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

Protocol Number: **274**

Protocol Title: **A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease.**

DocID#	Receipt Date	Event Date	Event Description
7318	06/10/2005	03/08/2004	Follow up Sponsor: Subject was hospitalized again due to infection of amputation wound and resection. The subject experienced both episodes of infection of amputation wound requiring two new amputations. Both events were then considered as recovered with sequelae. Infection of amputation wound is considered by the investigator as not related to study medication (NV1-FGF or placebo), but related to underlying/concomitant illness. This subject, who developed deep vein thrombosis at lower limb about 6 weeks after study medication initiation, had several risk factors for venous thrombosis; PAID with poor/bad circulation, age over 50, overweight, possible immobilization and at least reduced mobility. Deep vein thrombosis and infection are not expected in the Investigator's Brochure for NV1-FGF.

Protocol Number: **360**

Protocol Title: **Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.**

DocID#	Receipt Date	Event Date	Event Description
7212	05/04/2005	03/31/2005	Subject received study agent intra-arterially followed by 4 doses of IL-2, stopping for fluid accumulation and swelling in lungs (pulmonary edema). Subject's post treatment was complicated by acute kidney failure and serum creatinine reaching a maximum of 3.9. Creatinine decreased to 2.2 and subject was discharged. On subject's 1 and 2 month follow-up visit, subject continued to complain of nausea and fatigue. Subject was admitted and received a blood transfusion for low hemoglobin and low hematocrit.

Protocol Number: **370**

Protocol Title: **Gene Therapy for Patients with Fanconi Anemia: A Pilot Study.**

DocID#	Receipt Date	Event Date	Event Description
7263	05/30/2005	05/28/2005	Subject developed fever and infection in bone marrow harvest site. Treated with antibiotics. Discharged stable on antibiotics.

Protocol Number: **407**

Protocol Title: **A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention.**

DocID#	Receipt Date	Event Date	Event Description
7241	05/16/2005	06/14/2002	Follow up Sponsor : Following completion of the study, subject treatment status was unblinded. Subject was randomized to and received the 1E9 viral particle dose of Ad2-HIF-1alpha/VP16.
7240	05/16/2005	03/08/2002	Follow-up Sponsor: Subject treatment status was unblinded. Subject was randomized to and received the 1 E9 viral particle dose of Ad2/HIF-1alpha/VP16.

Protocol Number: **520**

Protocol Title: **Transplantation of Unrelated or Mismatched Related Donor T cells Containing the HSV-TK Suicide Gene to Facilitate Engraftment and Control Graft-versus-Host Disease in Patients with Fanconi Anemia. A Phase I Trial.**

DocID#	Receipt Date	Event Date	Event Description
7262	05/27/2005	05/27/2005	Subject, enrolled under a single subject exemption, expired due to an arrhythmia. The Investigator reports that the cell processing and transduction was uneventful as was the cell infusion. However, in the weeks after the infusion, subject had been very ill, with infectious complications and renal insufficiency. There is no evidence of graft versus host disease, although there was a question of marrow aplasia that could possibly be related to donor lymphocyte infusion of engineered cells. Autopsy has been consented. Results pending.
7317	06/13/2005	05/27/2005	Follow up Investigator: Report states infection and organ system failure as "expected, unlikely related to gene transfer". Arrhythmia as "unusual and unexpected and possibly related to gene transfer." Detailed summary of infusion toxicity, hematologic observances, respiratory arrest details, infectious disease status and tumor staging was provided.

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 Date	Event Description
7199	04/27/2005	12/16/2004	Follow up Sponsor: Subject underwent a right partial colectomy with primary anastomosis. Pathology report showed colonic adenocarcinoma (cancer). Regional lymph nodes were negative for malignancy. Investigator considered this adenocarcinoma as possibly related to the investigational agent. The Sponsor Medical Monitor considers the malignancy unlikely to be related to the investigational agent.

Protocol Number: **567**

Protocol Title: **A Multicenter, Randomized, Double-Blind, Dose Ranging Placebo-Controlled Study Evaluating Defined Doses of Percutaneously Delivered Via Boston Stilletto™ 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 Date	Event Description
7205	04/26/2005	12/29/2004	Follow up sponsor: The subject reports four bouts of fever going up to 104F, increased joint pain, weakness in legs, chest pain, a possible lung infiltrate on initial chest x-ray and mediastinal lymph nodes. Follow-up chest x-rays were negative for pneumonia and cardiac enzymes were within normal limits. The subject was treated with antibiotics. The subject had a follow-up visit with pulmonologist and underwent a repeat CT scan and was advised that no further scans would be required for one year. The Investigator judged the event as not related to study drug, device or procedure. The event of fever of unknown origin is expected in this subject population. The Sponsor medical monitor judged the event as not related to study drug, device or procedure. The event of fever of unknown origin is by definition without other causality.
7253	05/13/2005	12/29/2004	Follow up Sponsor: The Investigator reported the final diagnosis as "fever of unknown origin," and determined that the event resolved. The Investigator judged the event relationship to the study agent, device and procedure as "unknown", and reported that a determination of causality has not been made at this time. Previously, the Investigator had judged the event (pneumonia) as not related to study agent, device or procedure. The Sponsor held a discussion with the Investigator. A mechanism by which the study agent may cause fever is not known, but without a clear etiology for the fever, a relationship to study agent cannot be excluded. The event of fever is expected.

Protocol Number: **600**

Protocol Title: **A Phase II Randomized, Double Blind, Controlled Study to Evaluate the Safety and Efficacy of PROSTVAC®-VF/TRICOM™ in Combination with GM-CSF in Patients with Androgen-Independent Adenocarcinoma of the Prostate.**

DocID#	Receipt Date	Event Date	Event Description
7360	06/23/2005	10/10/2004	Follow up Investigator : The Investigator amended causality assessment again from "not related to study agent administration" to "possibly related." The subject was to begin chemotherapy and was noted to look well. Subject was receiving hemodialysis twice a week.
7361	06/23/2005	04/02/2005	Subject developed back pain and became lethargic. By noon, the subject was unresponsive. Upon admission to a local hospital, subject's blood thinning medication level was high. A preliminary head CT showed a large thalamic bleed. Subject was initially treated with Vitamin K, and was transferred to a tertiary care facility. Upon admission, platelets were 56x10³/µL, PT and PTT were 14.9 and 28.0 seconds respectively. Subject received fresh-frozen plasma, factor IX, and platelet transfusions. The subject was comatose, unresponsive to noxious stimuli, with minimal brainstem reflexes intact. A non-contrast head CT confirmed a large left thalamic hemorrhage with extension into the four ventricles and into the subarachnoid space of the sulci. Lytic changes were noted in the skull at the right posterior parietal region, associated with soft tissue scalp swelling which could be suspicious for a neoplastic process vs. infection.
7362	06/23/2005	04/03/2005	The subject died from a thalamic hemorrhage. The examining physician considered that the hemorrhage was due to high blood pressure and a high level of blood thinning medication.

Protocol Number: **611**

Protocol Title: **Modulation of Vascular Endothelial Growth Factor (VEGF) Using an Engineered Zinc-finger Transcription Factor to Treat Lower Limb Intermittent Claudication.**

DocID#	Receipt Date	Event Date	Event Description
7438	07/26/2005	07/16/2005	Subject admitted to hospital with chest pain and diagnosed with evolving acute inferior (MI) myocardial infarction (heart attack). Treated with medications. Initially stabilized, but later that day, subject experienced another MI and was transferred to a larger hospital . Catheterization attempted unsuccessfully due to inablity to cross the narrowed area with the balloon catheter. Catheterization also showed one of the bypass grafts was completely blocked.
7437	07/26/2005	06/01/2005	Subject found to be "babbling", seemed to understand questions posed to them but was unable to answer with appropriate words. Subject was falling to one side. Taken to ER, where symptoms continued and was admitted for 72 hours. Symptoms resolved with no treatment or diagnostic workup. Discharged and prescribed Aggrenox 200 mg and Aspirin 25 mg. Subject may have not been compliant with medications prescribed (as per family), but states taken twice a day for one week. Family reports memory impairment has worsened with each episode. Investigator considers that the symptoms are compatible with a cerebrovascular event, although diagnosis remains uncertain. Subject is pursuing evaluation at another Neurological Center.
7439	07/26/2005	05/01/2005	Subject was found to be unable to speak or answer questions appropriately by spouse. Transported to ER and observed for eight hours with no diagnostic testing or treatment. During that time, symptoms resolved and was discharged home.

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 Date	Event Description
7383	07/07/2005	06/29/2005	Subject experienced increased post-operative subcortical myoclonus, considered by Investigator to be possibly related to the gene transfer vector, but probably associated with the neurosurgical procedure in the setting of the subject's baseline seizure disorder. The increased myoclonus is considered a "medically significant event" because the event required an extended period of continuous EEG monitoring and an extended ICU admission.
7410	07/22/2005	06/29/2005	Follow up Investigator: Correction amendment to report, should state "the electric signaling does not correlate any seizure activity with the myoclonic jerks."
7626	09/02/2005	06/29/2005	Follow up Investigator: Reconfirmation of the prior correction amendment to report that "the electric signaling does not correlate any seizure activity with the myoclonic jerks."
7435	07/25/2005	07/11/2005	Subject was re-admitted and initiated 24 hour continuous EEG video monitoring, as per the protocol. Parents reported that the subject's increased post-operative subcortical myoclonus had resolved over the weekend, with the myoclonus returning to its pre-operative baseline level. The subject experienced what was described by the pediatric neurology attending as a generalized seizure, of clonic sub-classification type, which lasted approximately 20 seconds and resolved without intervention. No further seizure activity was reported for the remainder of the morning and the subject was discharged to home.
7436	07/25/2005	07/18/2005	Subject's parent reported that subject had experienced six generalized tonic-clonic seizures the previous day, with one additional seizure that morning, all lasting approximately 40 seconds each and all resolved without intervention. Parents were instructed to contact their home pediatric neurologist, who advised them to increase the subject's evening seizure medications. The parents report no further seizure activity since this change in the subjects medication dosage.

Protocol Number: **633**

Protocol Title: **Phase I Trial of Immunotherapy with BHT-3009 Alone or Combined with Atorvastatin in Patients with Multiple Sclerosis.**

DocID#	Receipt Date	Event Date	Event Description
7569	06/17/2005	01/11/2005	Subject had recently become severely depressed, was having severe pain from a migraine headache, admitted to a mental health center. Per Sponsor, it is not possible to exclude a causal relationship with the study treatment because the event has developed during the study and the event is more severe than previous episodes of depression, which did not require hospitalization. Atorvastatin labeling includes depression as a possible side effect and depression is not known to be associated with the study agent.

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 Date	Event Description
7209	05/02/2005	04/13/2005	Subject was hospitalized for worsening abdominal pain which did not respond to increasing doses of continuous narcotic analgesia administered via PCA. The subject was not eating or drinking at the time of admission. A CT scan demonstrated an increase in size and number of hepatic lesions, biliary obstruction, and increased pancreatic mass size with encasement of the celiac, hepatic and splenic arteries. The subject was enrolled in hospice care.
7258	05/26/2005	03/09/2005	Approximately 8 days post study agent vaccine, and 5 days post GM-CSF, subject presented in clinic complaining of persistent nausea and vomiting that was unresponsive to anti-nausea medication. Subject complained of abdominal pain and was admitted for intravenous fluids/hydration and pain control measures. Underwent a celiac axis block. Appetite returned and subject's nausea, vomiting and abdominal pain resolved. A CT scan showed peri-pancreatic inflammatory changes as well as liver, spleen and retro-peritoneal metastasis. Discharged stable and improved. The investigator considered the nausea and vomiting as being possibly related to study drug administration, as well as the concomitant medications MSIR and Duragesic. The abdominal pain and disease progression were not considered related to study drug administration.