
**Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
June 2013**

Protocol Number: 591

Protocol Title: **An Open-Label Safety Study of Escalating Doses of SGT-53 for Systemic Injection in Patients with Advanced Solid Tumor Malignancies.**

DocID#	Receipt Date	Event Description
11709	03/21/2013	Subject had received two doses of the study agent and started chemotherapy and was admitted for syncope and slow heart rate. Subject had a history of atrial fibrillation that was chronic. Due to the slow heart rate the subject was given a pacemaker. Subject also developed neutropenia that was likely due to the chemotherapy. Subject recovered.

Protocol Number: 702

Protocol Title: **A Phase I Study Open-Label Safety Study of Escalating Doses of SGT-RB94 Alone, and in Combination with Gemcitabine for Injection in Patients with Advanced Solid Tumor Malignancies.**

DocID#	Receipt Date	Event Description
11766	05/01/2013	Subject developed an extremely low blood pressure about eight hours after receiving the gene transfer agent. Subject was transferred to the intensive care unit and recovered with intravenous fluids and a transfusion of red blood cells.

Protocol Number: 940

Protocol Title: **Assessment of the Safety and Feasibility of Administering T cells Expressing an anti-CD19 Chimeric Antigen Receptor to Patients with B cell Lymphoma**

DocID#	Receipt Date	Event Description
11771	05/06/2013	Approximately five days after infusion of gene transfer agent, subject developed expressive aphasia (difficulty speaking). A CAT scan of the brain did not show signs of a stroke or bleed. Neurology consult and a brain magnetic resonance imaging (MRI) was ordered. Subject was transferred to MRI and reportedly had a "seizure-like" episode and was intubated for airway protection. Once stabilized, the brain MRI was completed and was negative for a stroke. An electroencephalogram was completed and subject developed myoclonus (involuntary muscle movements). Intravenous anti-seizure medication started. Sedation was lightened with fewer myoclonic movements. He was arousable and able to track with his eyes, but unable to follow commands. Subject was extubated and remained in intensive care unit (ICU) for observation. His anti-seizure medication was weaned and it was noted that his mental status improved as his white blood cell count recovered from chemotherapy and he completed his course of antibiotics (raising the possibility that infection may have contributed). At one month follow-up after this event, subject had largely recovered but did have some residual gait problems, a tremor and some hyperreflexia. This event is being reported due to the life-threatening event possibly related to gene modified T cells.

Protocol Number: 952

Protocol Title: **Phase Ib Study of Autologous Ad-ISF35-Transduced CLL B Cells and Fludarabine, Cyclophosphamide, and Rituximab (FCR) in Subjects with Fludarabine-Refractory and/or del(17p) Chronic Lymphocytic Leukemia (CLL)**

DocID#	Receipt Date	Event Description
11763	02/13/2013	Subject developed a fever after the second dose of the gene transfer agent and was hospitalized because of neutropenia (low white blood cell count).

Protocol Number: 977

Protocol Title: Direct CNS Administration of a Replication Deficient Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis

DocID#	Receipt Date	Event Description
11718	03/27/2013	Update provided on subject's most recent MRI, in which changes seen at six months are also present on the month 12 MRI, with some increase in the intensity of the lesions. No clinical correlation between the imaging and behavior seen. For background on these events, see the March 2012 meeting of the RAC. http://osp.od.nih.gov/sites/default/files/RAC_Minutes_03-12.pdf
11778	05/15/2013	Thirteen days after the intracranial administration of the gene transfer agent, the subject was noted to have a seizure during the electroencephalogram. The seizure was more severe than the subject's usual seizures. An MRI done showed subdural fluid collections, which were likely secondary to the surgical procedure. The sponsor also reported that there was a deviation during the surgical procedure for this subject, in which there was an unexpected catheter leak and less vector administered.

Protocol Number: 1037

Protocol Title: Phase I/II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of Tumor Infiltrating Lymphocytes Genetically Engineered to Express IL-12

DocID#	Receipt Date	Event Description
11775	05/10/2013	Approximately one week after the first dose of study agent, subject was found to have an elevated serum liver enzyme test (an AST up to 1000). This event is being reported as possibly related to the gene modified T-cells. Subject was discharged home and local oncologist repeated the blood work. The serum liver enzyme tests returned to baseline and subject is continuing to respond to treatment.

Protocol Number: 1060

Protocol Title: "A Phase I/II, Open Label Study of A d-RTS-hIL-12, an Adenovirus Vector Engineered to Express hIL-12, in Combination with an Oral Activator Ligand, in Subjects with Unresectable Stage III or IV Melanoma."

Extension Study: An Open-Label Extension Study of Ad-RTS-hIL-12, an Adenovirus Vector Engineered to Express hIL-12, in Combination with an Oral Activator Ligand, in Subjects Who Completed Protocol ATI001-101 with Evidence of Ongoing Clinical Benefit" (ATI001-101-EXT)

DocID#	Receipt Date	Event Description
11702	03/11/2013	This elderly subject (> 85 years old) had an acute change in mental status one day after dosing with the gene transfer agent. At home, subject had fever, lethargy and confusion. Subject was brought to the emergency room and found to have fever, acute renal failure (possibly due to dehydration) and hypercapnic respiratory failure (increased CO2) of unclear etiology. Subject received BiPAP for the respiratory failure, steroids, intravenous fluids and antibiotics. Subject recovered and kidney function improved.
11731	04/10/2013	About a week after the first dose of the gene transfer agent and the activator drug, the subject developed fevers, chills, a rash and confusion. Subject was admitted and noted to have elevated blood liver enzyme tests and bilirubin, low white blood cell count and decreased platelets. The symptoms were assessed as being related to cytokine release due to the gene transfer agent. Subject recovered.

Protocol Number: 1108

Protocol Title: A Phase 2b Randomized Open-Label Trial of JX-594 (vaccinia GM-CSF/TK-deactivated virus) Plus Best Supportive Care Versus Best Supportive Care In Patients With Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment (TRAVERSE)

DocID#	Receipt Date	Event Description
11743	04/23/2013	Subject experienced severe hypotension with an initial low blood pressure (BP) reading of approximately 80/60 mm/Hg about one hour after treatment (versus BP 100/70 immediately after completion of intratumoral (IT) injection), and a nadir blood pressure of approximately 70/50 about six hours after completion of IT treatment. Subject also developed fevers up to 39° C. Subject recovered with intravenous fluids and midodrine.

Protocol Number: 1129

Protocol Title: A Phase 1 Open-Label, Ascending-Dose trial of AskBio009 in Patients with Severe Hemophilia B

DocID#	Receipt Date	Event Description
11770	05/06/2013	Subject developed elevated liver enzyme blood levels about a month after the administration of the vector. Of note, also developed extremely high creatine kinase (CK) (>15,000) but had recently engaged in strenuous physical activity. Subject admitted to the hospital and provided intravenous fluids and recovered. Blood CK and liver enzyme levels trended back towards normal. There was no evidence of T cells directed against the capsid or transgene. The relationship of the elevated CK to the gene transfer agent is unclear but a relationship cannot be definitively ruled out.