Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
December 2006

Protocol Number: **4**

Protocol Title: **Autologous Bone Marrow Transplant for Children with Acute Myelogenous Leukemia in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.**

DocID#	Receipt Date	Event Description
8761	09/14/2006	More than ten years after gene transfer, subject was diagnosed with moderate to severe avascular necrosis (death of bone tissue)(AVN) in the hips and shoulders and underwent bone grafting of hips and a shoulder replacement. AVN is an expected post transplant complication; however AVN is typically found to be more common in patients who received radiation treatment and long term, high dose steroids. Subject did not receive radiation treatment for leukemia and received only rare, intermittent steroids. Per the principal investigator, this event of severe AVN requiring multiple surgeries and persistent disability is unexpected in the context of the autologous transplant and gene marking and the relationship to the gene product can only be considered unknown at this time.
8811	10/25/2006	Subject was diagnosed with acute myelogenous leukemia 15 years ago and underwent a bone marrow transplant with gene transfer for marking of cells. Subject relapsed within a year and underwent another bone marrow transplant with gene transfer for marking purposes. Both gene transfers used retroviral vectors. Subject was diagnosed with thyroid nodule in long-term follow-up but it was determined to be benign. The adverse event initially reported as possibly related until the biopsy results confirmed benign process. Thyroid adenomas are a known side effect of the transplant conditioning regimens that subject received in the past.

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
8677	07/31/2006	On the day of gene transfer, subject was admitted to the hospital for fever and chills. The chills stopped after approximately 20 minutes, however, the temperature remained elevated. Labs were drawn to rule out a possible infection. The event resolved and the participant was discharged from the hospital.
8678	07/31/2006	When subject arrived to receive the fourth injection of the study drug, subject's temperature was found to be elevated. The subject's temperature decreased on the same day, however, a decision was made to hold the dose of study drug. The participant complained of vague left sided flank pain and imaging was obtained and labs drawn. An abdominal computed tomography (CT) scan revealed a loculated subpulmonic left pleural effusion. The liver had a heterogeneous appearance and there was splenomegaly (enlarged spleen) and a small amount of free fluid. There was a slight decrease in the size of the pancreatic mass. The subject underwent a left thoracentesis without significant fluid removal. The subject was referred to the thoracic service for further evaluation. The thoracentesis culture result was negative. The investigator judged the event as possibly related to the study drug, probably unrelated to the administration procedure and possibly related to the underlying disease.
8731	08/31/2006	Approximately one month after receiving the first injection of the study drug, the subject received the fifth and final study drug injection. Five days later, the subject presented to an emergency room with complaints of increased abdominal pain, nausea and vomiting suggestive of a drug induced ileus. Participant was afebrile with stable vital signs. Per the subject, for ten days prior to admission, he/she was unable to take significant amounts of food and experienced decreased bowel movements. On the day prior to the admission, the subject developed bilious green colored vomit and severe abdominal pain with oral intake. Upon physical exam the subject's abdomen was diffusely tender with hypoactive bowel sounds. The abdominal x-ray series showed no free air, normal cardiopulmonary silhouette, a non-specific bowel gas pattern and air in the small bowel. The participant was admitted for further evaluation. During the hospitalization, the subject was treated with antiemetic, pain medications, and laxatives. Total parental nutrition was also suggested. The PI initially judged the event as possibly related to study drug, unrelated to the administration procedure and possibly related to the underlying disease but after more information was obtained the PI now considers this event to be unrelated to the study drug and probably related to the chemotherapy and radiation treatments.
8713	08/15/2006	Subject was hospitalized due to diarrhea after the third injection of study drug. Intravenous fluids were administered. This event resolved and the subject received a fourth dose of study drug. The PI deemed this event, as possibly related to study drug, probably unrelated to the administration procedure, and possibly related to underlying disease. The sponsor noted that in analyzing similar serious adverse events, no reports of diarrhea have been submitted for this study.
8765	09/21/2006	Subject underwent a CAT scan of the chest and abdomen as part of the study protocol (one month after completing the five doses of the study agent) and was found to have a thrombus (blood clot) in the aortic arch. This finding was not present on a CAT scan obtained prior to start of the study treatment. The subject was admitted for anticoagulation therapy. The principal investigator judged the event as possibly related to the study drug and possibly related to the underlying disease.

Protocol Number: **568**

Protocol Title: **A Phase II Multi-Center, Double-Blind, Placebo-Controlled, Trial of VLTS-589 in Subjects with Intermittent Claudication Secondary to Peripheral Arterial Disease.**

DocID#	Receipt Date	Event Description
8753	09/07/2006	Subject was diagnosed with lung cancer during long term follow-up.
8754	09/07/2006	Subject admitted for surgery for lung cancer during long-term follow-up. Subject's primary care physician assessed the lung cancer as not related to the study drug and related to subject's smoking history. The principal investigator assessed the lung cancer as possibly related to the study drug.

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
8716	08/18/2006	Subject expired about two months after gene transfer. No further information is available at this time.

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
8673	07/26/2006	About six months after gene transfer, subject experienced an increase in clusters of brief seizures while attempting to fall asleep. The subjects seizure medications were adjusted. Subject had a decrease in seizure activity with adjustment of medications but seizures resumed. In the six months after the increase in seizures, subject had experienced several seizures that lasted "hours." A decision has been made to have subject treated at home for recurrent seizures.

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
8813	10/26/2006	Subject had a screening chest x-ray performed upon entry into the study that was read as normal. The Study Week 52 chest x-ray performed revealed multiple small pulmonary nodules and a left supraclavicular mass suspicious for malignancy. A repeat review of the screening chest x-ray revealed one of the nodules may have been present on the screening chest x-ray but it was much smaller. A biopsy of lung revealed non-small cell carcinoma.

Protocol Number: **665**

Protocol Title: **A Phase II study of the Efficacy, Safety and Immunogenicity of ONCOVEX GM-CSF in Patients with Inoperable Malignant Melanoma.**

DocID#	Receipt Date	Event Description
8736	09/05/2006	Approximately ten days after receiving an injection of the study agent, the subject was admitted to the hospital with complaints of shortness of breath and pain in the arm and chest. The subject's pulse oximeter indicated hypoxemia (low oxygen level in the blood). A ventilation-perfusion scan did not reveal a pulmonary embolism. Laboratory tests for myocardial infarction were also negative. A chest CAT scan showed numerous bilateral nodules that were consistent with metastasis. There were also signs of interstitial disease that could be edema or infection. An consultation was obtained from the infectious disease service but no infectious agent was identified. A lung biopsy showed extensive progression of melanoma. The subject's respiratory status declined and subject required intubation. Subject did not improve and could not be weaned from the respirator. The decision was made to provide comfort care.
8771	09/28/2006	Subject expired after being hospitalized with shortness of breath and hypoxemia (low oxygen level). The cause of death was respiratory failure as a result of progression of pulmonary metastasis. The possibility that the study drug contributed to the progression the disease could not be ruled out.

Protocol Number: **683**

Protocol Title: **A Staged Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1, Followed by Radiation Therapy.**

DocID#	Receipt Date	Event Description
8696	08/07/2006	The day after the study agent was injected into the brain, the subject experienced a seizure. Subject has a history of prior seizures. The subject experienced some mild hemiparesis (partial paralysis) and developed a fever. The fever resolved and the subject was discharged from the hospital without sequelae. The principal investigator assessed the seizure as possibly related to the investigational agent and the fever as probably related to the investigational agent.
8693	08/07/2006	Four months after intratumoral gene transfer, the subject experienced a seizure with increased left-sided paresthesias, gait difficulties and dysphasia (impairment of speech). The subject's anti-convulsant dose was increased and subject was referred to physical and speech therapy. The subject's symptoms improved and subject was discharged from the hospital.

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
8786	10/06/2006	Approximately one month after receiving the study agent, the subject was admitted to the hospital with a complaint of weakness, nausea and vomiting. In addition, subject reported decreased urination for a few days prior to hospital admission. Laboratory tests revealed that the subject was anemic and in renal failure. An ultrasound was ordered to rule out obstructive uropathy. The ultrasound showed normal kidneys. The subject also received a blood transfusion for anemia. The investigator judged the event as possibly related to the study drug/biologic, unrelated to the administration procedure and probably related to the underlying disease.