to all investigators participating on a clinical trial using the Investigational Agent through a secure, password-protected website or by secure email. Distribution will be accompanied by a statement about the confidentiality of the document and will be electronic. All electronic distribution will be done using Adobe Acrobat PDF. Electronic versions should be emailed to the IB Coordinator at IBCoordinator@mail.nih.gov. Any IB received by the PMB should be formatted according to the current FDA Portable Document Format Specifications. Any IB received by the PMB that is not in this format will be converted before distribution at Collaborator’s expense.

3.9 **Investigational Agent Delivery and Usage**. Collaborator will ship the Investigational Agent and, if required, Placebo to NCI or its designee in containers marked in accordance with 21 C.F.R. § 312.6. NCI agrees that the Clinical Investigators will keep appropriate records and take reasonable steps to ensure that the Investigational Agent is used in accordance with the Protocol(s) and applicable FDA regulations. In addition, NCI agrees that the Investigational Agent (and all Confidential Information supplied by Collaborator relating to the Investigational Agent) will be used solely for the conduct of the CRADA Research Plan. Furthermore, NCI agrees that no analysis or modification of the Investigational Agent will be performed without Collaborator’s prior written consent. At the completion of the Research Plan, any unused quantity of Investigational Agent will be returned to Collaborator or disposed as directed by Collaborator. The contact persons for PMB and Collaborator are identified on the Contacts Information Page.

3.10 **Auditing and** **Monitoring**.

3.10.1 DCTD, NCI will be primarily responsible for monitoring Clinical Research Sites and for assuring the quality of all clinical data, unless otherwise stated in the Research Plan. Auditing will comply with the DCTD guidelines as described on the CTEP website at:

http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring.htm. NCI clinical trials must be conducted in accordance with the FDA Good Clinical Practices (GCP).

3.10.2 Subject to the restrictions in Article 8 concerning IPI and any applicable restrictions of NCI and the relevant Data Safety Monitoring Board, and with reasonable advance notice and at reasonable times, NCI will permit Collaborator or its designee(s) access to Clinical Research Sites to review the conduct of the research and to obtain updates on ongoing clinical trials at times convenient to Clinical Research Sites. Randomized phase 2 and phase 3 studies are conducted under the oversight of a DSMB and Collaborator will not have access to the Clinical Research Sites to audit during the conduct of the study, except under exceptional circumstances. Collaborator may also make arrangements with NCI to audit Raw Data and source documents, at the completion of the Protocol primary end point (or sooner, in exceptional or justified circumstances as agreed by the Parties prior to such completion) and at Collaborator’s expense, to the extent necessary to verify compliance with FDA Good Clinical Practice and the Protocol.

DCTD will provide reasonable assistance to Collaborator to access additional data during the course of clinical study if appropriate and approved by the Data Safety Monitoring Board if there is one, or at the conclusion of the clinical study, for purposes of supporting Collaborator’s regulatory submissions related to the Investigational Agent, in the United States and abroad. Collaborator will be responsible for the costs associated with such access to additional data. Access and use of such additional data will be consistent with the restrictions in Article 8.

3.11 **FDA Meetings/Communications**. All formal meetings with the FDA concerning any clinical trial within the scope of the Research Plan will be discussed by Collaborator and NCI in advance. Each Party reserves the right to take part in setting the agenda for and to participate in these meetings. The Sponsor will provide the other Party with copies of FDA meeting minutes, all transmittal letters for IND submissions, IND safety reports, formal questions and responses that have been submitted to the FDA, Annual Reports, and official FDA correspondence, pertaining either to the IND(s) under this CRADA or to the Clinical Investigators on Protocols performed in accordance with the Research Plan, except to the extent that those documents contain the proprietary information of a third party or dissemination is prohibited by law.

3.12 **Steering Committee and CRADA Research.** The Parties agree to establish a Steering Committee comprising at least the NIH CRADA Extramural Investigator/officer(s) and CRADA Collaborator PIs to conduct and monitor the proposed and ongoing clinical studies and non-clinical research using the Investigational Agent in accordance with the CRADA Research Plan. Members of the Steering Committee shall continue to remain employed by their respective employers under their respective terms of employment. If a member of the Steering Committee ceases to be employed by their respective employer, such member will be replaced with a new member that is an employee of that employer.

Additional CRADA information, including Steering Committee meeting reports, Protocol Review Committee records, clinical Protocols, IND and general regulatory information, and non-clinical and clinical data in NCI's possession and control shall remain on file with NCI.

**Article 4. Reports**

4.1  **Research Plan Reports**. The NIH CRADA Extramural Investigator/Officer(s) and CRADA Collaborator PI(s) may exchange information regularly, in writing.

NCI will provide Collaborator with standard quarterly reports that outline the progress of the clinical trials under this CRADA. Other interim report may include, but not limited to, meeting minutes, circulation of draft manuscripts, abstracts or publications, Steering Committee reports, copies of IND Annual Reports or relevant portion concerning the Protocol(s), invention reports or patent applications. In addition, the Parties must exchange updated Investigator’s Brochure, formulation and preclinical data, and toxicology findings, as they become available.

4.2 **Final Research Plan Reports**. After the expiration or termination of this CRADA, NCI will provide Collaborator with any abstracts and publications arising from the Research Plan provided by NCI Investigators; and invention disclosures of potential CRADA Subject Inventions and/or any corresponding Patent Applications, as well as a copy of the relevant portion of the IND(s) Annual Report.

4.3 **Fiscal Reports**. If Collaborator has agreed to provide funding to NCI under this CRADA, and upon the request of Collaborator, then concurrent with the exchange of final Research Plan reports according to Paragraph 4.2, NCI will submit to Collaborator a statement of all costs incurred by NCI for the CRADA. If the CRADA has been terminated, NCI will specify any costs incurred before the date of termination for which NCI has not received funds from Collaborator, as well as for all reasonable termination costs including the cost of returning Collaborator property or removal of abandoned Collaborator property, for which Collaborator will be responsible.

4.4 **Safety Reports**

4.4.1 DCTD shall report all serious and unexpected possible, probable and definite Adverse Events to FDA in accordance with the reporting obligations of 21 CFR 312.32 and will, within 24 hours of notification to FDA, forward all such reports to Collaborator. All other Adverse Event reports received by DCTD shall be reported to the FDA consistent with 21 CFR 312.32 and 312.33. In the event that Collaborator informs the FDA of any serious and unexpected Adverse Events, Collaborator must notify the NCI at the same time. NCI will then notify the Clinical Investigator(s) conducting studies under DCTD-sponsored Protocols, if appropriate.

4.4.2 During and for a period of two years after the completion of a Protocol, the Collaborator shall promptly provide to the NCI any information that Collaborator has reasonably determined could directly affect the health or safety of past or current Human Subjects or influence the conduct of the Protocol. Such information may arise from any source, for example, Safety Reports provided to the FDA, study results, information in site monitoring reports or data safety monitoring committee reports. In each case, the NCI shall be free to communicate these findings to each Clinical Investigator to share with Human Subjects and the IRB, as appropriate.

4.5 **IND Annual Reports or Development Safety Update Reports (DSURs).** DCTD will provide Collaborator a copy of the Annual Report(s) or DSURs for IND(s) filed pursuant to Paragraph 3.7.1, or such portion(s) concerning the Protocol(s), concurrently with the submission of the Annual Report to the FDA. Annual Reports will be kept confidential in accordance with Article 8. Collaborator will provide DCTD with a copy of its Annual Report(s) or DSURs to the FDA, or such portion(s) concerning the Investigational Agent in the Protocols, if Collaborator is sponsoring studies of Investigational Agent under its own IND. Annual Reports or DSURs will be kept confidential in accordance with Article 8.

**Article 5. Staffing, Financial, and Materials Obligations**

5.1 **NCI and Collaborator Contributions**. The contributions of any staff, funds, materials, and equipment by the Parties are set forth in Appendix B. The Federal Technology Transfer Act of 1986, 15 U.S.C. § 3710a(d)(1) prohibits NCI from providing funds to Collaborator for any activities under this CRADA.

5.2 **NCI Staffing**. No NCI employees will devote 100% of their effort or time to the Research Plan. NCI will not use funds provided by Collaborator under this CRADA for NCI personnel to pay the salary of any permanent NCI employee. Although personnel hired by NCI using CRADA funds will focus principally on the Research Plan, Collaborator acknowledges that these personnel may nonetheless make contributions to other activities, and these activities will be outside the scope of this CRADA.

5.3 **Collaborator Funding**. Collaborator acknowledges that Government funds received by Collaborator from an agency of the Department of Health and Human Services may not be used to fund NCI under this CRADA. If Collaborator has agreed to provide funds to NCI then the payment schedule appears in Appendix B and Collaborator will make payments according to that schedule. If Collaborator fails to make any scheduled payment, NCI will not be obligated to perform any of the Research Plan or to take any other action required by this CRADA until the funds are received. NCI will use these funds exclusively for the purposes of this CRADA. Each Party will maintain separate and distinct current accounts, records, and other evidence supporting its financial obligations under this CRADA and, upon written request, will provide the other Party a fiscal report according to Paragraph 4.3, which delineates all payments made and all obligated expenses, along with the final research report described in Paragraph 4.2.

5.4 **Capital Equipment**. Collaborator’s commitment, if any, to provide NCI with capital equipment to enable the activities under the Research Plan appears in Appendix B. If Collaborator transfers to NCI the capital equipment or provides funds for NCI to purchase it, then NCI will own the equipment. If Collaborator loans capital equipment to NCI for use during the CRADA, Collaborator will be responsible for paying all costs and fees associated with the transport, installation, maintenance, repair, removal, or disposal of the equipment, and NCI will not be liable for any damage to the equipment.

**Article 6. Patenting and Licensing**

Patenting and Licensing of inventions generated by NCI Investigators (whether intramural or extramural) conducting the Research Plan will be managed in a manner consistent with the IP Option. In addition, inventions generated during Secondary Research conducted by investigators, including NIH Intramural Investigators, will be subject to the terms of the IP Option.

**Article 7. NIH Inventions Under the IP Option**

For Inventions generated by NIH Intramural Investigators, the Parties recognize that the text of the IP Option uses the term “Invention” but that the Federal Technology Transfer Act (15 USC Section 3710) only allows the Federal Government to provide rights to CRADA Subject Inventions as defined in this CRADA. For clarity, the Parties recognize that the term “Invention” in the IP Option shall be understood as CRADA Subject Invention for the purposes of this CRADA. Further, the parties recognize that the term “Institution” in the IP Option shall be understood as NIH for the purposes of a CRADA Subject Invention under this CRADA.

**Article 8. Rights of Access and Use of Data and Materials**

8.1 **Use of CRADA Data, CRADA Materials and Biospecimens**. NCI and Collaborator agree to exchange all CRADA Data and to share all CRADA Materials. The Parties will be free to utilize CRADA Data and CRADA Materials in their possession internally for their own purposes, consistent with their obligations under this CRADA. NCI may share CRADA Data or CRADA Materials with any contractors, grantees, or agents it has engaged to conduct the Research Plan, provided the obligations of this Article 8.1 are simultaneously conveyed. Collaborator may share CRADA Data or CRADA Materials with any contractors, Affiliates, development partners or agents it has engaged to conduct the Research Plan, provided the obligations of this Article 8.1 are simultaneously conveyed. Collaborator shall not transfer CRADA Data to any third party other than those set forth in this section unless it receives the written permission from the NCI and enters into a Confidential Disclosure Agreement with such third party with confidentiality terms at least as stringent as those set forth herein.

8.1.1 **CRADA Data**. Collaborator and NCI will use reasonable efforts to keep CRADA Data confidential until published. To the extent permitted by law, each Party will have the right to use any and all CRADA Data in and for any regulatory filing by or on behalf of the Party. However, any unpublished CRADA Data provided by NCI or directly by NCI Investigators to Collaborator will be treated by Collaborator as Confidential Information until published.

8.1.2 **CRADA Materials**. Collaborator and NCI will use reasonable efforts to keep descriptions of CRADA Materials confidential until published. Collaborator acknowledges that the basic research mission of NIH includes sharing with third parties for further research those research resources made in whole or in part with NIH funding. Consistent with this mission and the tenets articulated in “Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts,” December 1999, available at <https://grants.nih.gov/grants/intell-property_64FR72090.pdf>, following publication either Party may make available to third parties for further research those CRADA Materials made jointly by both NCI and Collaborator. Notwithstanding the above, if those joint CRADA Materials are the subject of a pending Patent Application or a Patent, or were created using a patent-pending or patented material or technology, the Parties may agree to restrict distribution or freely distribute them. Either Party may distribute those CRADA Materials made solely by the other Party only upon written consent from that other Party or that other Party’s designee.

8.1.3. **Biospecimens**. If Collaborator possesses any human Biospecimens from clinical trials under the CRADA, the Biospecimens must be handled as described in the Protocol or as otherwise directed by NCI before the termination date of the CRADA.

8.2. **Secondary Research: NCI Data Sharing and Biospecimens Sharing Policies**

8.2.1. Data Sharing Policies

1. In order to comply with the NIH clinical data sharing policies, NCI/CTEP has created a database for NCI National Clinical Trials Network clinical trial data for randomized phase 2 and phase 3 clinical trial (referred to as a “Randomized Study”) de-identified clinical trial datasets (CRADA Data) known as the “NCTN Data Archive.”
2. In addition to the exchange CRADA Data and “Raw Data” by NCI and Collaborator as described above in Article 8.1., within 6 months after publication of the primary endpoint data of a Randomized Study that includes Collaborator Investigational Agent, Collaborator will receive a complete de-identified subset of CRADA Data (“Dataset”) that includes the underlying data that support the publication from the Network Group and/or NCI Investigators and/or NIH Intramural Investigators (collectively the NCI Network), conducting the Randomized Study. This Dataset will be entered into the NCTN Data Archive (a controlled access database that takes requests from qualified individuals) 6 months, but no later than 18 months after the Collaborator receives the Dataset, unless the Parties agree to an extended time period for completion of regulatory filings to health authorities; however, in no case will the time period extend beyond a total of 36 months with extensions made in 6 month increments after the original 12-month extension period to 18 months. The Dataset may be released to the NCTN Data Archive prior to this timeframe with the mutual consent of NCI, the Collaborator and the NCI Network. Earlier submission to the NCTN Data Archive would be expected for a Randomized Study that is not going to be used for a regulatory filing, for example. Collaborator must notify NCI [NCICTEPACG@mail.nih.gov] within 6-months of receiving the Dataset to request more review time than the initial 6-month period. Collaborator’s extension request during this review period is proforma and NCI will extend the period to 18-months upon Collaborator request to continue reviewing the Dataset for potential regulatory uses. Collaborator will provide timely written notice to NCI if Collaborator subsequently needs more time to pursue, or decides not to pursue or continue to pursue regulatory filings with the Dataset, so that NCI may anticipate release of the Dataset to the NCTN Data Archive. Should Collaborator request extensions beyond the original 18-month period, said extensions will be granted by NCI in 6-month increments so long as the extensions are to actively pursue or continue to pursue regulatory filings of the Dataset.
3. In addition, NCTN Data Archive Datasets will be made available via the Project Data Sphere (PDS) database (as defined at https://www.projectdatasphere.org), following the processes and terms outlined above.
4. In harmony with the NIH genomic data sharing policies, NCI has implemented policies requiring that de-identified genomic data of Human Subjects obtained under clinical protocols be submitted to the database of Genotypes and Phenotypes (dbGaP as defined at https://www.ncbi.nlm.nih.gov/gap) or the Genomic Data Commons (as defined at https://gdc.nci.nih.gov) following processes and terms substantially similar to those outlined above.

(e) Secondary Research Proposals

Collaborator will receive a copy of each Secondary Research request for access to a submitted Dataset in the NCTN Data Archive or de-identified genomic data, and be provided an opportunity to provide comments within 2 weeks of Collaborator receiving the request. Manuscripts or any form of public presentation or disclosure resulting from the requested use of such a Dataset or genomic data will also be provided to Collaborator for review at least thirty (30) days before submission for publication, or 5 calendar days for presentations or other disclosures (e.g. posters, abstracts). Each requestor seeking access to a submitted Dataset in the NCTN Data Archive or to genomic data must sign NCI’s Data Use Agreement prior to receiving a Dataset or genomic data. All such Data Use Agreements will contain provisions providing for Collaborator manuscript review and other reviews as described above, as well as the IP Option for licensing and the data use rights.

8.2.2 Biospecimens Sharing Policies

1. The Parties acknowledge that Biospecimens collected during any NCI Network sponsored clinical trials are subject to NCI policies implementing NIH policies on data sharing and public access to publications, and will be subject to NCI processes and terms substantially similar to those described above, and subject to the terms of the Relevant Collaborative Agreements.
2. Any Secondary Research conducted using Biospecimens obtained on Human Subjects enrolled on a Protocol under this CRADA and/or non-publicly available data generated from research utilizing Investigational Agent are subject to the terms of this Agreement, and to the IP Option. Requests for Biospecimens from investigators to conduct Secondary Research will be through the NCI Navigator (a web based application) or the Core Correlative Science Committee to CTEP. The requests will be reviewed and approved by CTEP’s Core Correlative Sciences Committee, and provided to the Collaborator for review and comment, before the Secondary Research can commence. Each requestor conducting Secondary Research using Biospecimens must sign a materials transfer agreement with NCI prior to receiving Biospecimens. All such materials transfer agreement will contain provisions providing for Collaborator manuscript review and other reviews as described above, as well as the IP Option for licensing and data use rights.

8.3 **Confidential Information**. Each Party agrees to limit its disclosure of Confidential Information to the amount necessary to carry out the Research Plan, and will place a confidentiality notice on all this information. A Party orally disclosing Confidential Information to the other Party will summarize the disclosure in writing and provide it to the other Party within fifteen (15) days of the disclosure. Each Party receiving Confidential Information agrees to use it only for the purposes described in the Research Plan. Either Party may object to the designation of information as Confidential Information by the other Party.

8.4 **Protection of Confidential Information**. Confidential Information will not be disclosed, copied, reproduced or otherwise made available to any other person or entity without the consent of the owning or providing Party except as required by a court or administrative body of competent jurisdiction, or federal law or regulation. Each Party agrees to use reasonable efforts to maintain the confidentiality of Confidential Information, which will in no instance be less effort than the Party uses to protect its own Confidential Information. Each Party agrees that a Party receiving Confidential Information will not be liable for the disclosure of that portion of the Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given a reasonable opportunity to seek a court order to enjoin disclosure.

8.5 **Human Subject Protection**. The research to be conducted under this CRADA involves Human Subjects or human tissues within the meaning of 45 C.F.R. Part 46, and all research to be performed under this CRADA will conform to applicable federal laws and regulations. Additional information is available from the HHS Office for Human Research Protections (http://www.hhs.gov/ohrp/).

8.6 **Duration of Confidentiality Obligation**. The obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined in Article 2 or three (3) years after the expiration or termination date of this CRADA, except for IPI, for which the obligation to maintain confidentiality will extend indefinitely. Collaborator may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

8.7 **Publications**.

8.7.1 The Parties are encouraged to make publicly available the results of their activities under the Research Plan. However, Collaborator will not publish or publicly disclose any CRADA Data provided by NCI Investigators under the CRADA without NCI’s permission. Before Collaborator or NCI Extramural Investigators or NIH Intramural Investigators submit a paper or abstract for publication about a CRADA Subject Invention, CRADA Data, or CRADA Materials, the other Party will have thirty (30) days to review proposed manuscripts and three business (3) days to review proposed abstracts to assure that Confidential Information is protected. Either Party may request in writing that a proposed publication be delayed for up to thirty (30) additional days as necessary to file a Patent Application.

8.7.2 Manuscripts to be submitted for publication by NCI Investigators will be sent to NCI’s Regulatory Affairs Branch [NCICTEPpubs@mail.nih.gov] for forwarding to Collaborator for review as soon as they are received and in compliance with the timelines outlined above. Abstracts to be presented by NCI Investigators will be sent to NCI’s Regulatory Affairs Branch [NCICTEPpubs@mail.nih.gov] for forwarding to Collaborator as soon as they are received, preferably no less than three (3) business days prior to submission, but prior to presentation or publication, to allow for preservation of U.S. or foreign patent rights.

8.8 **NCI Investigators’ Research and Development Activities**. In pursuing the development of Investigational Agent pursuant to this CRADA, NCI utilizes NCI Investigators that are not NCI employees for part or all of the completion of this Research Plan, which may cover Non-Clinical Studies and clinical studies, through Funding Agreements and MTAs. Participation in DCTD-sponsored clinical trials by these investigators shall be determined after competitive solicitation and review of Protocol Letters of Intent (LOIs) or concepts and Protocols by CTEP, NCI. All Funding Agreements and MTAs for the conduct of extramural clinical trials and Non-Clinical Studies will include the CTEP IP Option.

8.8.1 All NCI Investigators are bound by confidentiality provisions at least as restrictive as those provided in this CRADA and to Collaborator’s use of CRADA Data for obtaining regulatory approval for marketing Investigational Agent.

8.8.2 If Collaborator wants access to Raw Data or any other data in the possession of the NCI Investigators working with Investigational Agent under a Funding Agreement or a MTA, Collaborator must first contact the CTEP Regulatory Affairs Branch (RAB), as identified on the Contacts Information Page. Subsequent to authorization by RAB, Collaborator may directly contact the NCI Investigators. Collaborator will bear any costs associated with Raw Data provided in formats customized for Collaborator, which costs will be paid by Collaborator directly to the NCI Investigators.

8.9 **Multi-Party Data Rights.** For clinical Protocol(s) and Non-Clinical Study(ies) where Investigational Agent is used in combination with another investigational agent supplied to NCI pursuant to a CTA or CRADA between NCI and an entity not a Party to this CRADA (hereinafter referred to as “Third Party”), the access and use of Multi-Party Data by the Collaborator and Third Party shall be co-exclusive as follows:

8.9.1 NCI will provide both Collaborator and Third Party with notice regarding the existence and nature of the agreements governing their collaborations with NCI, the design of the proposed combination Protocol(s) or Non-Clinical Study(ies), and the existence of any obligations that might restrict NCI's participation in the proposed combination Protocols or Non-Clinical Study(ies).

8.9.2 Collaborator shall agree to permit use of the Multi-Party Data from these trials by Third Party to the extent necessary to allow Third Party to develop, obtain regulatory approval for, or commercialize its own investigational agent(s). However, this provision will not apply unless Third Party also agrees to Collaborator’s reciprocal use of Multi-Party Data, which is documented by the signed Drug Approval Form.

8.10 **Access, review and receipt of Identifiable Private Information.** Collaborator access to and review of Identifiable Private Information shall be only for on-site quality auditing. Collaborator will receive Identifiable Private Information only if necessary for purposes of satisfying FDA or other health authorities' reporting requirements, and for internal research purposes, directly related to obtaining regulatory approval of Investigational Agent. Collaborator is prohibited from access, review, receipt, or use of such information for other purposes. All IRB approved Protocols and informed consent documents related to this research project will clearly describe this practice. If the Collaborator will have access to Identifiable Private Information, the Protocol and the informed consent must clearly state (i) the existence of the Collaborator; (ii) the Collaborator's access to Identifiable Private Information, if any; and (iii) the extent to which confidentiality will be maintained. For clinical Protocol(s) involving a third party, the other party's access, review, receipt, or use of Identifiable Private Information shall be subject to the same limitations as described in this Article 8.10.

**Article 9. Representations and Warranties**

9.1 **Representations of NCI**. NCI hereby represents to Collaborator that:

9.1.1 NCI has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that NCI’s official signing this CRADA has authority to do so.

9.1.2 To the best of its knowledge and belief, neither NCI nor any of its personnel involved in this CRADA is presently subject to debarment or suspension by any agency of the Government that would directly affect its performance of the CRADA. Should NCI become aware that any of its personnel involved in this CRADA are debarred or suspended during the term of this CRADA, NCI will notify Collaborator within thirty (30) days.

9.2 **Representations and Warranties of Collaborator**. Collaborator hereby represents and warrants to NCI that:

9.2.1 Collaborator has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that Collaborator’s official signing this CRADA has authority to do so.

9.2.2 Neither Collaborator nor any of its personnel involved in this CRADA, including Affiliates, agents, and contractors are presently subject to debarment or suspension by any agency of the Government. Should Collaborator become aware that any of its personnel involved in this CRADA are debarred or suspended during the term of this CRADA, Collaborator will notify NCI within thirty (30) days.

9.2.3 Subject to Paragraph 12.3, and if and to the extent Collaborator has agreed to provide funding under Appendix B, Collaborator is financially able to satisfy these obligations in a timely manner.

9.2.4 The Investigational Agent provided has been produced in accordance with the FDA’s current Good Manufacturing Practice set out in 21 C.F.R. §§ 210-211, and ICH Q7, and meets the specifications cited in the Certificate of Analysis and Investigator’s Brochure provided.

**Article 10. Expiration and Termination**

10.1 **Expiration**. This CRADA will expire on the last date of the term set forth on the Summary Page. In no case will the term of this CRADA extend beyond the term indicated on the Summary Page unless it is extended in writing in accordance with Paragraph 13.6.

10.2 **Termination by Mutual Consent**. NCI and Collaborator may terminate this CRADA at any time by mutual written consent.

10.3 **Unilateral Termination**. Either NCI or Collaborator may unilaterally terminate this CRADA at any time by providing written notice at least sixty (60) days before the desired termination date. NCI may, at its option, retain funds transferred to NCI before unilateral termination by Collaborator for use in completing the Research Plan. If Collaborator terminates this Agreement before the completion of all approved or active Protocol(s), then Collaborator will supply enough Investigational Agent (and Placebo, if applicable) and enough CRADA Materials (if applicable) to complete these Protocol(s) unless termination is for safety concerns.

10.4 **Funding for NCI Personnel**. If Collaborator has agreed to provide funding for NCI personnel and this CRADA is mutually or unilaterally terminated by Collaborator before its expiration, then Collaborator agrees that funds for that purpose will be available to NCI for a period of six (6) months after the termination date or until the expiration date of the CRADA, whichever occurs sooner. If there are insufficient funds to cover this expense, Collaborator agrees to pay the difference.

10.5 **New Commitments**. Neither Party will incur new expenses related to this CRADA after expiration, mutual termination or a notice of a unilateral termination and will, to the extent feasible, cancel all outstanding commitments and contracts by the termination date. Collaborator acknowledges that NCI will have the authority to retain and expend any funds for up to five (5) years subsequent to the expiration or termination date to cover any unpaid costs obligated during the term of the CRADA in undertaking the activities set forth in the Research Plan.

10.6 **Collaborator Failure to Continue Development**.

10.6.1 If Collaborator suspends development of the Investigational Agent without the transfer of its active development efforts, assets, and obligations to a third party within one hundred eighty (180) days of discontinuation, Collaborator agrees that NCI may continue developing the Investigational Agent. In that event, Collaborator agrees to transfer to NCI all information necessary to enable NCI to contract for the manufacture of the Investigational Agent and, unless abandoned for reasons relating to safety as determined by the Data Safety Monitoring Board, to provide the Investigational Agent (and Placebo, if any) in Collaborator’s inventory to NCI or arrange for an independent contractor to manufacture and provide Investigational Agent to NCI for two years or until the completion of ongoing mutually agreed to Protocols.

10.6.2 If Collaborator abandons development or commercialization of Investigational Agent without the transfer of its development efforts to a third party within one hundred eighty (180) days of abandonment, NCI has the right to make CRADA Data and Raw Data available to a party other than the Collaborator.

**Article 11. Disputes**

11.1 **Settlement**. Any dispute arising under this CRADA which is not disposed of by agreement of the NIH CRADA Extramural Investigator/Officer(s) and CRADA Collaborator PI(s) will be submitted jointly to the signatories of this CRADA. If the signatories, or their designees, are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the Assistant Secretary for Health (or his/her designee or successor) will propose a resolution. Nothing in this Paragraph will prevent any Party from pursuing any additional administrative remedies that may be available and, after exhaustion of such administrative remedies, pursuing all available judicial remedies.

11.2 **Continuation of Work**. Pending the resolution of any dispute or claim pursuant to this Article 11, the Parties agree that performance of all obligations will be pursued diligently.

**Article 12. Liability**

12.1 **NO WARRANTIES**. EXCEPT AS SPECIFICALLY STATED IN ARTICLE 9, THE PARTIES MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER, INCLUDING THE CONDITIONS OF THE RESEARCH OR ANY INVENTION OR MATERIAL, WHETHER TANGIBLE OR INTANGIBLE, MADE OR DEVELOPED UNDER OR OUTSIDE THE SCOPE OF THIS CRADA, OR THE OWNERSHIP, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE RESEARCH OR ANY INVENTION OR MATERIAL, OR THAT A TECHNOLOGY UTILIZED BY A PARTY IN THE PERFORMANCE OF THE RESEARCH PLAN DOES NOT INFRINGE ANY THIRD-PARTY PATENT RIGHTS.

12.2 **Indemnification and Liability**. Collaborator agrees to hold the Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by Collaborator for any purpose of the CRADA Data, CRADA Materials or CRADA Subject Inventions produced in whole or part by NCI employees under this CRADA, unless due to the negligence or willful misconduct of NCI, its employees, or agents. The Government has no statutory authority to indemnify Collaborator. Each Party otherwise will be liable for any claims or damages it incurs in connection with this CRADA, except that NCI, as an agency of the Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Chapter 171.

12.3 ***Force Majeure***. Neither Party will be liable for any unforeseeable event beyond its reasonable control and not caused by its own fault or negligence, which causes the Party to be unable to perform its obligations under this CRADA, and which it has been unable to overcome by the exercise of due diligence. If a *force majeure* event occurs, the Party unable to perform will promptly notify the other Party. It will use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the *force majeure* event.

**Article 13. Miscellaneous**

13.1 **Governing Law**. The construction, validity, performance and effect of this CRADA will be governed by U.S. federal law, as applied by the federal courts in the District of Columbia. If any provision in this CRADA conflicts with or is inconsistent with any U.S. federal law or regulation, then the U.S. federal law or regulation will preempt that provision.

13.2 **Compliance with Law**. NCI and Collaborator agree that they will comply with, and advise any contractors, grantees, or agents they have engaged to conduct the Research Plan to comply with, all applicable Executive Orders, statutes, and HHS regulations relating to research on human subjects (45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56) and relating to the appropriate care and use of laboratory animals (7 U.S.C. §§ 2131 *et seq*.; 9 C.F.R. Part 1, Subchapter A). NCI and Collaborator will advise any contractors, grantees, or agents they have engaged to conduct clinical trials for this CRADA that they must comply with all applicable federal regulations for the protection of Human Subjects, which may include the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164 and Corporate Integrity Policy. Collaborator agrees to ensure that its employees, contractors, and agents who might have access to a “select agent or toxin” (as that term is defined in 42 C.F.R. §§ 73.4-73.5) transferred from NCI is properly licensed to receive the “select agent or toxin.”

13.3 **Waivers**. None of the provisions of this CRADA will be considered waived by any Party unless a waiver is given in writing to the other Party. The failure of a Party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, will not be deemed a waiver of any rights of any Party.

13.4 **Headings**. Titles and headings of the articles and paragraphs of this CRADA are for convenient reference only, do not form a part of this CRADA, and will in no way affect its interpretation.

13.5 **Severability**. The illegality or invalidity of any provisions of this CRADA will not impair, affect, or invalidate the other provisions of this CRADA.

13.6 **Amendments**. Minor modifications to the Research Plan may be made by the mutual written consent of the NIH CRADA Extramural Investigator/Officer(s) and CRADA Collaborator PI(s). Substantial changes to the Research Plan (Appendix A of this CRADA) and any changes to the CRADA including extensions of the term will become effective only upon a written amendment signed by the signatories to this CRADA or by their representatives duly authorized to execute an amendment. A change will be considered substantial if it directly expands the range of the potential CRADA Subject Inventions, alters the scope or field of any license option governed by Article 7, or requires a significant increase in the contribution of resources by either Party.

13.7 **Assignment**. Neither this CRADA nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party. The Collaborator acknowledges the applicability of 41 U.S.C. § 15, the Anti Assignment Act, to this Agreement.  The Parties agree that the identity of the Collaborator is material to the performance of this CRADA and that the duties under this CRADA are nondelegable.

13.8 **Notices**. All notices pertaining to or required by this CRADA will be in writing, signed by an authorized representative of the notifying Party, and delivered by first class, registered, or certified mail, or by an express/overnight commercial delivery service, prepaid and properly addressed to the other Party at the address designated on the Contacts Information Page, or to any other address designated in writing by the other Party. Notices will be considered timely if received on or before the established deadline date or sent on or before the deadline date as verifiable by U.S. Postal Service postmark or dated receipt from a commercial carrier. Notices regarding the exercise of license options will be made pursuant to Paragraph 7.3. Either Party may change its address by notice given to the other Party in the manner set forth above.

13.9 **Independent Contractors**. The relationship of the Parties to this CRADA is that of independent contractors and not agents of each other or joint venturers or partners. Each Party will maintain sole and exclusive control over its personnel and operations. If Collaborator elects to perform any portion of the Research Plan through a contractor(s) or consultant(s), Collaborator agrees to incorporate into such contract all provisions necessary to ensure that the work of such contractor(s) or consultant(s) is governed by the terms of the CRADA, including, but not limited to a provision for the assignment of inventions of the contractor(s) or consultant(s) to the Collaborator.

13.10 **Use of Name; Press Releases**. By entering into this CRADA, the Government does not directly or indirectly endorse any product or service that is or will be provided, whether directly or indirectly related to either this CRADA or to any patent or other intellectual-property license or agreement that implements this CRADA by Collaborator, its successors, assignees, or licensees. Collaborator will not in any way state or imply that the Government or any of its organizational units or employees endorses any product or services. Each Party agrees to provide proposed press releases that reference or rely upon the work under this CRADA to the other Party for review and comment at least five (5) business days before publication unless an expedited review is needed for patient safety reasons. Either Party may disclose the Title and Abstract of the CRADA to the public without the approval of the other Party.

13.11 **Reasonable Consent**. Whenever a Party’s consent or permission is required under this CRADA, its consent or permission will not be unreasonably withheld.

13.12 **Export Controls**. Collaborator agrees to comply with U.S. export law and regulations, including 21 U.S.C. 382 and 21 CFR Part 312.110. If Collaborator has a need to transfer any CRADA Materials made in whole or in part by NCI, or NCI Materials, or NCI’s Confidential Information to a person located in a country other than the United States, to an Affiliate organized under the laws of a country other than the United States, or to an employee of Collaborator in the United States who is not a citizen or permanent resident of the United States, Collaborator will acquire any and all necessary export licenses and other appropriate authorizations.

13.13 **Entire Agreement**. This CRADA constitutes the entire agreement between the Parties concerning the subject matter of this CRADA and supersedes any prior understanding or written or oral agreement, including (add other related agreements).

13.14 **Survivability**. The provisions of Paragraphs 3.3, 3.4, 3.8, 4.2, 4.3, 4.4, 5.3, 5.4, 6.1-9.2, 10.3-10.6, 11.1, 11.2, 12.1-12.3, 13.1-13.3, 13.7, 13.10 and 13.14 will survive the expiration or early termination of this CRADA.

 SIGNATURES BEGIN ON THE NEXT PAGE

**SIGNATURE PAGE**

 **ACCEPTED AND AGREED**

By executing this agreement, each Party represents that all statements made herein are true, complete, and accurate to the best of its knowledge. Collaborator acknowledges that it may be subject to criminal, civil, or administrative penalties for knowingly making a false, fictitious, or fraudulent statement or claim.

**FOR NCI:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_

James H. Doroshow, M.D. Date

Deputy Director, National Cancer Institute

**FOR COLLABORATOR:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_

Signature Date

Typed Name:

Title:

 **CONTACTS INFORMATION PAGE**

**CRADA Notices**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| Sherry S. Ansher, Ph.D.Regulatory Affairs BranchCancer Therapy EvaluationProgram, DCTD, NCI9609 Medical Center Dr., Room 5-W526Rockville, MD 20850 Email: anshers@mail.nih.govTel: (240) 276-6580Fax: (240) 276-7894 |  |

 **Patenting and Licensing**

For NCI: For Collaborator

(if separate from above):

|  |  |
| --- | --- |
| Technology Transfer Center, NCI NCI Shady Grove Mailing Address:9609 Medical Center Dr.Room 1E-530, MSC 9702Bethesda, MD 20892-9702Courier Address:9609 Medical Center Dr.Room 1E-530, MSC 9702Rockville, MD 20850-9702Phone: 240-276-5530 Fax: 240-276-5504 |  |

 **Investigational Agent Delivery**

For NCI: For Collaborator:

Mr. Charles Hall

Pharmaceutical Management

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**Investigator’s Brochure**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| IB Coordinator,Pharmaceutical Management Branch, CTEP, DCTD, NCI9609 Medical Center Drive, Rm 5W240Rockville, MD 20892-9704Tel: (240) 276-6575 |     |

e-mail: IBCoordinator@mail.nih.gov

**Review of Manuscripts and Abstracts**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| NCICTEPpubs@mail.nih.gov |  e-mail:  |

**Adverse Events, Safety Reports**

For NCI: For Collaborator:

CTEPSupportAE@tech-res.com

**Protocols, LOIs or concepts**

For NCI: For Collaborator:

CTEPprotcolcomments@tech-res.com

**SUMMARY PAGE**

*EITHER PARTY MAY, WITHOUT FURTHER CONSULTATION OR PERMISSION,*

*RELEASE THIS SUMMARY PAGE TO THE PUBLIC.*

**TITLE OF CRADA:**

**NIH Component**: National Cancer Institute

**NIH CRADA Extramural Investigator/Officer(s)**: Drs.

**Collaborator:**

**CRADA Collaborator Principal Investigator:**

**Term of CRADA:** Five (5) years from the Effective Date

**ABSTRACT OF THE RESEARCH PLAN:**

Collaborator and the National Cancer Institute have entered into a Cooperative Research and Development Agreement (“CRADA”) under which they will collaborate on the non-clinical and clinical development of XXX, a DESCRIPTION proprietary to COLLABORATOR, as an anti-cancer agent.