AMENDMENTS TO HUMAN GENE THERAPY PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
MARCH 6 AND 7, 1997

10-24-96	**9608-157 Maria, et.al.**	**Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly, Diagnosed, Previously Untreated Glioblastoma (GTI Protocol 0115).** **Amendment:** *The addition of five new investigators.* Michael Fetell, M.D., at Columbia Presbyterian Medical Center, New York, New York; Prof. Dr. med. Johannes Schramm, Neurochirurgische Universitatsklinik, Sigmund-Freud-Straße 25, Bonn, Germany; PD Dr. med. Manfred Westphal, University Clinic Eppendorf, Hamburg, Germany; PD Dr. med. Jörg-Christian Tonn, University Kliniken, Neurochirurgische Klinik und Poliklinik, Würzburg, Germany; Dr. Robert Moumdjian, Notre-Dame Hospital, Montreal, Quebec, Canada
11-07-96	**9503-103 Morgan, Walker**	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.** **Amendment:** *The NIH Biosafety Committee approved the amendment submitted to ORDA on 10-03-96 (letter date: 9-20-97) concerning the addition of a new vector.*
11-17-96	**9608-157 Maria, et.al.**	**Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly, Diagnosed, Previously Untreated Glioblastoma (GTI Protocol 0115).** **Amendment:** *Minor revisions have been made to the protocol.* One of the key inclusion criteria has been revised to read as follows: "Patients must have a surgically accessible lesion which is amenable to an attempt at gross total resection as indicated by the pre-treatment MR scan." Also under inclusion criteria, a statement has been added that "blood or platelet transfusions may not be administered in order to achieve the hemoglobin and platelet requirements for entry into study." In the key exclusion criteria, "cerebellum" has been added so that it reads as follows: "Patients with tumors involving the brainstem, both hemispheres, corpus callosum, cerebellum, or patients with multifocal disease. Patients in whom the resection cavity communicates with the ventricle". Another exclusion criteria (Section 5.2.3.6) has been rewritten for clarification: "Prior history of surgery, radiation

		therapy, chemotherapy, or immunotherapy for treatment of brain tumors. (Patients who have had an open or stereotactic biopsy within 30 days prior to Study Day 0, or patients with a prior resection within 30 days prior to Study Day 0, who are candidates for re-operation and gross total resection are eligible.) The following exclusion criteria revised: "Patients in whom the post -operative treatment plan includes...or patients receiving alternate therapies" such as antineoplastin or laetrile." The following two key exclusion criteria have been added: - Patients in whom the radiation therapy treatment plan does not include at least 56 Gy of radiation. - History of multiple sclerosis. In the treatment strategy for both the HSV-TK1 vector producer cell arm and the standard treatment arm, wording has been added to emphasize that whenever possible the enhanced MR scan will be performed within 24 hours following surgery (versus 48 hours). Patients may now be administered steroids other than Dexamethasone prior to surgery. Section 5.4.5: *Surgical Procedures* has been revised to better describe injection of the vector producer cells. For evaluation of the primary efficacy endpoint, a subsidiary analysis may be carried out censoring patients who have died from causes clearly unrelated to the disease or its treatment (Section 5.6.7.1). For evaluation of the secondary efficacy endpoint, the duration of high quality survival time or time to clinical deterioration will be considered as equal to the time to progression in patients in whom the Karnofsky score is greater than 50 or has not fallen by 20 or more points at the time when "progression" is declared (Section 6.3.2.2). In addition, as requested by FDA, the proportion of patients surviving at one year and two years will be compared between the treatment groups using Fisher's exact test. Additional revisions submitted to ORDA, and an amended clinical study protocol.
11-22-96	**9412-095 Hersh, Rinehart**	**Phase I Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Solid Malignant Tumors or Lymphomas by Direct Gene Transfer.** **Amendment:** The addition of John Rinehart as a PI is approved by Vical's (the sponsor) IBC, in a letter dated 1-9-96.
11-22-96	**9508-115 Chang, et.al.**	**Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.** **Amendment:** *The addition of a new site/new PI is IRB and IBC Approved.* Robert Sobol, M.D., at the Sidney Kimmel Cancer Center in San Diego, California, is added, as well as three new sub-investigators: Hal Coons, M.D., Bruce Bowers, M.D., and Gregg Alzate, M.D. Sub-investigators changes are as follows: at the Scott and White Clinic Donald Quick is removed, and Robyn Young, M.D., and Tulio Rodriguez, M.D., are added. At the University of Michigan Cancer Center, John W. Smith is removed, and Ronald O. Bude, M.D., is added.
11-26-96	**9403-069 Walker**	**A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins.**

		Amendment: *The PI submitted the following amendment to theNIAID IRB Chair:* In order to evaluate trafficking of the cells*in vivo*, the PI wishes to amend the protocol to permit radiolabeling of the lymphocytes immediately prior to infusion in a subset of individuals.
12-05-96	**9608-157 Maria, et.al.**	**Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly, Diagnosed, Previously Untreated Glioblastoma (GTI Protocol 0115).** **Amendment:** *The addition of six new investigators.* Mark Shaffrey, M.D., University of Virginia, Charlottesville, Virginia; Anthony Asher, M.D., Charlotte Neurosurgical Associates, Charlotte, North Carolina; Mel Epstein, M.D., Brown University, Providence, Rhode Island; Frau Prof. Dr. med. Gabriele Anna Maria Schmitz-Schackert, University Klinikum Karl-Gustav-Carus, Dresden, Germany; Ivar Mendez, M.D., Victoria General Hospital, Halifax, Nova Scotia, Canada; Mark Bernstein, M.D., The Toronto Hospital, Toronto, Ontario, Canada.
1/07/97	**9608-157 Maria, et.al**	**Prospective, Open-Label, Parallel-Group, RandomizedMulticenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection ofMurine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.** **Amendment:** *Result of a telephone conversation.* Jeff Carey at GTI (Sponsor) telephoned to informORDA that protocol #9608-157 is a phase III study (not a phase II). Protocol #9611-167 offers the standard arm patients from #157 the possibility of enrolling in the gene therapy arm; another telephone conversation with Jeff Carey on 1/17/97 confirmed #9611-167 is phase **II.**
1/17/97	**9608-157 Maria, et.al.**	**Prospective, Open-Label, Parallel -Group, RandomizedMulticenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection ofMurine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.** **Amendment:** *The addition of six new investigators.* Timothy F. Cloughesy, M.D., UCLA Department of Neurology, Reed Neurological Research Center, Los Angeles, California; JamesMarkert, M.D., University of Alabama, Birmingham, Division of Neurosurgery, Birmingham, Alabama; Matti Vapalahti, M.D.,

		Kuopio University Hospital, Department of Neurosurgery, Kuopio, Finland; Yasuhiro Yonekawa, M.D., University Hospital, Ramistrasse 100, Zurich, Switzerland; Nanno Harrie Mulder, M.D., Academic Hospital Groningen, Department of Internal Oncology, Groningen, The Netherlands; Susanne Osanto, M.D., Academic Hospital Leiden, Department of Clinical Oncology, Leiden, The Netherlands
1-28-97	**9611-167 Maria, et.al.**	**Prospective, Open-Label, Multicenter Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.** **Amendment:** (1) The exclusion criteria have been revised to add the following: - Patients will be excluded if the initial diagnosis of glioblastoma multiforme is not confirmed upon central pathology review. - Patients with tumors involving the cerebellum will be excluded. (2) The inclusion criteria have been revised: - Two lab values for adequate baseline organ function (before surgery) have been increased: platelet count ³100,000 platelets (up from 75,000)/FL or ³100,000 GI/L (up from 75,000) (SI units), and hemoglobin ³10.0 g/L (up from 8.5), or greater than 100 g/L (up from 85) (SI units), or 6.2 mmol/L (up from 5.3)(SI units) (3) The following lab value has been added to the inclusion criteria: white blood cell count ³ 3,000/FL (conventional units) < b> ³3,000 GI/L (SI units) (4) The following two paragraphs added to Section 5.4.5 - *Surgical Procedures* to clarify administration of the vector producer cells: "*If the thickness of the remnant of tissue between the resection cavity and the ependyma is estimated to be less than 3 mm, the needle may be bent to allow injection parallel to the ependyma. The injection tracts should be 1 cm apart and parallel to the ependyma. When injecting residual tumor or tissue in areas where ventricular entry is possible, the surgeon must confirm that the needle is not in the ventricle by aspirating to ensure that no CSF is drawn into the syringe.*" (5) For evaluation of the secondary efficacy endpoint, a subsidiary analysis may be carried out censoring patients who have died from causes clearly unrelated to the disease or its treatment (sections 5.6.7.2 and 6.2.1) Also, in patients in whom the Karnofsky score has not fallen by 20 or more points at the time when "progression" is declared, the time to clinical deterioration will be considered as equal to the time to progression for purposes of the analysis. (Section 5.6.7.2) (6) Section 5.5 *Risks, Hazards and Discomforts* has been revised: - 5.5.1: The following has been revised: "Patients with an intracranial space-occupying lesion often present with symptoms attributable to increased intracranial pressure (ICP). *This increased ICP is frequently caused by cerebral edema."*... - 5.5.2 : (Ventricular/meningeal reaction) The following has been revised: "Despite the lack of a meningeal reaction in the model laboratory animals, meningitis or meningitis-like symptoms *have been associated with the injection or rapid diffusion of the vector producer cell solution directly into the ventricle or subarachnoid space."*... - 5.5.7: (Surgical Procedures) The following has been revised: "The surgical procedures carry a risk....non-neurological complication (*including hemorrhage, deep vein thrombosis, pulmonary embolism, infection and localized pain...*" Section 5.5.9: *Transduction of Non-Tumor Cells* has been revised as follows: "*Some transduction of the HSV-TK into the genome of normal dividing cells within the CNS (endothelial and astroglial cells) could occur in the vicinity of the tumor. Necrosis of most of these cells would be expected at the time of ganciclovir treatment. Vasculitis-like symptoms (bleeding, headache, convulsions) could be expected only if transduction was extensive, but*

		this is highly unlikely. It has not been observed in preclinical studies involving injections of GLI-328 into normal brain tissue of animals. (next page)
-continued-	**-continued-**	*Transduction of circulating blood cells has been observed on occasions and always transiently. It is presumed that such transduction must have occurred during the passage of these cells in the CNS, in the proximity of the VPCs, before the administration of ganciclovir. The destruction of most transduced cells should occur during ganciclovir administration. Some cells could escape this destruction but any theoretical risk linked to their transduction (mutagenesis) is extremely remote (see section 5.5.8).* Section 5.5.11 (Ganciclovir sodium (Cytovene)): The first paragraph has been revised as follows: "To date, no serious toxicities related to ganciclovir...*CSF concentration obtained 0.25 to 5.67 hours post-dose in three patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h ranged form 0.31 to 0.68 ug/ml representing 24% to 70% of plasma concentration.*"... The third paragraph has been revised: "*GCV can cause permanent or temporary infertility and may be associated with birth defects. Women should practice strict birth control during treatment. Men should practice strict birth control during treatment and three months after GCV treatment.* There are a number of other possible toxicities related to ganciclovir administration..." - Section 5.6.4 (Follow -up Evaluations) This section has some minor revisions in regards to patient follow-up: 1) the study coordinator will maintain telephone contact with those patients no longer participating in study visits for any reason, and 2) "Patients in whom progression has been declared by central MR review after treatment on this protocol may receive any treatment modality which the patient and his or her physician deems appropriate." Section 8.1 (Vector Producer Cells) Incineration of vector producer containers is revised to include "whether or not the VPCs were used". If VPCs arrive at the clinical site in unacceptable condition, the "sponsor will be notified...and the product will be destroyed at the clinical site"... Appendix 5 MR Protocol 2.1: The following has been revised: "Pre-contrast T1-weighted images, in the sagital and *coronal* plane."
2-10-96	**9611-167 Maria, et.al.**	**Prospective, Open-Label, Multicenter, Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.** A facsimile transmission sent from GTI states that all of the clinical trial sites from #9608-157 are eligible to participate in this protocol.