

**Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Committee Meeting
September 2008**

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II/III 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
9678	04/24/2008	Subject died unexpectedly approximately three weeks after the last dose of the study agent. No further details available. A possible relationship to the gene transfer can not be ruled out.
9687	04/28/2008	Four days after administration of the first dose, the subject developed increased levels of bilirubin, a substance cleared by the liver, and became jaundiced. The subject required a tube in the bile duct to help clear this product.
9686	04/28/2008	The subject was found to have an abnormal blood test related to the time it takes blood to clot, partial thromboplastin time. The subject had no associated symptoms. It is unclear whether this abnormal blood test was caused or worsened by the study treatment or is related to the underlying disease as subject had some evidence of abnormal coagulation laboratory values prior to enrolling in the study.
9692	05/02/2008	The subject was diagnosed with a lung clot four months after the last dose of TNFerade was received. The subject was asymptomatic and the clot was detected on a computed tomography scan done for the protocol. The investigator concluded it was possibly related to the TNFerade and probably related to the underlying disease.
9755	05/28/2008	The subject was diagnosed with a blockage at the narrow part of the stomach where it joins the small intestine, likely due to radiation. The event occurred nine months after the last dose of TNFerade.
9756	05/28/2008	Just over one month after the last dose of the gene transfer, a blood clot in the splenic vein was seen on a computed tomography scan.
9786	06/18/2008	The subject experienced bleeding from the gastrointestinal tract almost two months after receiving the last dose of TNFerade. A computed tomography scan revealed that dead tissue from the pancreatic mass had eroded into the stomach and that this may have been the cause of the bleeding. The bleeding stopped the day after subject was hospitalized.
9844	07/18/2008	The subject was admitted for dehydration and abnormal kidney function three days after the last dose of TNFerade. The subject also reported diarrhea that was felt to be secondary to the chemotherapy. Results of diagnostic testing were pending at the time of the report.
9809	07/08/2008	About one week after the fifth dose of the gene transfer by endoscopic ultrasound, the subject was brought to an emergency room due to severe abdominal pain and confusion. A computed tomography scan revealed findings consistent with sudden inflammation of the pancreas as well as partial dead tissue in the pancreas. It was also noted that there were inflammatory changes and a collection of fluid in the upper abdomen. Previous fluid collections lateral to the tail of the pancreas demonstrated changes that were concerning for a localized collection of pus.

Protocol Number: **632**

Protocol Title: **pVGI.1 (VEGF-2) Gene Transfer for Diabetic Neuropathy.**

DocID#	Receipt Date	Event Description
9743	05/29/2007	The subject was admitted with severe pain in both legs with walking. A blood vessel scan showed decreased flow so a stent was placed in the right leg. Subject recovered.
9745	05/29/2007	The subject was admitted to the hospital for an elective procedure to examine the blood vessels of the heart following an abnormal electrocardiogram. Subject had a stent placed to open an artery.
9746	05/29/2007	A year after the study agent was given, the subject was electively admitted to the hospital for a minimally invasive procedure to open the blood vessels going to the heart and to place a stent in an artery in the neck.

Protocol Number: **649**

Protocol Title: **A Phase II Study of Active Immunotherapy with PANVAC™ or Autologous Cultured Dendritic Cells Infected with PANVAC™ After Complete Resection of Hepatic Metastasis of Colorectal Carcinoma.**

DocID#	Receipt Date	Event Description
9777	03/06/2007	After the second dose of the gene transfer vaccine the subject experienced a fever of 104 degrees fahrenheit, which was considered a dose-limiting toxicity.

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
9682	04/25/2008	The subject was admitted for severe pelvic pain that was considered possibly related to the study agent or progression of disease. Subject also experienced a gastrointestinal bleed that was not felt to be related 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)-1 α /VP16 in Patients with Intermittent Claudication.**

DocID#	Receipt Date	Event Description
9716	05/09/2008	The subject, who is a former smoker with a 70 pack year smoking history, developed lung cancer approximately 8 months after receiving the study agent.
9717	05/09/2008	Approximately 9 months after administration of the study agent, the subject was admitted to the hospital with shortness of breath and diagnosed with pneumonia. The subject had been recently diagnosed with a lung mass, that on a biopsy performed during the hospitalization, was determined to be lung cancer. The subject had a significant smoking history.

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
e-Filed	07/23/2008	The subject was admitted for confusion and possible hallucinations 15 days after direct administration of the study agent into the brain. The altered mental status may have been due to a low blood sodium level or to steroid therapy. The subject was admitted for treatment of the low sodium level, elevations in blood sugar and for observation after being taken off the steroids. The subject recovered and was discharged.
9840	07/16/2008	Subject admitted for a second time due to confusion and agitation approximately three weeks after the administration of the gene transfer agent. Subject was also diagnosed with a urinary tract infection. Subject noted to have a remote history of psychiatric illness. Subject was treated with antipsychotics and antibiotics and was discharged after responding to the medications. However, the subject refused to continue the radiation treatments that were to follow the gene transfer.
e-Filed	08/15/2008	The subject was admitted a second time for a change in mental status about three weeks after intratumoral dosing. The subject was treated with antipsychotics and continued treatment for a urinary tract infection. The subject recovered from the acute event but continued to suffer from dementia that was considered worsening of a preexisting condition. A relationship of this event to the study agent could not be ruled out.

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
9708	05/07/2008	<p>Following the first dose of the study agent, the subject developed redness and localized firmness on the upper thighs consistent with an injection site reaction. Eight days later, the reaction had spread and progressed into the development of blisters on both thighs, described as "water-filled" lesions, approximately 2-3 inches away from the injection sites. The subject developed bilateral lower extremity swelling, worse in the left leg. The subject's upper thighs were described as "very swollen" and "very red and inflamed" with pitting edema noted in the left ankle and calf. The subject was admitted to the hospital. The white blood cell count was elevated but blood and wound cultures did not show any evidence of infection. A Doppler ultrasound of the legs was performed and showed no evidence of clots. The subject was treated with antibiotics and local skin care.</p> <p>Approximately 10 days after the first admission, the subject returned to clinic for a second administration into the upper extremities. The subject was doing well one day following these injections but on day two, developed blisters on both arms coinciding with a fever. Subject was subsequently admitted to the hospital on the same day with redness, swelling and blisters on both arms at the injection sites.</p> <p>Subject's symptoms resolved and subject received the third dose of the study medication in the legs. Subject developed some redness and blisters on one leg. The subject developed a fever and was hospitalized and given intravenous antibiotics.</p> <p>The sponsor of the study noted that both fever and injection site reactions have been seen with this product.</p>
9707	05/07/2008	<p>The subject was admitted to the hospital with mental status changes. The subject had received a total of six doses of study agent. The last one was about 2 weeks prior to this hospitalization. The subject was treated for viral encephalitis but did not improve. The diagnosis was leukoencephalitis of unclear etiology. Initially, the etiology of this event was unknown and therefore a relationship to the gene transfer could not be ruled out. Subject passed away during this hospitalization. An autopsy revealed metastatic melanoma to the brain. The primary melanoma lesion was not determined. The melanoma was not considered related to the gene transfer and, therefore, the event was not considered related to the study.</p>

Protocol Number: 741

Protocol Title: **A Phase 2 Double-Blind, Placebo Controlled, Multi-center Adjuvant Trial of the Efficacy, Immunogenicity, and Safety of GI-4000; an Inactivated Recombinant Saccharomyces cerevisiae Expressing Mutant Ras Protein Combined with a Gemcitabine Regimen Versus a Gemcitabine Regimen with Placebo, in Patients with Post-resection R0/R1 Pancreatic Cancer with Tumor Sequence Confirmation of Ras Mutations.**

DocID#	Receipt Date	Event Description
9858	07/25/2008	<p>On Day 327 of the study, the subject experienced worsening low blood sodium level associated with weakness and abdominal pain. The subject was hospitalized and a computed tomography scan revealed intestinal narrowing. During the surgery to relieve the stricture, it was discovered that the subject had a partial intestinal obstruction along with extensive cancer of the abdomen secondary to advancing disease. Due to progression of the subject's disease, study therapy was discontinued. The low sodium resolved after the surgery and placement of a feeding tube.</p>

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
9791	06/18/2008	The subject was admitted for vomiting and dizziness after receiving 13 doses of the study agent over two months. Sunitinib was discontinued with resolution of the symptoms. The principal investigator could not rule out a contribution from the gene transfer.
9837	07/14/2008	The subject was admitted to the hospital with a fractured hip. The subject had known metastatic disease to the hip.
9814	06/30/2008	During a planned computed tomography scan for week 26, a lung clot was identified. The subject was asymptomatic and was started on blood thinners.
9825	07/03/2008	After receiving the study agent at set intervals for 7 months, subject experienced severe pain and decreased sensation in the right leg. The subject was admitted for suspected spinal cord compression.
9872	08/06/2008	The subject was admitted with acute anemia that was thought to be related to the spread of the kidney cancer.

Protocol Number: 792

Protocol Title: **A Phase I, Dose-Escalation, Single Center Study to Assess the Safety and Tolerability of VM202 in Subjects with Critical Limb Ischemia**

DocID#	Receipt Date	Event Description
9710	05/07/2008	One year after dosing, this elderly subject, with a history of tobacco use and chronic obstructive pulmonary disease, developed lung cancer with metastases to the liver. This is the first case of cancer on this trial. Although preclinical data do not support a role for the gene transfer, a possible role of the gene transfer can not be definitively ruled out.

Protocol Number: 853

Protocol Title: **A Phase 1, Open-Label, Dose-Escalation, Multiple Dose Study of the Safety, Tolerability, and Immune Response of CRS-207 in Adult Subjects with Selected Solid Tumors Who Have Failed or Who Are Not Candidates for Standard Treatment**

DocID#	Receipt Date	Event Description
9899	08/26/2008	Subject experienced fever and low blood pressure during infusion necessitating support with intravenous fluids and observation in the intensive care unit the night following infusion.