SERIOUS, POSSIBLY ASSOCIATED AND UNEXPECTED ADVERSE EVENTS
REPORTED FOR HUMAN GENE TRANSFER PROTOCOLS
REPORTING PERIOD: 02/01/02 -- 05/01/02
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
June 2002

Event #	OBA Date	Event Date	Protocol #	Event Description
			9902-288	**Phase I Pilot Trial of Adenovirus p53 and Radiotherapy on Non-Small Cell Lung Cancer. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
4101	02/05/2002	03/28/2001		F/U (to 4086): Cytology and culture reports provided for pleural fluid . No growth on cultures and no malignant cells seen in pleural fluid. Etiology of pleural effusion still unclear but possible relationship with gene transfer product cannot be ruled out.
4126	02/13/2002	03/28/2001		Follow-up from sponsor. Confirms information in reports 4086 and 4101.
			9906-322	**A Phase I Study of NGF *Ex Vivo* Gene Therapy for Alzheimer's Disease**
4195	03/11/2002	03/07/2002		Subject sustained 3 cm right cortical hemorrhage during surgical procedure to implant gene transfer product. Both a superficial vessel on the surface of the cortex and underlying cortex involved. Approximately 100-150 cc of blood aspirated and 1.5 hours needed to control bleed. CT scan 1 hour after bleeding controlled showed 3 cm hemorrhage approximately 2 cm below site of the cortical bleeding site.
4259	04/15/2002	03/07/2002		F/U(to 4195 and 4258) from PI : Subject had cardiac evaluation one week pre-operatively and was cleared for surgery. Initial hemorrhage (see report 4195) was controlled after approx. 15 minutes. Subject then had bleeding from an intracortical source that required another hour to control. Etiology of second bleed unclear; may have been related to attempt to control superficial hemorrhage (e.g., cautery of cortex) or another event such as venous congestion through site of needle passage and superficial bleeding. The cardiac arrest (see report 4258) was determined by the PI to be due to prolonged hospitalization following the surgical procedure over a month prior.
4290	05/10/2002	03/07/2002		F/U (to 4195) from PI: Subject had prolonged period of hospitalization, immobility and developed medical complications secondary to this including MI, cardiac arrest and death. Not related to gene transfer agent. Hemorrhage and subsequent death resulted from surgical procedure. PI made 5 changes to protocol so as to avoid future problems of this nature (see amendments table for details).
4258	04/15/2002	04/10/2002		F/U to 4195: Subject abruptly and unexpectedly developed v-tach during repositioning of endotracheal tube. Full cardiac arrest and death.

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			9907-327	**A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation**
4216	03/27/2002	03/15/2002		Subject complained of acute intermittent pain bottom of right foot which continues on a daily basis. Treated with hydrocodone for pain as needed. The investigator deemed this possibly related to the study agent.
			9912-366	**A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety off Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)**
4127	10/20/2000	10/11/2000		One week after receiving gene transfer product, subject admitted with fever of 104.7 and with chills. Subject also complained of some difficulty breathing. Event possibly related to study agent but suspected to be more likely due to an infected portacath.

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			0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**
4256	04/17/2002	04/03/2002		Subject admitted with redness and swelling left foot, considered worsening peripheral artery disease. Treated with IV antibiotics and bed rest. AE started 7 days after study drug administration. PI and sponsor disagree in regard to causality. PI believes that due to progression of PAD and not study drug. Sponsor does not rule out study drug as cause.
4280	05/02/2002	05/01/2002		Subject admitted for renal insufficiency and ascites of unknown etiology. Presented with severe epigastric pain and ascites. Six liters of fluid drained during paracentesis. Elevated BUN/Creatinine/Potassium on admission. Subject with no history of renal problems and at this time causality of ascites and renal insufficiency is deemed as unknown but possibly related to gene transfer product.
4283	05/07/2002	05/01/2002		F/U (to 4280) telephone contact with study coordinator at site: Subject in ICU due to vasopressor requirements for hypotension. Respiratory status fine. Blood, urine and ascitic fluid cultures all negative. Cardiac echo: LV function is lower limits of nl. Small pericardial effusion noted. Cardio consult to r/o clot. Subject treated with Heparin. Renal status: BUN and creatinine back to normal, renal problems resolved per nephrologists. Possible cause of renal problems is use of NSAIDs. Further work-up pending. Cytology report of ascitic fluid showed presence of adenocarcinoma. In regard to finding source, CA-125 and CEA negative. Colonoscopy did not reveal source. Upper GI showed adhesions believed to be due to intra-abdominal carcinomatosis. Source of adenocarcinoma not yet identified. Of note, subject underwent age-appropriate cancer screening recommended by American Cancer Society with negative results.
4291	05/10/2002	05/01/2002		F/U (to 4280 and 4283) from PI: Ascites fluid positive for adenocarcinoma. Primary site still uncertain, ovarian is suspected. 5/4/02, subject developed tachycardia, hypotension. Transferred to ICU. Tx'd with Dopamine. Echo: severe global left ventricular dysfunction with 20-25% ejection fraction (EF) and possible thrombus left ventricle. This compares to 5/3/02 Echo: 50-55% EF. Viral workup in progress due to cardiac deterioration, but Coxsackie, EBV, CMV and Mycoplasma serologies all pointing away from acute infection. 5/5/02 subject demonstrated mild confusion, numbness left leg. Brain MRI showed acute left-sided (PCA distribution) stroke. Subject remains alert, oriented.

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			0005-399	**An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFerade™ Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors. Sponsor: GenVec**
4119	02/11/2002	02/04/2002		Subject presented for WK2 Day1 visit with previous injection site red, hot and indurated and complained of pain. No fever. WBC normal. Admitted on suspicion of cellulitis of the left groin. Treated with IV Vancomycin and Ceftriaxone. Study drug interrupted. Radiation postponed.
4264	04/19/2002	02/04/2002		F/U (to 4119) from the Sponsor. The subject recovered from the cellulitis without sequelae and completed four treatments without complications.
4263	04/15/2002	03/27/2002		An elderly subject experienced altered mental status while an inpatient, was diagnosed with acute delirium and the study agent was discontinued and radiation therapy was not begun. The event was deemed possibly related to the study agent, the underlying disease, and the subject's advanced age.
4249	04/10/2002	04/02/2002		A subject with a history of rectal cancer, who had finished radiation therapy and the administration of gene transfer about 25 days prior, was admitted for severe dehydration, fever, and chills. Results of the workup for this admission were pending at the time of report submission.
			0006-403	**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. Sponsor: Berlex Laboratories**
4074	01/23/2002	01/10/2002		Subject admitted with increasing frequency of anginal chest pain 5 months after study injection. Angiography done, found 95% lesion in proximal left anterior descending coronary artery and a stent was placed. Lesion reduced to 0%. No further chest pain noted.
4134	02/15/2002	01/10/2002		This is another report of event 4074 submitted from another site in this multi-site trial.
4158	02/21/2002	01/14/2002		F/U (to 4074) from Sponsor: Medical Monitor narrative states that the contribution of the gene transfer product to the subject's new stenosis is difficult to assess. The Sponsor believes that progression of disease could be expected in view of the subject's extensive underlying atherosclerotic disease and newly diagnosed diabetes.

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			0007-407	**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. Sponsor: Genzyme Corporation**
4244	04/05/2002	03/08/2002		Subject experienced ventricular tachycardia and an ICD pacemaker was implanted.
4245	04/05/2002	03/15/2002		Subject's ICD pacemaker recorded a single 500 joule shock for sustained ventricular tachycardia, however the subject was asymptomatic and unaware of this event. The Principal Investigator deemed the event possibly related to the blinded study agent.
			0104-462	**A Phase I Trial of Genetically Modified Salmonella typhimurium Expressing Cytosine Deaminase (TAPET-CD, VNP20029) Administered by Intra-Tumoral Injection in Combination with 5-fluorocytosine for Patients with Advanced or Metastatic Cancer. Sponsor: Vion**
4246	04/09/2002	04/02/2002		An elderly subject was admitted with complaints of weakness, nausea, indigestion, elbow pain, and chest symptoms 6 days after the third dose of study agent. An extensive cardiac workup showed no evidence of significant coronary artery disease or heart damage. Chest symptoms resolved. The PI felt that the TAPET-CD and/or 5-FC were possibly related to the chest pain as chest pain and EKG changes can be seen with 5-FU and 5-FC administration.

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			0105-472	**Phase I/II Study of Vaccination with Irradiated Autologous Lung Tumor Cells Mixed with a GM-CSF Secreting Bystander Cell Line (Lung Bystander GVAX®) in Advanced Non-Small Cell Lung Cancer. Sponsor: Cell Genesys, Inc.**
4110	02/06/2002	01/30/2002		Subject admitted with severe back pain which began three days earlier after a coughing spell. Bone scan showed increase uptake in the left parietal-temporal area of the skull and the mid to lower thoracic spine (T9-T10). The T9 lesion was more prominent on a bone scan. Spinal MRI showed loss of signal intensity in the body of T9 and reduced height of the vertebral body consistent with a compression fracture. Treated with opioid analgesics.
4170	02/27/2002	02/19/2002		Same subject as in event 4110. Subject hospitalized because of increased dyspnea and cyanosis. Chest X-Ray showed bilateral lung infiltrates and CT scan showed consolidation of the entire left lung. Status Post radiation therapy (completed 2 days prior) for spinal mets described in event 4110.
4171	02/27/2002	02/19/2002		Same subject as in events 4110 and 4170. Expired due to respiratory failure. Possibly related to study treatment; only 2 weeks separated start of vaccinations and onset of AE described in event 4110.
4206	03/22/2002	03/05/2002		Subject admitted with 3 week history of increasing shortness of breath. Occurred 2 weeks after completing last vaccination. CXR revealed complete opacification of right lung with pleural effusion or tumor mass increased in severity vs. CXR of 3/4/02. No left sided disease. Therapeutic thoracentesis: 2.5 L exudative pleural fluid from right lung with improvement in dyspnea. Deemed possibly related to study

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			0107-481	**An Open-Label, Phase Ib/II Study of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally to Subjects with Recurrent Malignant Glioma. Sponsor: MediGene, Inc.**
4124	02/12/2002	01/20/2002		F/U (to 4081) from PI: Subject seen in follow-up on 1/30/02. Has not fully regained function present before ictal event, which occurred 72 hrs post-op. Remains w/o fevers, headaches, eye sensitivity, nuchal rigidity or mental status changes. Subject with history of seizures due to tumor, but in the past has had much quicker return to baseline after seizures. Due to persistence of difficulties, PI calling this AE "possibly related" to gene transfer product.
4151	02/19/2002	01/20/2002		F/U (to 4124) from PI: Subject seen in follow-up on 1/30/02. Has not fully regained pre-study function. Event deemed by PI to be possibly related to study agent due to unusual length of the persistence of symptoms of this event compared to subject's past medical history.
4278	04/30/2002	04/27/2002		Two days after gene transfer agent injected intracranially into tumor bed, subject had deterioration in mental status, left hemiparesis, neglect, elevated temperature reaching max of 39.7 °C. MRI scan benign. EEG: no seizure activity. Labs wnl. LP results showed PCR positive for HSV. G207 testing pending. Deemed by PI to be probably related to gene transfer agent.
4279	05/02/2002	04/27/2002		F/U (to 4278) from PI: Subject transferred to NICU for observation and treated with Decadron. Within 12 hrs, defervesced, neurological status returned to baseline. No antibiotics given. PI considers event resolved. G207 testing pending. PI continues to deem that events are probably related to gene transfer
4286	05/07/2002	04/27/2002		F/U (to 4278 and 4279) from PI: Subject improved rapidly within 12 hrs of admission to ICU on increased amounts of Decadron and was discharged a few days later. PCR testing for *lacZ* gene was positive, indicating that the HSV strain is the gene vector strain (G207). All cultures are negative for HSV growth. Etiology of event is unclear at this time. Subject presently well and due for full clinic evaluation (post-op day 28 visit) in a few weeks.
4292	05/14/2002	04/27/2002		F/U (to 4124 and 4278, and their subsequent follow-up reports) from PI: Error noted under dosing recorded in prior SAE submissions. Subjects received a total of 0.15×10^9 pfu more vector than initially reported.