MINUTES OF THE
PEDIATRIC ADVISORY COMMITTE

The Legacy Hotel, 1775 Rockville Pike, Rockville, Maryland

December 9th, 2008

On December 9th, 2008 the meeting was convened at approximately 3:30 p.m.

Members Present for December 9, 2008
Amy Celento (*Patient Health Care Representative*)
Avital Cnaan, Ph.D.., M.S.
Carl D'Angio, M.D.
Brahm Goldstein (*Industry Representative*)
Melissa Hudson, M.D.
Keith Kocis, M.D., M.S.
Daniel Notterman, M.D.
Marsha Rappley, M.D. *(Chair)*
Geoffrey Rosenthal, M.D.
Elaine Vining (*Consumer Representative*)

Pediatric Ethics Subcommittee Participants
Jeffrey R. Botkin, M.D., M.P.H. *(Pediatric Ethics Subcommittee Chair)*

Executive Secretary
Carlos Peña, Ph.D., M.S.

FDA Participants
M. Dianne Murphy, M.D.
Robert M. Nelson, M.D., Ph.D.

Office for Human Research Protections (OHRP) Participants
Jerry Menikoff, M.D., J.D.

Open Public Hearing Speakers
None

Meeting Summary
Prepared by Marsha Rappley, M.D.
Chair, Pediatric Advisory Committee

Introduction

The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met on December 9, 2008, to review a clinical investigation entitled "Children's Oncology Group Protocol ASCT0631: A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor (G–CSF) Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation." (ClinicalTrials.gov Identifier: NCT00450450) The review was requested by the Nemours Oncology Institutional Review Board (IRB) under 21 CFR 50.54 / 45 CFR 46.407. The recommendations and stipulations of the PES were presented to the PAC with the recommendation of acceptance and forwarding to the FDA Commissioner. The full report of the PES can be found at the dockets website. The Summary of Subcommittee Determinations, Stipulations, Recommendations and Vote are included below. The PAC met to consider the recommendations of the PES. The PAC accepted the PES recommendation that the protocol could be approved using 21 CFR 50.54 / 45 CFR 46.407. However, the PAC made some modifications (detailed below) to the PES stipulations.

Summary of Pediatric Ethics Subcommittee Determinations

(1) The research risks that should be considered when evaluating the inclusion of the healthy sibling donors is the incremental research risks of the G-CSF administration.
(2) The risks of G-CSF administration are more than a minor increase over minimal risk. Thus the protocol cannot be approved (for the healthy sibling donors) using 21 CFR 50.51 / 45 CFR 46.404 or 21 CFR 50.53 / 45 CFR 46.406.
(3) There are benefits to the donor (although some panel members thought these benefits somewhat speculative), but these should be considered indirect. Thus the protocol cannot be approved using 21 CFR 50.52 / 45 CFR 46.405.
(4) The donors do not have a condition with respect to this protocol. Thus, in addition to the risk of G-CSF administration, the lack of a condition means that the inclusion of healthy sibling donors cannot be approved using 21 CFR 50.53 / 45 CFR 46.406.
(5) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
(6) The research can be conducted in accord with sound ethical principles (with one dissenting vote), assuming the following changes (below) are made to the protocol and consent documents.
(7) The inclusion of healthy sibling donors in this research protocol can be approved using 21 CFR 50.54 / 45 CFR 46.407.

PES Stipulations (required for approval)

(1) All donors with any increased risk for BM donation (not simply high risk) should be excluded. For example, the presence of an uncontrolled infection as an exclusion criterion should be altered to any child with an active infection, especially pulmonary.
(2) Last two bullet points in the parental informed permission document (ARDS, leukemia) should indicate that they are potentially life-threatening.

(3) Each research site should appoint an independent person to function as an advocate for the potential sibling donor.
(4) All things being equal, preference should go to an older sibling donor.

PES Recommendations (preferred but not required for approval)
None.

PAC Discussion:
The PAC expressed concern that an unwarranted precedent for children undergoing other medical procedures might be set by approval of this protocol given the determination that the sibling BM donors do not have a "condition." The PAC determination that the sibling BM donors lack a "condition" only applies to this investigation of sibling bone marrow donation.

The PAC believed that the sibling BM donor follow-up should be extended from 6 to 10 years (as in the RDSafe study), given the risks of subsequent leukemia. It was noted that BM donor participants in this protocol would be offered enrollment in this long-term follow-up study.

The PAC had considerable discussion about the importance of limiting any stipulations to the research aspects of the protocol, rather than the more general clinical context of sibling BM donation. More specifically, the PAC sought to focus the stipulations on those aspects of the sibling BM donation which are affected by the administration of G-CSF. Thus, the additional exclusion criteria should focus on the additional increased risk of G-CSF administration. In addition, the PAC recognized that there are a number of different institutional arrangements and qualified personnel to serve in the role of an advocate for the sibling BM donor. The PAC goal was to provide clear direction while allowing for flexibility for how that stipulation is met.

The PAC discussed the need for a more focused set of DSMB guidelines for complications arising out of the BM donation procedure.

Finally, the PAC agreed that the two PES stipulations concerning the parental permission document and the preference for an older sibling as donor (all else being equal) are acceptable.

PAC Determination:
The research protocol can be approved using 21 CFR 50.54 / 45 CFR 46.407 with the following stipulations.

Stipulations
(1) The PAC believed that the PES language "All donors with any increased risk for BM donation (not simply high risk) should be excluded" did not provide clear guidance on how this risk would be determined. Rather than offer specific criteria, the PAC chose to address the medical clearance of the potential BM donor by requiring an independent assessment, based on testimony before the PAC about possible researcher conflict of interest. Thus, the PAC approved the following stipulation: "All donors at increased risk for BM donation following G-CSF administration, as determined by an independent physician, should be excluded."
(2) The PAC agreed with the PES that the sibling BM donor exclusion criteria should be strengthened, focusing on the potential risks of G-CSF administration. Thus, the PAC agreed with the PES stipulation that: "The presence of an uncontrolled infection as an exclusion criterion should be altered to any child with an active infection, especially pulmonary." However, the PAC also added the donor exclusion criteria (relative to the

risks of G-CSF administration) of "(a) splenomegaly or a history of splenic injury, and (b) an active or recent pulmonary disease or condition as determined by a physician separate from the research team."

(3) The PAC recommended strengthening the DSMB safety monitoring for the sibling BM donor by adding other suspension criteria (in addition to death) such as splenic rupture, acute lung injury or a hematological malignancy in a donor.

(4) The PAC agreed with the stipulation for a BM donor advocate: "Each research site should appoint an independent person to function as an advocate for the potential sibling donor." However, the PAC added: "The advocate should participate in the research decision in a meaningful way, acting on behalf of the potential sibling donor."

(5) The PAC agreed that the last two bullet points in the parental informed permission document (ARDS, leukemia) should indicate that they are potentially life-threatening.

(6) The PAC also agreed that, all things being equal, preference should go to an older sibling donor.

Recommendations
None.

Vote:
The PAC voted unanimously to approve the study with the above stipulations, including five (5) PAC members and three (3) PAC members who also voted at the PES meeting.

The meeting adjourned at approximately 5:45 p.m. on June 9th, 2008.

Please see transcript for details

I certify that I attended the December 9th, 2008 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

Carlos Peña, Ph.D., M.S.
Executive Secretary

Marsha Rappley, M.D.
Chair