



# IHGT The Institute for Human Gene Therapy

## Preliminary Findings

### Preliminary Findings Reported on the Death of Jesse Gelsinger

(Philadelphia, December 2, 1999) Preliminary findings from a thorough autopsy and exhaustive laboratory studies to discover the factors that led to the death of gene therapy clinical trial volunteer Jesse Gelsinger on September 17, 1999, were made public today by physician scientists at the University of Pennsylvania's Institute for Human Gene Therapy. The findings suggest that the experimental drug used in the trial -- a modified cold virus, or vector, incorporating a potentially corrective gene for Mr. Gelsinger's genetic disease -- initiated an unusual and deadly immune-system response that led to multiple organ failure and death.

A review of extensive animal studies performed prior to the launch of the clinical trial and the experiences of the previous 17 participants in the trial to treat ornithine transcarbamylase (OTC) deficiency revealed no information that would have predicted the events that led to Mr. Gelsinger's death. There was no evidence for human error in his clinical management.

Overall, Mr. Gelsinger's clinical autopsy and laboratory study results indicate that the most significant factor in his death was oxygen deprivation brought on by Adult Respiratory Distress Syndrome (ARDS) -- a severe lung dysfunction not seen previously in any study animals or clinical-trial volunteers. Immediately following vector infusion there was a diffuse activation of his innate immune system associated with fever. This was followed by an injury to the liver and inappropriate coagulation of blood; both processes began to resolve within 48 hours. His underlying genetic defect made it difficult for him to handle the stress of the immune activation -- resulting in an accumulation of ammonia in the blood, and then coma. Mr. Gelsinger appeared to be improving three days after the vector until the onset of ARDS, which could not be reversed in time leading to his death. Although analysis of the findings is ongoing, it is the belief of the investigators that the injection of the vector triggered the sequence of events that led to Mr. Gelsinger's death.

The trial (which began in April 1997) proceeded over a two-year period without major interruptions until the death of Jesse Gelsinger, the 18th patient to participate in Penn's OTC gene therapy trial. [Mr. Gelsinger is identified in the protocol literature as patient "OTC.019" -- and this tag references his position as the 19th person to be accepted in the trial. Of all 19 enrolled, one patient voluntarily left the protocol before the administration of the drug.]

Given the researchers' understanding (based on their own preclinical animal studies) that liver toxicity may be dose-related, and also given that the protocol was designed to deliver the adenovirus directly into the liver, the trial's principal investigators carefully monitored all patients for liver inflammation and/or injury using liver-function tests and liver biopsies. While there was evidence of liver inflammation in some patients, all such episodes proved transitory in nature (in that the inflammation self-corrected, with the patients' liver-function

tests returning to baseline within two weeks); and little, if any, episodes of liver inflammation were seen in the three patients who immediately preceded Mr. Gelsinger in the study.

The specific lot of vector administered to Mr. Gelsinger has been retested and contract laboratories used to help evaluate its safety have been audited. The dose of vector administered to the patient and the DNA sequence of the corrective gene inserted into the vector were confirmed to be correct. An exhaustive characterization of the remaining sequences in the vector revealed variants -- duplication of an area representing less than 0.4% of its total length. This variation was not unique to the lot administered to Mr. Gelsinger. The researchers' investigation to date has failed to reveal a specific characteristic of the vector lot that could have caused the complications observed in Mr. Gelsinger.

One unexpected finding was a marked abnormality in Mr. Gelsinger's bone marrow -- which, at the time of autopsy, revealed a total absence of precursors responsible for production of red blood cells and an abnormality in the state of maturity of the precursors that produce white blood cells. The relevance of the finding to Mr. Gelsinger's death is unclear, although it may reflect a problem with his bone marrow that predated the gene therapy experiment.

In the context of this unexpected tragedy, the researchers remain committed to fully evaluating all potential leads. Their analysis of the data and attempts to develop animal models that simulate the clinical findings continues with vigor. The FDA's advice and input during the course of the investigation has been useful. The researchers look forward to presenting the data to the Recombinant DNA Advisory Committee on December 9, 1999.

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