Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
June 2007

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II, Study of TNFerade™ Biologic with 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer.**

DocID#	Receipt Date	Event Description
9013	02/22/2007	After a CAT scan revealed a superior mesenteric vein non occlusive thrombus (blood clot), the subject was hospitalized for further evaluation and treatment. Subject started anticoagulation and was discharged. The event occurred about one month after the gene transfer. The subject recovered and the event was considered resolved.
9017	02/23/2007	Approximately 3 months after receiving the final dose of the TNFerade, the elderly subject was seen in clinic with a complaint of right hand weakness. Subject also reported a history of right foot weakness that had resolved and headaches that occurred in the prior week. A CAT scan of the head was done that day and it revealed probable small lacunar infarcts in the bilateral basal ganglia as well as hypodensities in the left parietal and left frontal lobe that could have represented infarcts or possible metastases. Subject was prescribed aspirin therapy and additional tests were ordered. A subsequent MRI of the brain revealed evidence of cerebral infarct and two punctate foci of enhancement that were concerning for metastases. There was additional abnormal enhancement that could be attributed to vasculitis, a toxic metabolic disorder or chemotherapy.
9008	02/21/2007	Approximately 3 1/2 months after completing the final dose of TNFerade, subject was found by husband sitting on floor unable to speak and with paralysis of one side. Subject was admitted to the hospital and diagnosed with a stroke. Subject had been seen approximately 2 weeks prior for symptoms of CVA and an MRI done at that time had revealed acute stroke, possible metastases and abnormal enhancement of unclear etiology. Subject's condition did not significantly improve during this hospitalization and a decision was made to stop any further treatments and proceed with comfort care.

Protocol Number: **552**

Protocol Title: **A Phase I/II Study of An Antitumor Vaccination using α(1, 3) Galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Refractory or Recurrent Non-Small Cell Lung Cancer.**

DocID#	Receipt Date	Event Description
8969	01/22/2007	Subject diagnosed with stage IV, non-small cell lung cancer with metastatic disease in the pelvic bone. Subject was treated with 4 cycles of chemotherapy with a partial response (PR). After 6 months of a stable PR, the subject developed new mediastinal adenopathy and pulmonary nodules. Subject was started on this gene transfer protocol and had no serious adverse events. The subject's serum amylase which was taken the day of dosing was elevated to approximately two times normal. Prior amylase levels were within the reference range. Subject had no complaints or physical findings suggestive of pancreatitis or sialo-adenitis. The elevated value was not recognized until after the subject was treated with gene therapy product. Repeat serum amylase was just above normal. The subject has continued with the series of gene transfer vaccines. Subject has remained asymptomatic.

Protocol Number: **580**

Protocol Title: **Phase II Study Examining the Biological Efficacy of Intratumoral INGN 241 (Ad-mda7) Administration in Patients with In Transit Melanoma.**

DocID#	Receipt Date	Event Description
9045	03/21/2007	The subject complained of chest pain, shortness of breath and sweating. Symptoms occurred three days after the local intratumoral injection of the study agent. Subject had eaten just before the event and symptoms recurred after subject slept for 6 hours. Subject was treated for symptoms of angina; however, follow-up analysis of the ECGs taken during the event did not reveal any changes that would support a diagnosis of unstable angina.

Protocol Number: **619**

Protocol Title: **Administration of a Replication Deficient Adeno-Associated Virus Gene Transfer Vector Expressing the Human CLN2 cDNA to the Brain of Children with Late Infantile Neuronal Ceroid Lipofuscinosis.**

DocID#	Receipt Date	Event Description
8481	04/13/2006	During subject's stay in the ICU in 2004, subject had edema in arms and legs that responded to diuretics.
9032	04/18/2006	During a stay in an intensive care unit in 2004, the subject experienced hypokalemia.
9033	04/18/2006	In 2004, approximately one month after administration of gene product, subject required a blood transfusion while in the intensive care unit.

Protocol Number: **661**

Protocol Title: **A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 in Patients with Intermittent Claudication.**

DocID#	Receipt Date	Event Description
8972	01/26/2007	Subject developed adenocarcinoma of the prostate which was previously reported. This report noted that the subject had a radical prostatectomy. The procedure was performed without difficulty. The subject was discharged from the hospital. A review of this follow-up report by the Sponsor does not suggest a change in the profile of risks for subjects currently participating in or entering this study. A review of this report by the Data Monitoring Committee is pending.
8999	02/20/2007	The subject's screening blood test for prostate specific antigen (PSA) level was normal as was the screening prostate exam performed one month prior to dosing with study agent or placebo. At Week 26, the PSA blood test was slightly elevated. The subject was called by the study site for a report of his general health status at week 56. Subject stated he had a prostate biopsy done approximately 4 months earlier and had been diagnosed with prostate cancer.

Protocol Number: **674**

Protocol Title: **A Phase I Study of ADV-TK + Valacyclovir Gene Therapy in Combination with Standard Radiation Therapy for Malignant Gliomas.**

DocID#	Receipt Date	Event Description
8992	02/13/2007	Subject was hospitalized 7 weeks after initial surgery and gene transfer for shunt placement due to an extra-axial fluid collection that had developed under the site of wound closure from the original surgery. Subject's post-operative course after shunt placement was complicated by fever, seizure, confusion, and agitation. Cultures done on the subdural fluid collection were negative for bacteria. Subject initially improved, however, prior to discharge developed pneumonia that progressed to acute respiratory distress syndrome. Subject died from acute respiratory disease syndrome. The principal investigator felt that the fluid collection was possibly related to the study but that the post-operative complications and death were not related.

DocID#	Receipt Date	Event Description
8966	01/19/2007	The subject was admitted to hospital with a three-day history of confusion and right knee pain. Subject was also noted to have had right leg pain for a few weeks prior to this event. The subject's family denied a history of fever, headache, dyspnea, chest pain, nausea, vomiting or diarrhea. Upon initial examination, the subject was noted to be disoriented and the right knee was hot to the touch, erythematous, and swollen. Subject was afebrile. An initial complete blood count (CBC) revealed a white blood cell (WBC) count. The neutrophil count was also elevated. A lumbar puncture was performed and the cerebral spinal fluid (CSF) was positive for staphylococcus epidermidis, initially indicating possible bacterial meningitis, for which the subject was treated empirically with antibiotics. However, the positive CSF result was later determined to be due to a contaminant. Additionally, the CSF showed a low WBC count, making bacterial meningitis an unlikely possibility. Blood, urine, and right knee drainage cultures were also negative, although the white blood cell count in the right knee joint fluid was very high and an the blood tests showed an elevated erythrocyte sedimentation rate (ESR), consistent with septic arthritis. Of note, the cultures were obtained after initiation of antibiotics. An echocardiogram was also performed, ruling out endocarditis. The subject underwent multiple right knee taps with surgical debridement, resulting in continuous knee drainage. Subject improved with treatment. The plan is to discharge to a rehabilitation facility for an additional 4 weeks of antibiotic therapy. The event was reported by the investigator as grade 3 septic arthritis and associated event of confusion, both related to CG1940/CG8711 and related to docetaxel.
9060	04/09/2007	Subject experienced a seizure 4 days after receiving the first dose of the study agent. The subject was found to have brain metastases that were not known about at the time of enrollment. The subject started radiotherapy and anti-seizure medication. Due to the time period between dosing and the seizure, a relationship to the study agent could not be ruled out.
9144	06/01/2007	Subject received chemotherapy and one dose of the gene transfer cancer vaccine. Five days later subject reported developing 2 painful lesions on right arm, at least one of which had purulent material. A single painless lump developed on the left arm. Subject continued to complain of pain in these lesions and developed an additional lesion on one leg. Subject cancelled an appointment one week after being seen for the leg lesion. At the time, subject's spouse reported that subject was experiencing more pain and drainage from the skin lesions. About one week after missing appointment, and almost three weeks after the gene transfer, the subject was taken to an emergency room for shortness of breath. Upon arrival to the emergency room, the subject was found to be comatose and required intubation and advanced cardiac resuscitation procedures. The subject could not be resuscitated and died. Follow-up information revealed that subject's ulcers on upper extremities were not at the injection sites for the vaccine. At least two of the lesions were noted to be red and painful at the initial followup. Subject also developed a patch of red skin about 6 inches by 3 inches around one of the injection sites on the lower extremity. The lesions progressed in terms of pain and subject developed some drainage. Treatment consisted of antihistamine and subsequently a strong topical steroid. Subject also complained of some dyspnea but it was not clear that this was different than subject's baseline dyspnea. The study site ordered repeat labs approximately 2 weeks after the subject first complained of lesions but this lab work was never completed. Approximately one week after the subject was seen for follow-up and repeat blood work ordered, the subject experienced a cardiopulmonary arrest. The Principal Investigator does not consider the cardiopulmonary arrest to be related to the gene transfer cancer vaccine but does consider the skin lesions related. The Sponsor does not know the cause of the cardiopulmonary arrest and cannot preclude a relationship to the cancer vaccine.

Protocol Number: **730**

Protocol Title: **GV-001.008 A Phase II, Open Label, Single Arm, "Proof of Concept" Study of TNFerade plus Radiation in Patients with Metastatic Melanoma.**

DocID#	Receipt Date	Event Description
9004	02/21/2007	Subject previously admitted for right pleural effusion and pneumonia. Subject's condition deteriorated and subject expired secondary to extensive pneumonia and extensive metastatic lesions from malignant melanoma.

Protocol Number: **742**

Protocol Title: **A Phase I Open-Label Study of the Safety and Feasibility of ZYC300 Administration with Cyclphosphamide Pre-Dosing**

DocID#	Receipt Date	Event Description
8987	02/08/2007	Subject was admitted for pain control for flank pain the night after completing the second cycle of therapy, which included the second dose of the gene product. Subject had ongoing flank pain prior to enrolling in the trial that was attributed to subject's known tumor. A CAT scan done during the admission showed no change in the tumor burden. It is unclear if the pain was related to the tumor or was aggravated by the study treatment.

Protocol Number: **772**

Protocol Title: **A Phase II Study of Direct Tumor Injection of TNFerade™ Followed by KLH-Pulsed Autologous Dendritic Cells in Patients with Unresectable Pancreatic Cancer**

DocID#	Receipt Date	Event Description
9077	04/19/2007	After the second injection of study agent, subject experienced elevated blood pressure, tachycardia and vomiting. Subject subsequently developed rigors, chills and a fever to 102.6 F. Subject was admitted and observed overnight and was clinically stable the following morning with resolution of symptoms.

Protocol Number: **785**

Protocol Title: **TRIST (TroVax Renal Immunotherapy Survival Trial) An International, randomized, double-blind, placebo controlled, parallel group study to investigate whether TroVax added to first-line standard of care therapy, prolongs the survival of patients with locally advanced or metastatic clear cell renal adenocarcinoma**

DocID#	Receipt Date	Event Description
e-Filed	02/20/2007	One week after being dosed with either Trovax or placebo and two days after receiving the final dose of interferon alpha, subject developed dyspnea, cough, and fever. One day later, subject was admitted to hospital after losing consciousness. The admitting diagnosis was bilateral pneumonia and respiratory distress. Despite intensive treatment, subject continued to decline and experienced a cardio-pulmonary arrest and died in the hospital. A CAT scan done about 2 weeks prior to the event revealed a likely mass obstructing the main right bronchus. A lung x-ray done the day of admission showed opacity in the right pulmonary window, and decreased pulmonary transparency in the upper two thirds of the left pulmonary window due to micronodular and peri-bronchovascular opaque areas that had diffuse margins. Initially, the investigator considered the event possibly related to the blinded study medication. However, after review of the imaging, the investigator now considers the event as unrelated to the gene transfer.