April 3, 2026

Martin A. Makary, MD, MPH
Commissioner
U.S. Food and Drug Administration
White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Makary:

On behalf of the Transplant Therapeutics Consortium, a public private partnership with the FDA, the American Society of Transplant Surgeons (ASTS), and the American Society of Transplantation (AST), we are writing to thank you and your staff for taking the time to meet with us on March 30. We appreciated the thoughtful discussion and your calling to our attention the need for professional societies to address growing concerns about the organ procurement practices in China and to clarify the impact of xenotransplantation on a patient's waitlist status. We recognize the importance of these issues, and ASTS and AST are currently discussing strategies on how to utilize our resources and work with other stakeholders to address both matters.

We also appreciated your commitment to streamlining administrative processes and facilitating innovation in new drug development. As we discussed, there is a pressing need for the development of new immunosuppressive drugs, which has stagnated for the last fifteen years. We were encouraged by your interest in bringing products to market that would benefit transplant patients and in particular the use of the iBOX score as an accepted surrogate (kidney transplant) outcome and as a reasonably likely surrogate endpoint (RLSE) in the Accelerated Approval Program. Pharmaceutical companies need an expedited pathway to demonstrate superiority over conventional (old) immunosuppressive drugs in order to invest resources into new immunosuppressive therapies. The qualification of the iBOX would be a regulatory landmark as the first RLSE qualified by FDA's Biomarker Qualification Program and heralded by the transplant community as a signal of FDA's recognition of the unmet need and partnership to address the stagnation in innovation. **Additionally, since the request is for iBOX to be a co-primary endpoint as an addition to the 1-year post-transplant efficacy failure endpoint, there is no compromise to existing efficacy or safety standards by the FDA.**

Dr. Siegel expressed concern that the iBOX predicted death-censored graft survival and that death with a functioning graft was considered a successful outcome. We want to clarify that in the iBOX model, death is NOT considered a "success", but that graft survival is censored at the point of death. The major causes of death after kidney transplant are infections, cardiovascular disease, and cancer. However, the major cause of graft loss is alloimmune injury. As an **efficacy** endpoint at five years, it is therefore appropriate to focus on death-censored graft survival as a direct extension of the intended pharmacologic effect of any novel new immunosuppressant, i.e. preventing acute rejection in the first year and preventing graft loss (primarily alloimmune mediated) through five years. A significant improvement in five-year death-censored graft survival is clinically very

meaningful and would be a remarkable advancement in the field. Death is the most important safety endpoint. It would also be collected and assessed at five years to ensure that a drug that improves death-censored graft survival does not increase the risk of death.

As stated in our meeting, transplant recipients are suffering from the significant side effects of current immunosuppressive medications and new medications are desperately needed. These deleterious side effects from existing FDA-approved immunosuppressives result in many patients skipping doses to avoid them, thus putting their organs at risk of failure. In order for new medications to be developed, industry needs an accelerated pathway to bring new products to market quickly and a means to demonstrate benefit (superiority) over the currently available regimens.

We do not believe that approval of the iBOX as a secondary endpoint would provide the incentive necessary to bring new immunosuppressives to market. Accordingly, if the FDA is not prepared to qualify iBOX as a reasonably likely surrogate endpoint for accelerated approval, we respectfully request that it defer any final determination and engage in a round-table forum with experts and patients in kidney transplantation to examine the issue further.

Thank you again for your leadership and for your commitment to advancing innovation to benefit our patients.

Respectfully,

James F. Markmann, MD, PhD
President, ASTS

David P. Foley, MD
President, AST

Timothy Pruett, MD
Past President, ASTS

William Fitzsimmons, Pharm.D., M.S.
Transplant Therapeutics Consortium