Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
December 2005

Protocol Number: **403**

Protocol Title: **A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina.**

DocID#	Receipt Date	Event Description
7633	08/24/2005	Approximately 4 years post receiving gene transfer or placebo, the subject was noted to have an elevated prostate surface antigen (PSA), and underwent a biopsy of the prostate. The pathology report confirmed the presence of adenocarcinoma (cancer) of the prostate. The subject's urologist recommended surgical removal of the prostate. Subject has not recovered from the event. The Investigator considered the event to be possibly related to gene transfer or placebo. Sponsor considered the prostate adenocarcinoma to be unlikely related to the gene transfer or placebo.

Protocol Number: **452**

Protocol Title: **A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina.**

DocID#	Receipt Date	Event Description
7617	09/17/2004	Approximately 19 months after injection of either the gene transfer vector or placebo, this subject presented to the emergency room with a four day history of left-sided chest pain with radiation to the left arm and neck. The symptoms were associated with nausea. The subject has an extensive cardiac history and this pain was similar to previous episodes of angina. A myocardial infarction was ruled out. Cardiac angiography revealed a new vascular lesion which was successfully treated with a drug eluting stent.
7612	09/17/2004	Subject experienced low oxygen levels, low potassium levels and fever, on the day of the injection of either the gene transfer vector or placebo. The Investigator reported the cause of the fever as possibly related to gene transfer or placebo.
7632	08/24/2005	Subject contacted the study site to report having been diagnosed with an early stage of a slow growing prostate cancer, approximately two years after receiving gene transfer or placebo. A CT scan revealed an enlarged prostate and calcifications. There were no clear signs of metastatic disease. The Investigator considered the event possibly related to gene transfer or placebo. The Sponsor considered the event as unlikely related to gene transfer or placebo.

Protocol Number: **502**

Protocol Title: **A Phase II, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Efficacy and Safety Study of Different Doses and Schedules of Administration of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease.**

DocID#	Receipt Date	Event Description
7640	09/13/2005	At regular scheduled visit post between injection two and three of either gene transfer vector or placebo, subject was found to have increased edema in the right leg. Approximately one month later, subject presented with improvement in leg edema. The intensity had decreased from moderate to mild. The edema was initially considered related to the investigational agent by the principal investigator, however, the attribution was subsequently changed to unrelated.

Protocol Number: **546**

Protocol Title: **A Phase I/II Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion in Critical Leg Ischemia.**

DocID#	Receipt Date	Event Description
7624	09/01/2005	Subject had a history of rectosigmoid carcinoma surgically treated. A follow-up colonoscopy done about ten years after this diagnosis showed no evidence of any recurrent cancer and no new polyps. The subject received the gene transfer or placebo about two years after that colonoscopy. About nine months later, subject had a colonoscopy as part of a work-up for anemia (low red blood cell count) and was found to have a recurrent colon cancer and underwent surgical resection. Adjuvant therapy was not recommended. Initially the Investigator reported event as unrelated to study agent. The Investigator reported the event was likely related to the subject's history of colon cancer, as the current colonoscopy confirmed the mass to be a recurrent cancer. In a follow up report, the Investigator changed the causality of the event to possibly related to study agent. The Investigator further stated that the relationship between recurrent colon cancer and the study agent could not be ruled out.

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
7821	10/06/2005	During administration of the study agent or placebo injection, subject developed chest pain and electrocardiogram showed ST segment elevations. These events continued to worsen in severity during the administration. Per Investigator, a medical monitor was consulted. An echocardiogram performed showed minimal effusion. Administration of study agent or placebo was stopped. The subject received narcotic pain medicine and intravenous nitroglycerin. The event was considered resolved and the subject was discharged the next day. The investigator judged the event as possibly related to the drug and device (injection catheter) and not related to the procedure.

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
8114	09/19/2005	Follow up received concerning episode of neutropenia (low white blood cell count) that occurred one and one half months after receiving the fourth dose of the gene transfer. Subject was treated with intravenous antibiotics and fluids during the hospitalization. The neutropenia resolved.
8115	09/19/2005	Dosing information provided by the Sponsor in a follow-up report. The last dose of gene transfer was about two months prior to event. Since subject was in the chemotherapy phase in the study when the SAE occurred the Sponsor did not consider this event to be possibly related to the gene transfer. The Data Safety Monitoring Board agreed with this assessment.

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
7557	08/19/2005	This is follow-up to a serious adverse event (SAE) report for “respiratory failure requiring re-intubation” in the setting of status epilepticus, which is most likely related to the medications administered to suppress seizure activity and to the subject’s decreased oropharyngeal tone and pulmonary toilet, and unlikely related to the gene transfer vector. The SAE occurred about one month after gene transfer. Because the associated risks of respiratory depression, airway congestion, airway obstruction, and shallow breathing are listed in the informed consent document, it is being reported as an expected serious adverse event. In follow-up, the Principal Investigator reported that subject remained intubated for approximately one month. The subject was extubated shortly after being taken home and died shortly thereafter.
7460	08/05/2005	Follow- up information received from the Investigator concerning subject's admission to the hospital just over a week after the gene transfer. The subject was admitted after the parents reported an increase in post-operative myoclonus of the extremities. The follow-up information concerned a parent's report that subject experienced a similar exacerbation of myoclonus the evening of the second day of the hospitalization. Subject had not displayed any post-operative myoclonus the morning of the second hospital day. Subsequent to the event that evening, the subject's previous increased post-op subcortical myoclonus resolved. The pediatric neurologist confirmed that non-epileptic myoclonic jerks described in the EEG report were consistent with subject's baseline condition. Principle Investigator categorized event as expected and possibly related.
7792	10/05/2005	Eight days after undergoing surgery to administer study agent, subject presented to emergency room following a seizure. Episode resolved without intervention. Subject's normal morning dose of anti-convulsant medication had not yet been administered prior to the seizure. A head CAT scan was performed, which showed resolution of prior post-op pneumocephalus, as well as improved bilateral subdural collections as compared with the post operative MRI performed approximately one week prior to this event. During initiation of the protocol required 24 hour continuous video electro-encephalogram (EEG) monitoring later that afternoon, the subject experienced another similar seizure. Subject's valproic acid dose was increased. Twenty-four hours continuous video EEG monitoring was completed in the afternoon, with no further seizure activity noted. Apart from the seizure, the EEG was comparable to two previous EEG's done in the past month. Subject was discharged to home in a medically stable condition. No further seizure activity has since been noted or reported at the time of this report. This is being reported as an expected and related serious adverse event.

Protocol Number: **635**

Protocol Title: **A Phase III Randomized, Controlled Study to Evaluate the Safety and Efficacy of PANVAC™-VF in Combination with GM-CSF Versus Best Supportive Care or Palliative Chemotherapy in Patients with Metastatic (Stage IV) Adenocarcinoma of the Pancreas Who Have Failed a Gemcitabine-Containing Chemotherapy Regimen.**

DocID#	Receipt Date	Event Description
7628	09/08/2005	Approximately ten days after receiving the gene transfer, the subject complained of frequent falls with walking and was admitted for lower extremity weakness. The subject reported having problems with walking for several months but the symptoms had recently worsened. On exam, subject found to have good dorsiflexion, but significant weakness in the lower extremities such that the subject was unable to elevate the legs. Chronic venous changes in the lower extremities and significant bilateral edema were also noted on exam. An MRI of the lumbar-sacral spine did not reveal spinal cord compression. Given the proximal muscle weakness and the history of chronic problems with acute worsening a paraneoplastic syndrome was suspected. An electromyography was performed. In addition, because of a rash on the knuckles that was consistent with Grotton's papules, labs were ordered to help confirm a suspected diagnosis of polymyositis or dermatomyositis. The event is ongoing.

Protocol Number: **657**

Protocol Title: **A Phase II Trial Using a Universal GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Autologous Tumor Cell-Based Vaccines for Patients with Malignant Melanoma.**

DocID#	Receipt Date	Event Description
	08/25/2005	Subject experienced slow heart and low blood pressure immediately following a punch biopsy three days after gene transfer vaccine. Blood pressure went as low as 40/20 and pulse dropped into the 40's. Subject was placed in a prone position and given intravenous fluids and recovered after about twenty minutes. Subject was admitted to the medical center and monitored for 24 hours. Cardiac enzymes were negative. Subject reported a similar incident approximately 4 months ago that occurred while flying. Subject was instructed to stop the beta blocker medication subject had been taking and an appointment with subject's cardiologist was arranged the week of discharge. The principal investigator did not provide an assessment of the attribution of the event.

DocID#	Receipt Date	Event Description
7629	09/01/2005	Subject received six doses of the gene transfer over a seven month period. Approximately two months after the last dose a significant elevation in liver tests was noted. Subject was admitted to the hospital and underwent liver ultrasound, a CT scan and MRI. A liver biopsy revealed hepatitis of unknown etiology. Subject was discharged after a prolonged hospitalization (approximately two months) but was quickly readmitted because liver function tests continued to worsen. During this second hospitalization a seroma was aspirated. Infection with Hepatitis B and C was excluded. The principal investigator reported that gallstones are not suspected and there is no evidence for target disease progression. The diagnosis remained hepatitis of unknown etiology. It was reported that the study agent is "unlikely" to be the cause of the subject's hepatitis.