Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
March 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
8856	11/22/2006	Approximately one month after the last dose of TNFerade, the subject was discovered, on follow-up CAT scan, to have an asymptomatic aortic arch thrombus (blood clot). Subject was admitted for anticoagulation.
8790	10/12/2006	The subject was administered first dose of TNFerade 78 days prior to the event. The last dose of TNFerade was administered 50 days prior to the event. The subject had a history of an aortic arch thrombus. The subject was seen in the clinic for follow up and the oncologist recognized that the subject was having difficulty with speech and the subject was admitted to the hospital for further evaluation. The subject underwent a MRI and MRA of the brain which revealed an acute left parietal lobe infarct. An INR done upon admission was subtherapeutic. The subject was treated with Lovenox and Coumadin. The event resolved 2 days after admission and subject was discharged from the hospital that day. INR was therapeutic on discharge. No action was taken with the TNFerade. The investigator judged the event as possibly related to the TNFerade and Standard of Care, probably unrelated to the administration procedure and possibly related to the underlying disease.
8824	11/03/2006	Approximately 10 days after the last dose of the TNFerade, the subject presented to the emergency room with intractable nausea and vomiting that required hospitalization for further evaluation and treatment. A series of radiographs were done to rule out bowel obstruction were negative. A chest x-ray also failed to reveal any abnormalities. Blood tests were significant for hypokalemia and hypoalbumin. The subject was treated with intravenous fluids, pain medication, antiemetics and potassium chloride. Cardiac, pulmonary, abdominal and neurological examinations were reported to be within normal limits. The subject's symptoms improved. The event was considered resolved and the subject was discharged.
8849	11/16/2006	Approximately one and one half months after the last dose of TNFerade, a CAT scan revealed a superior mesenteric vein nonocclusive thrombus. The subject was hospitalized for further evaluation and treatment. Subject was started on anticoagulation and was discharged. The subject recovered and the event was considered resolved.

Protocol Number: **567**

Protocol Title: **A Multicenter, Randomized, Double-Blind, Dose Ranging Placebo-Controlled Study Evaluating Defined Doses of Percutaneously Delivered Via Boston Stiletto™ Endocardial Direct Injection Catheter System pVGI.1 (VEGF2) (placebo, 20, 200, or 800µg) in Patients with Class III or IV Angina.**

DocID#	Receipt Date	Event Description
	12/18/2006	Approximately one year after the gene transfer subject was admitted with complaints of flank pain and bood in urine. An 11 x 8 centimeter right upper pole renal mass was seen on CAT scan with focal thrombus within the right renal pelvis and proximal ureter, moderate right hydronephrosis, and at least three lung nodules at the right base concerning for metastatic disease. A magnetic resonance imaging and angiography of the abdomen and angiogram of the abdominal aorta revealed a large 11 x 11 centimeter heterogeneous/mixed signal mass arising from the right kidney causing mass effect on the liver suggesting subcapsular invasion of the liver, a small filling defect in the right renal vein likely consistent with hemorrhage, multiple perinephric varices suggesting physiologic right renal vein obstruction, and a widely patent aorta with atherosclerotic disease bilaterally in the common iliac arteries. These finds were consistant with a primary renal cell carcinoma. A decision was made that the subject would not have surgery or a biopsy; rather, palliative care would be provided. Subject was discharged on from the hospital.
8865	11/30/2006	Approximately 8 months after the gene transfer, the subject, who had a history of coronary artery disease, had a fatal myocardial infarction. The investigator judged the event as an unknown association with the gene transfer device and procedure.

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
8827	11/03/2006	The subject complained of chest pain, shortness of breath and sweating. Symptoms occurred three days after the sixth local intratumoral injection of the gene transfer vector. Subject had eaten just before Serious Adverse Event (SAE) and symptoms recurred after subject slept for 6 hours. Subject was treated for symptoms of angina. Additional information regarding the clinical outcome has been requested by sponsor.

Protocol Number: **615**

Protocol Title: **Phase II Study in metastatic melanoma using lymphocytes reactive with the gp100 antigen following the administration of a nonmyeloablative lymphocyte depleting regimen.**

DocID#	Receipt Date	Event Description
8843	11/14/2006	Subject admitted for dypsnea and chest pain one hour after receiving cells and gene transfer vaccine. Subject had prolonged hospitalization with treatment for pneumonia. Despite initial improvement, almost 2 months after being admitted subject had decline in respiratory status and developed multiorgan failure.
8842	11/14/2006	The subject expired after prolonged hospitalization. Initial results from lung autopsy specimen show changes consistent with chronic inflammation and pulmonary hypertension but no tumor.

Protocol Number: **616**

Protocol Title: **A Phase I/II, Open-Label Study (with a Sequential Dose Escalation Stage Followed by an Expansion of a Selected Dose Cohort), to Evaluate the Safety and Anti-Tumor Effects of NV1020, Administered Repeatedly Via Hepatic Artery Infusion Prior to Second-Line Chemotherapy, in Patients with Colorectal Adenocarcinoma Metastatic to the Liver.**

DocID#	Receipt Date	Event Description
7468	08/12/2005	Following the second infusion of the gene transfer vector, the subject experienced intermittent fevers over 10 days which resolved. Follow-up CAT and PET scans done one month after dosing showed a significant increase in the size of the tumor masses. Subject expired at home from disease progression just over one month after receiving the gene transfer. The investigator considered the death to be unrelated to the study agent.
7625	09/02/2005	Autopsy report received for subject who died approximately one month after last dose of study agent. The autopsy revealed that more than 80% of the liver was replaced by tumor and there was extensive abdominal metastases. There was no evidence of the viral vector used for the gene transfer within the liver.
8908	12/15/2006	Subject received second dose of study agent and shortly after reported right upper quadrant and mid-epigastric pain. Subject admitted 11 days after dosing and workup revealed tumor progression in liver and new findings of gallbladder thickening with peri-cholecystic fluid. Cholecystotomy was performed. The material aspirated was sent for routine bacterial and fungal cultures, which were negative. Virology studies of the aspirate are pending. Serological analysis of Herpes Simplex Virus (HSV) DNA was negative. A percutaneous cholecystotomy tube was placed. An acalculous cholecystitis was the suspected diagnosis. Information received in follow-up indicated that the subject was discharged from the hospital with percutaneous cholecystostomy. Subject was taken off the study due to persistant elevated blood lab values. The investigator initially considered the event unlikely related to the study agent, but in view of the close temporal relationship between the gene transfer and the onset of the events, investigator changed the causality to possibly related. Additional follow-up was received that showed the fluid aspirated from around the gallbladder was negative for HSV. PET scans showed marked tumor progression in size and location. The principal investigator stated that after review of the rapid increase in the arcino embryonic antigen (CEA) blood level, tumor progression was the likely cause of the acalculous cholecystitis and liver insufficiency. Therefore, he assessed the event as unlikely related to the gene transfer.
8912	12/18/2006	Following the second infusion of gene transfer product, the subject developed shaking chills and modest temperature elevation. A second temperature elevation occurred several hours later. The subject reported that intermittant fevers occurred for several days after dosing of gene product. Subject also reported fatigue and some abdominal pain. A decision was made to delay the next infusion of gene transfer product.

Protocol Number: **636**

Protocol Title: **An Open Label Pilot Study to Evaluate the Safety and Tolerability of PANVAC™-V and PANVAC™-F in Combination with Sargramostim in Patients with Metastatic Adenocarcinoma.**

DocID#	Receipt Date	Event Description
8947	01/08/2007	Subject received the gene transfer cancer vaccine (day 1 of 4 days) and in the evening of that day experienced a fever (101.1 F), chills and dry heaves. Early in the morning of the next day, subject got up to go to the bathroom and upon returning from the bathroom the subject felt lightheaded and then fainted and fell on the floor of the bathroom. There were no witnesses and subject estimated that the loss of consciousness to be just minutes. Subject reported no post-ictal confusion to indicate seizure and reported no injury. The next day subject continued to have nausea but no further episodes of syncope. The protocol's consent does have lowering of blood pressure as a uncommon side effect of GM-CSF. The examining physician at the study site felt this syncopal episode was secondary to vasovagal influence of nausea/dry heaves versus hypotension secondary GM-CSF or flu-like syndrome. In a follow-up report the principal investigator concluded that the episode of syncope was probably related to the GM-CSF but could possibly be related to the gene transfer vaccine. The nausea was probably related to the GM-CSF and probably related to the vaccine, and possibly related to the ovarian cancer. The Grade 1 fever was probably related to the GM-CSF, but could possibly be related to the vaccine.

Protocol Number: **653**

Protocol Title: **A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer Who are Chemotherapy-Naïve**

DocID#	Receipt Date	Event Description
8832	11/06/2006	During the study agent treatment period, which started about 2 months prior to event and ended 8 days prior to event, laboratory test findings revealed an intermittent rise in serum calcium levels as well as a progressive rise in serum creatinine and urea nitrogen levels indicating worsening renal function. Subject presented to the emergency room eight days after the final dose of product with a one week history of worsening nausea, vomiting and anorexia. Subject also complained of fatigue and a light cough with dyspnea. Upon initial exam, subject was found to have a fever and initial lab tests revealed acute renal failure, hypercalcemia and anemia. The white blood cell count was normal. Urinalysis showed trace ketones, moderate blood and protein. An initial electrocardiogram showed atrial fibrillation with rapid ventricular rate. Bone scan showed progression of metastatic lesions. Subject gradually improved with treatment and was discharged. In follow-up, subject was noted to have improving serum creatinine levels with continuing nausea and anorexia. The event was reported by the PI as Grade III dehydration, related to study agent, with the associated events of nausea, vomiting, acute renal failure and hypercalcemia, related to study agent. The anemia, atrial fibrillation and fever was thought to be unrelated to the study agent.

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
	11/17/2006	Subject had study screening chest x-ray performed which was normal. The Study Week 52 chest x-ray revealed multiple small pulmonary nodules and a left supraclavicular mass suspicious for malignancy. In follow-up, the sponsor reported that a re-review of the screening chest x-ray revealed one of the nodules but it was significantly smaller on that screening chest x-ray. A biopsy of the lung mass revealed non small cell carcinoma.
8861	11/28/2006	Subject's screening prostate exam was normal and the serum prostate specific antigen (PSA) level was at the upper limit of normal. The Study Week 26 PSA level was just above the upper limit of normal and the subject was instructed to follow-up with his physician. At Study Week 52 , the subject had not seen a physician about the elevated PSA and subject was again instructed to seek follow-up. The subject was seen by an internist for routine physical examination at which time a prostate nodule was noted. The remaining physical exam was unremarkable. Subject denied any genitourologic complaints other than a history of erectile dysfunction. Repeat PSA was again elevated. Subject was subsequently diagnosed with prostate adenocarcinoma, Gleason score 6. In the opinion of the Investigator, the event was of severe intensity and possibly related to study treatment.
8939	01/04/2007	Subject's screening prostate exam was reported as normal although prostate specific antigen (PSA) blood level was elevated. It was decided that the elevated PSA was "normal for age" given normal exam. At week 26, PSA again noted to be elevated at same level. Subject referred for urological evaluation and prostate nodule detected. A prostate biopsy revealed prostate cancer, Gleason score 6. The investigator continues to consider event as possibly related to study treatment.
8923	12/22/2006	Subject entered study with prostate specific antigen (PSA) blood level above normal range but given age and normal rectal exam the PSA value was considered to be "normal for age." The PSA rose slightly at 26 weeks post dosing and again at week 52. Subject was referred for urological examination.

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
8942	01/03/2007	Subject was admitted with low serum sodium and confusion one week after resection of tumor and receipt of gene transfer. Analysis of cerebrospinal fluid revealed signs of inflammation. MRI revealed a scalp fluid collection overlying craniotomy. The principal investigator felt that event could be related to blood in the cerebral spinal fluid or possibly related to gene transfer. Subject recovered and continued in protocol.

Protocol Number: **708**

Protocol Title: **A Phase 3 Randomized, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane-Naive Patients with Metastatic Hormone-Refractory Prostate Cancer with Pain.**

DocID#	Receipt Date	Event Description
8888	12/08/2006	Subject presented to clinic complaining of swelling and erythema in arm one week after receiving 6 intradermal injections of the study agent. Subject was admitted to hospital the same day. The subject had areas of patchy redness with mild scaling on the arm that were warm to touch and mildly tender consistent with cellulitis. A complete blood count revealed a low white blood cell count. The subject was treated with intravenous antibiotics with considerable improvement in cellulitis. Subject remained afebrile and hemodynamically stable during hospital course. The white blood cell count continued to drop until the time of discharge. This decline was felt to be associated with the nadir of the subject's most recent docetaxel cycle. Subject was discharged on a 10-day course of oral antibiotics. Subject returned to the clinic for follow up fully recovered with no significant erythema at the previously documented site of cellulitis. Subject's repeat labs showed improved white blood cell count. The event was reported by the principal investigator as Grade III neutropenic infection, related to study agent and docetaxel.

Protocol Number: **729**

Protocol Title: **A Phase I Clinical Trial of Repeated Dose Intrapleural Adenoviral-Mediated Interferon-Beta Gene Transfer for Pleural Malignancies.**

DocID#	Receipt Date	Event Description
8837	11/13/2006	The subject required admission nine days after receiving the second dose of gene transfer. An echocardiogram was ordered after the subject experienced decreased blood pressure, two falls, worsening vomiting and shortness of breath. The echo showed a large pericardial effusion and signs of early tamponade. Pericardiocentesis was done and subject's condition stabilized. Subject had an asymptomatic pericardial effusion present at baseline that was seen on computed tomography scan of the chest.

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
9003	02/21/2007	Subject was admitted approximately 28 days after the last dose of TNFerade and was diagnosed with a right pleural effusion and pneumonia requiring care in the intensive care unit. Subject's condition continued to deteriorate and subject died. The final diagnosis was respiratory failure due to extensive metastasis from malignant melanoma with evidence of metastases to the lungs. Additional diagnosis included urinary tract infection, severe anemia, GI bleed, asthmatic bronchitis, and renal failure.

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
8943	01/04/2007	The subject was found dead at home five days after receiving the gene transfer. No autopsy done and cause of death remains unknown.

Protocol Number: **801**

Protocol Title: **A Phase II Trial Using a GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Allogeneic Tumor Cell-Based Vaccines in Combination with ATRA, and Cyclophosphamide for Patients with Stage IV Adenocarcinoma of the Lung**

DocID#	Receipt Date	Event Description
8933	12/27/2006	Subject admitted to the hospital one week after receiving gene transfer and was diagnosed with pneumonia. Initially, the principal investigator (PI) stated that an association with gene transfer is unknown but could not be ruled out. The PI also stated that an association with another study medication, all-trans retinoic acid could not be ruled out. In a follow-up report, the PI stated that subsequent studies of cytokine levels make it less likely that the event is related to gene transfer and more likely the event is related to a combination of age and multiple co-morbidities.