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Robert M. Califf, MD
Commissioner, U.S. Food and Drug Administration
10903 New Hampshire Avenue
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Re: *Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment (FDA-2023-D-3900)*

Dear Dr. Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance on *Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment (FDA-2023-D-3900)*.

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease (SCD), thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

ASH commends the FDA for releasing this draft guidance. Acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) represent serious challenges to the patients our members treat, and developing better treatment for these diseases is an important priority for the Society. The patient population we represent is at risk of acquiring aGVHD or cGVHD through hematopoietic stem cell transplantation (HSCT) for their underlying hematologic conditions. With cGVHD being the leading cause of late morbidity and mortality after allogeneic HSCT, better treatment options for aGVHD and cGVHD can lead to a higher quality of life and increased functional status, and in some cases mean the difference between life and death.

The Society is pleased to see this draft guidance as investigators and hematologists conducting stem cell transplants can benefit from the Agency's guidance around aGVHD and cGVHD. To ensure that this guidance serves patients effectively and is comprehensive, it will be helpful for the Agency to provide guidance on the use of composite endpoints such as GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free relapse-free survival (CRFS). These endpoints are already being used in prospective studies and including them in this guidance can help sponsors feel comfortable incorporating them into future studies. We also believe the guidance would be strengthened with an additional appendix dedicated to Second-Line Plus Treatment of cGVHD.

Finally, ASH believes that industry sponsors would benefit from the inclusion in the guidance of a crossover design option which would be more ethical for clinical trial participants, and that any response assessment should be based on clinical criteria and not biomarkers.

LINE SPECIFIC COMMENTS

The Society also encourages FDA to consider the following comments.

Section III A 3: Clinical Pharmacology Considerations

- (Line 147) GVHD in the liver is rare, and while evaluating liver metabolism in those with liver GVHD is important, the Society asks for clarification of the mandate of this evaluation in all patients in clinical trials with GVHD. A mandate would likely slow drug development for patient populations with stem cell transplants, resulting in further delays in access to new therapies.

Section III A 8: Organ-Specific Topical Therapies

- (Line 312) The Society asks the FDA to consider the importance of confirming whether organ-specific topical therapies in clinical trials have a local and limited effect given there are documented instances where topical therapies can have systemic, potentially disease modifying effects. See, for example, the impact of topical tacrolimus on Netherton syndrome.

Section III B 3: Pivotal Trial Considerations

- (Line 472) The Society asks the Agency to clarify the statement contained in this line. Currently, the practice of transplant includes all donor types regardless of human leukocyte antigen (HLA) type. Conducting studies on the separate donor types is therefore extremely difficult to confirm GVHD prophylaxis. Furthermore, limiting studies to HLA-matched related and/or unrelated donors affects access and ensures a significant lack of diverse trial enrollee representation due to the association between common HLA types and race/ethnicity. With numerous data suggesting that modern approaches to GVHD prophylaxis lead to similar outcomes in HLA-matched and HLA-unmatched donors, we find that this requirement is unnecessary and out of step with current practice.
- (Line 506) The Society cautions that designating the base regimen for an add-on design approach may lead to patient exposure to agents without an appropriate expectation of benefit.

Section III C 1: Efficacy Endpoints

- (Line 583) Given that aGVHD can reoccur nearly 2 months after cessation of prophylaxis treatment, the Society recommends extending the time period for evaluation from 4 weeks to 8 weeks.

Section III C 1: Pivotal Trial Considerations

- (Line 703) We ask that FDA share the underlying scientific justification for permitting up to only 72 hours of ≥ 1 mg/kg methylprednisolone equivalents for first line cGVHD trials. This is a very limiting requirement without clear precedent.

- (Line 709) The Society requests that the FDA clarify why treatment with $\geq 2\text{mg/kg/day}$ is the standard for defining Steroid Refractory aGVHD (SR-aGVHD), given some patients are treated with different doses, including 1 mg/kg/day or other dose levels.

Section III D 1: Efficacy Endpoints

- (Line 850) The Society suggests that the “Complete Response” criteria be adjusted by including symptom and objective measures where both are captured.
- (Line 869) In the current guidance, Duration of Response (DOR) is defined as the time from the date of first response to the date of progression, new systemic therapy for cGVHD, or death from any cause, whichever occurs first. The Society believes that the Agency should consider current, more commonly used outcomes regarding duration of response. Using Failure-free survival (FFS) where events are death, relapse, and use of next-line systemic immune suppressive therapy is a less ambiguous measure of failure. The failure measurement in the proposed guidance could flag a mild change in organ score as progression and have equal weighting to death and could also over call failure in ways that are not viewed as clinically meaningful. The organ score is also subject to inter-observer variability in scoring cGVHD organ site severity per visit. We recommend the FDA consider conducting observational studies to assess how this proposed outcome measure performs against the traditional FFS before finalizing this guidance.

Section III D 1: Exploratory Trial Considerations

- (Line 926) The Society asks for FDA to clarify what constitutes a first-in-human (FIH) trial in cGVHD. We believe that banning testing of a novel approach for existing drugs in humans for cGVHD treatment will hamper efforts in conducting innovative clinical trials testing steroid-free regimens.
- (Line 975) The Society notes that the field is in the process of moving away from steroids as a treatment and is instead optimizing steroid sparing approaches. Thus, requiring a study into patients on steroids alone may pose an added risk and represent a step backward in therapy for impacted patients.

Section III D 1: Pivotal Trial Considerations

- (Line 1025) We ask that the FDA clarify whether it is excluding steroid-dependent cGVHD patients from steroid-refractory cGVHD treatment trials or from trials only relating to cGVHD. We recognize that steroid-dependent cGVHD patients were enrolled in a previous study (REACH 3) that led to an FDA indication for SR-cGVHD. Therefore, it might be helpful for the Agency to expand in this guidance its rationale for excluding this patient group if that is what the guidance is indicating.

Section IV A: Assessment of Efficacy

- (Line 1199) The Society believes that the significance of thrombocytopenia and muscle weakness in patients with cGVHD must be further emphasized. To that end, we recommend considering two additional raw data points for inclusion in the raw data file: platelet count for assessing thrombocytopenia and creatine kinase (for assessing the effect on muscle weakness).

- (Line 1334) This Appendix could be strengthened with the inclusion of a steroid dosage consistent with treatment failure. Of note, this is consistent with what is included in Appendix 2.

ASH appreciates the opportunity to provide these comments and looks forward to any response you might have. Please consider ASH a resource; we would be pleased to provide additional information regarding this matter. If you have any questions, please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (skaplan@hematology.org or 202-776-0544) as your point of contact.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Brodsky", with a stylized flourish at the end.

Robert A. Brodsky, MD
President