DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Center for Biologics Evaluation and Research
Biological Response Modifiers Advisory Committee

SUMMARY MINUTES
Meeting #34, February 28, 2003
Holiday Inn, Silver Spring, Maryland

COMMITTEE MEMBERS
Daniel R. Salomon, M.D., Chair
Jonathan Allan, D.V.M
Bruce R. Blazar, M.D.*
David M. Harlan, M.D.
Katherine A. High, M.D.
Joanne Kurtzberg, M.D.
Alison F. Lawton
Richard C. Mulligan, Ph.D.
Mahendra S. Rao, M.D., Ph.D.
Anastasios A. Tsiatis, Ph.D.
Alice J. Wolfson, Esq.

TEMPORARY VOTING MEMBERS
Barbara Ballard
John Coffin, Ph.D.
Kenneth Cornetta, M.D.
John French, Ph.D.
Warren Leonard,M.D.
Crystal Mackall, M.D.
Abbey S. Meyers
Thomas Murray, Ph.D.
Bruce E. Torbett, Ph.D.
Linda Wolff, Ph.D.

GUEST SPEAKERS
Claudio Bordignon, M.D.
Marina Cavazzana-Calvo, M.D., Ph.D.
Adrian Thrasher, M.D., Ph.D.

FDA PARTICIPANTS
Philip Noguchi, M.D.
Raj Puri, M.D., Ph.D.
Cynthia Rask, Ph.D.
Carolyn Wilson, Ph.D.

NIH REPRESENTATIVES
Amy Patterson, M.D.
Stephen M. Rose, Ph.D.

COMMITTEE MANAGEMENT SPECIALIST
Rosanna L. Harvey

EXECUTIVE SECRETARY
Gail M. Dapolito

*not attending

The summary minutes for the February 28, 2003 meeting of the Biological Response Modifiers Advisory Committee were approved on .

I certify that I attended the February 28, 2003 meeting of the Biological Response Modifiers Advisory Committee and that this report accurately reflects what transpired.

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Gail Dapolito, Executive Secretary

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Daniel R. Salomon, M.D., Chair

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
MEETING #34, February 28, 2003

The Biological Response Modifiers Advisory Committee (BRMAC) met on February 28, 2003 at the Holiday Inn, Silver Spring, MD. In open session, the committee discussed adverse events recently identified related to a retrovirus gene therapy for the treatment of patients with X-linked severe combined immunodeficiency (X-SCID). The committee also discussed safety issues related to retrovirus gene therapies for ADA-SCID and other retrovirus gene transfer trials using hematopoietic stem cells

Daniel Salomon, M.D., Chair, called the meeting to order and introduced the members, consultants, guests and guest speakers. The executive secretary read the conflict of interest statement into the public record. This statement identified members and consultants of the committee with an appearance of a conflict of interest, who were issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided 1) a review of the consensus points from the BRMAC meeting on October 10, 2003 when the committee initially discussed this issue, 2) an update on the FDA actions taken in response to the October 10, 2003 BRMAC meeting and the subsequent notification of another adverse event in the French trial, and 3) a review of recommendations from other federal or international committees who have deliberated on these events.

Guest experts provided presentations to the committee on:

- a retroviral gene transfer trial in France to treat children with X-SCID and the subsequent detection and confirmation of leukemia in two patients related to the therapy
- clinical and preclinical data compiled from ADA-SCID gene transfer trials in Europe, Israel and Japan
- clinical data from an X-SCID retroviral gene transfer trial in England

The Chair then commenced the open public hearing. The committee heard comments from the audience representing

- American Society of Gene Therapy
- Stop ALD Foundation
- Citizens for Responsible Care in Research

The committee also heard data from preclinical and clinical studies at Beth Israel Deaconess, Harvard Medical School on retroviral gene therapy to treat several types of cancer in adults.

Following the open public hearing, the committee engaged in a discussion of the following issues:

1) Ethical issues and informed consent related to the confirmation of a second adverse event in the French trial. The committee did not propose any changes to the October 10, 2002 committee consensus on informed consent for retrovirus gene transfer trials to treat X-SCID.

2) Differences in what is known at this time vs. at the previous meeting (October 10, 2002). The most important difference being that at this meeting it is known that a second adverse event occurred, indicating this event is not random.

3) Distinguishing characteristics of the patients in the French X-SCID trial that may have contributed to leukemogenesis in two patients. The committee listed several factors that need to be considered including, the age of the 2 patients, extent of cell proliferation during the ex-vivo expansion, cell dose administered, kinetics or T cell reconstitution,
vector (integrations), transgene and time on study.

4) Pre-clinical models. The committee and members of the public mentioned several factors that need to be considered in evaluation of animal models including, the age of the animals, the immune competence of the animal and the length of time animals are maintained and followed.

5) Retroviral vector-mediated insertional mutagenesis. The committee noted that this will be an inherent risk of all trials using retroviral vector-mediated gene therapy and recommended that further research be undertaken to determine the number of vector integrants that can be statistically predicted to have a reduced risk of insertion into known oncogenes.

6) Retrovirus gene transfer (gamma-c transgene) as first-line therapy for patients with X-SCID/Jak3 deficiency/IL-7 deficiency. The committee discussed alternative therapies and alternative gene therapy approaches for patients with X-SCID. Given the current evidence and until new data are available (in 18-36 months), the committee in a unanimous vote (19 yes, 0-no, 0-abstain) advised that the FDA only allow gene therapy trials (using a retroviral vector, with the

gamma-chain transgene) in patients with X-SCID, when there are no effective alternative therapies available.

7) Retrovirus gene therapy to treat patients with ADA-SCID. The committee discussed whether disease differences in ADA-SCID vs. X-SCID affect the safety of retroviral gene therapy to treat ADA-SCID. Several viewpoints were presented by members of the committee:

a. There is an effective FDA-approved drug therapy for ADA-SCID, PEG-ADA, therefore, only patients failing drug therapy be considered for retrovirus gene therapy. The committee also acknowledged that the typical alternative for patients failing PEG-ADA is a bone marrow transplant, however the committee was not sure whether BMT should also be tried prior to retrovirus gene therapy.

b. Patients on PEG-ADA lose the advantage of in-vivo selection provided by retroviral gene therapy. Therefore, PEG-ADA treatment should be suspended in patients who receive retroviral gene therapy, in order to provide the in-vivo selective advantage of the therapy.

c. There are not sufficient data on the important biological parameters that could affect insertion and cell growth to make a recommendation on the use of retrovirus gene therapy in ADA-SCID patients.

d. Some committee members stated ADA-SCID is a sufficiently different disease and should be considered differently for retrovirus gene therapy. Other stated the principle is the same as for X-SCID, namely risk/benefit analysis.

7. Other retrovirus gene transfer studies using hematopoietic stem cells (HSC). Again the committee expressed varying viewpoints:

a. There are no data to predict if the same adverse event is or is not a significant risk in other HSC retrovirus gene therapies.

b. It is difficult to extrapolate data on adverse events from one trial to all studies using the same vector and target cells, as different transgenes and different clinical indications may prove to be important variables regarding relative risk of tumorigenesis.

The committee voted 18-yes, 1-no, 0-abstain advising the FDA to remove the clinical hold on retroviral gene therapy trials in hematopoietic stem cells after case-by-case review with the following provisions:

there is appropriate risk/benefit to the therapy
there are appropriate consent form documents
the risk/benefit of alternative therapies is considered

The dissenting member encouraged the FDA to request an analysis from sponsors of the probability of a similar adverse event (leukemogenesis) occurring in the individual trials.

8. The committee requested the FDA publicly disclose (for example, posting on a website) information on future agency measures related to HSC retrovirus gene transfer trials currently on hold. Publicly available information should also include updated data on questions of concern to the committee, including cell dose, vectors, integration sites and clonality. The committee members recognized however, that they did not specifically address, at this meeting, the questions prepared by the FDA related to cell dose, vector and several other issues

9. The committee also noted the importance of a number of other issues that they did not have time to adequately discuss:

    a. The committee encouraged the scientific community to develop retroviral vectors with improved design to reduce the risk of insertional tumorigenesis, such as deletion of retroviral vector enhancer elements and use of insulator elements or suicide genes.

    b. The committee acknowledged the critical importance of cell dose relative to vector integration sites to the safety of retroviral gene therapy.

    c. The committee advised that investigators participating in gene therapy clinical trials provide documentation of their familiarity with best practices for informed consent.

This completed the committee discussion and the Chair officially adjourned the meeting.

For more detailed information concerning the open session presentations and committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at http://www.fda.gov/ohrms/dockets. Please submit all external requests to the FDA Freedom of Information Office.