AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036-4929 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

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Elizabeth Fowler, Ph.D., J.D.
Deputy Administrator and Director of the Center for Medicare and Medicaid Innovation
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: ASH Comments for the *Cell & Gene Therapy Access Model for Sickle Cell Disease*

Dear Dr. Fowler:

On behalf of the American Society of Hematology (ASH), thank you for the opportunity to provide comments on the Center for Medicare and Medicaid Innovation's (CMMI) Cell & Gene Therapy Access Model (CGT Access Model) for Sickle Cell Disease (SCD). The Society commends the Innovation Center's commitment to SCD and believes that all patients should have access to the most appropriate treatment options, inclusive of new and innovative gene therapies.

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 non-malignant conditions such as 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, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

ASH has a longstanding commitment to combating inequities in healthcare and research. As part of this commitment, in 2015, ASH launched a transformative, multi-faceted, patient-centric initiative to improve outcomes for individuals living with SCD–a disease that illustrates critical health disparities and inequities. The ASH initiative supports advances in research, improving provider training and education, advocating for policies to expand access to care, and enhancing data collection.

SCD is a rare disease primarily impacting African Americans and Hispanics. Additionally, people suffering from SCD have traditionally faced significant barriers to health care. ASH believes that individuals with SCD should have access to high-quality, comprehensive care comprising of a clinical protocol they decide is most appropriate in conjunction with their physician. New gene therapies represent a significant breakthrough for the SCD community. ASH appreciates the collaboration and work CMMI has done to develop the CGT Access Model and the potential impact these gene therapies and appropriate access could have on the patients our members treat. ASH supports this model as gene therapy is a potentially curative treatment option for SCD, but recognizes that for it to be successful, comprehensive care is needed to fully optimize health outcomes.

The Society believes framing these innovative gene therapies in the broader context of comprehensive care is critical for delivering whole-person care for individuals with SCD. ASH is pleased to take this opportunity to share feedback and recommendations as CMMI prepares to implement the CGT Access Model. We will address several elements of care for consideration in the model, including:

1) Patient Engagement Prior to CGT Treatment
2) Comprehensive Care: Fertility Preservation, Mental Health, Pain Management, etc.
3) Care After CGT Treatment
4) Wrap Around Services: Transportation, Lodging, Child Care, etc.
5) Long-Term Outcomes

Patient Engagement Prior to CGT Treatment

We are pleased to see more therapies available for individuals with SCD; but current treatments and models of care do not adequately address the complex challenges of SCD. ASH wants to ensure that the CGT Access Model contemplates these challenges from the outset. Today, many patients experience access barriers with the existing therapies and interventions; many individuals with SCD receive uncoordinated, inconsistent care, leading to poor clinical outcomes, avoidable complications, low quality of life, and increased costs to the healthcare system. As a core priority, ASH continues to advocate for policies to improve outcomes for individuals living with SCD. ASH has an ongoing dialogue with federal agencies, including leaders at the U.S. Department of Health and Human Services and CMS to help enhance and expand government activities in SCD research, training, and services.

ASH urges CMMI to consider how patients will learn about and access gene therapies and enter the model. For this reason, ASH underscores the importance of multi-disciplinary care teams that include hematologists, obstetricians and gynecologists, reproductive health specialists, urologists, ophthalmologists, neurologists, nephrologists, psychologists, psychiatrists, orthopedists, cardiologists, pulmonologists, care coordinators, and social workers to adequately treat an individual for SCD and its many complications. ASH recommends that CMMI consider the requirements and needs of care teams developing individualized, comprehensive, patient-centered care plans for individuals with SCD that accommodate patient preferences in a culturally and linguistically appropriate manner.

Notably, gene therapies are expected to be available to only a fraction of the SCD population. Testing is important in identifying the population eligible for these treatments, and patients must complete the following tests prior to initiating gene therapy treatment:

- Pulmonary function tests to assess for sickle lung disease.
- Echocardiogram to include cardiac evaluation and pulmonary hypertension.
- Brain MRI to evaluate for previous strokes and other sickle cell-related brain injuries.
- Hepatic evaluation, including liver MRI and liver biopsy.
- Bone marrow aspirate and biopsy.
- Blood tests of liver and kidney function.

Additionally, not all eligible patients will elect to pursue gene therapy. We urge CMMI to consider developing a SCD comprehensive care model from which patients could transition to the CGT Access Model should they choose to pursue treatment with gene therapy. This program could set the stage for future coverage policies, and it is important to have all interventions (and their benefits) available

to avoid unintended consequences, prevent further access barriers, and lead to denied access for patients. Regardless of the treatment a patient with SCD may elect, it is important they have access to all available options.

Comprehensive Care: Fertility Preservation, Mental Health, Pain Management, etc.
As previously mentioned, ASH encourages CMMI to ensure that individuals who choose gene therapy treatment and are included in the CGT Access Model have access to comprehensive care. As such, it is important for the model to ensure SCD patients are provided with coordination of, and access to, the following services, as determined to be clinically appropriate:

- Appropriate hematology services, including transplant and late-effects specialists.
- Treatments and medications, including chronic and exchange transfusions.
- Appropriate diagnostic testing, such as magnetic resonance imaging.
- Pain management treatment and palliative care.
- Fertility preservation.
- Services provided by subspecialists, such as obstetrician/gynecologists, reproductive health specialists, urologists, ophthalmologists, neurologists, nephrologists, psychologists, psychiatrists, orthopedists, cardiologists, wound care specialists and pulmonologists.
- Supportive clinical services, including vision and dental care.
- Mental health services and substance use disorder treatment.
- Any other therapies approved by the U.S. Food and Drug Administration and any other services deemed appropriate for the treatment of SCD or its complications.

Each of the above noted services are critical for whole person SCD care, as underscored in the Center for Medicare & Medicaid Services' SCD Action Plan, but often a number of these critical support services are omitted. Mental health, substance use, vision, and dental care services are standard of care for this patient population but are far too often not accessible. The Society encourages CMMI to prioritize these services in addition to fertility preservation, pain management, and other appropriate treatments.

ASH strongly recommends that CMMI integrate flexibility in the CGT Access Model by allowing the provision of other services or other actions deemed necessary to improve treatment of SCD as determined by the patient in conjunction with their physician, inclusive of their hematologists and other specialists in SCD care and treatment.

Care After CGT Treatment
Comprehensive care pre-and-post therapy will be essential to the success of any treatment option. Once again, the model needs to ensure SCD patients are provided with clinically appropriate treatment and follow-up care. Close surveillance and supportive care are critical for the first 100 days after the day of infusion. For the initial follow up, appropriate treatments and medications include, but are not limited to:

- Daily blood tests of blood counts to assess the risk of infection and the need for blood and platelet transfusions, electrolytes to assess kidney function, and liver enzymes to assess liver function.
- Daily assessments of lung and heart function, bowel function, mentation, and monitoring for signs of infection.
- Echocardiogram to examine heart function.

- CT scans to assess for infections in the lungs or abdomen, or bleeding in the brain.
- Bone marrow assessments including complete blood count (CBC) tests, reticulocyte count, lactate dehydrogenase (LDH) test, and hemoglobin electrophoresis.
- Intensive pain management services.
- After 30 days, post-discharge, the frequency of the above tests can be reduced to a twice-weekly, blood-work-only regime, as determined by the physician and patient.
- Comprehensive care, as noted above, including services provided by subspecialists, vision and dental care, mental health services, and any other therapies or services as deemed appropriate.

After the initial follow up, ongoing care is absolutely essential to monitor engraftment and the patient's overall status. A care plan is necessary to monitor stability or progression of existing organ damage. Appropriate treatments and medications may include:

- A brain MRI if initially indicated by a prior stroke or cerebral vasculopathy.
- A liver MRI if initially indicated.
- Pulmonary function tests, including spirometry pre- and post- bronchodilator, total lung volumes, a lung diffusion test (DLCO), a 6-minute walk test, sleep study and a pulse oximetry on an annual basis if indicated.
- An echocardiogram for heart function if initially indicated.
- Renal-urine microalbumin and serum creatinine test to further assess kidney function.
- Endocrine tests to assess TSH, free T4, LH, FSH, estrogen and testosterone levels.
- Eye assessment, such as a dilated eye exam for retinopathy.
- Bone health tests including a dual x-ray absorptiometry (DEXA) scan, vitamin D and calcium levels, evaluate avascular necrosis, and x-rays if indicated.
- Bone marrow tests including complete blood counts (CBC) tests, reticulocyte count, lactate dehydrogenase (LDH) test, and hemoglobin electrophoresis.
- Monitoring for clonal hematopoiesis.
- Blood assessments to assess for the presence of the genetic modification and the assessment of the hemoglobin driven by the genetic modification.
- Continuity of intensive pain management services as it may take up to 6 months or more to wean patients off pain medications.
- Access to iron chelation therapy and iron burden assessments with MRI of liver and heart.
- Continuity of comprehensive care, including services provided by subspecialists, vision and dental care, mental health services, and any other therapies or services as deemed appropriate.

Ensuring patients with SCD continue to receive comprehensive care is critical for optimal health outcomes. While gene therapy is a potentially curative treatment, it is new and innovative with limited data to understand the full scope of long-term implications. For example, after undergoing gene therapy, patients may experience borderline anemia, increased reticulocyte counts, and mildly elevated lactate dehydrogenase (LDH), which is a marker of hemolysis. Regular follow up with a hematologist and access to comprehensive care to determine an individualized treatment plan is therefore important for patients with SCD, even after a potentially curative treatment. At a minimum, patients should be monitored for two years and then should see a hematologist at least once a year, thereafter. Follow up with patients who elect these treatments is especially important to track outcomes and long-term effects for a minimum of 15 years. Additionally, we recommend CMMI make considerations during this period of follow-up for patients across different states and the variances in coverage across

Medicaid programs. As such, ASH urges CMMI to continue to support the implementation of multi-disciplinary care teams that include the physicians needed to adequately treat an individual for SCD and its complications.

Wrap Around Services: Transportation, Lodging, Child Care, etc.
ASH urges CMMI to cover wrap-around services supporting access to CGT treatment. Often these ancillary services are not included but are especially crucial to support patient access to treatment. When choosing to undergo gene therapy for SCD, an individual is committing to a rigorous transfusion regime that begins three to six months prior to the cell collection to manufacture the gene therapy. Patients are typically admitted as inpatients for the chemotherapy required prior to the gene therapy transfusion. Patients then return to the clinic regularly for 100 days post-infusion. This regime is taxing on the patient and their families as it requires frequent trips for treatment and a lengthy hospital admission.

ASH recommends CMMI consider including the following:

- Transportation to medical services. (Must include long-term annual visits for comprehensive annual evaluations.)
- Housing and lodging support.
- Childcare services.
- Social support services, including social workers and care coordinators to help manage barriers to accessing care, such as scheduling appointments and accessing resources to help with out-of-pocket costs.
- Referrals to community-based organizations.

Long Term Outcomes
Lastly, ASH recommends that CMMI consider the long-term follow-up of individuals who undergo these treatments in the CGT Access Model for a minimum of 15 years, as previously mentioned. Follow up will be critical to ensure the best outcomes for those patients and will help inform the research and use of these therapies over time. It is imperative to have comprehensive data on these patients, toxicities, and clinical management strategies.

The ASH Research Collaborative (RC) Data Hub, a shared data resource for the global hematology community, is a resource for industry, the Food and Drug Administration, and others to efficiently collect post-approval cell and gene therapy product data, especially in multiple myeloma and SCD. The real-world data can generate actionable insights for research, regulatory needs, and quality improvement. As we prepare for broader use of gene and cell therapies, we must be ready to meet the need for continued monitoring when these approaches are applied in real-world treatment settings. We encourage CMMI to leverage the ASH RC Data Hub, the recommendations from the ASH RC Innovative Genomics Institute Accelerating Genomic Therapies with Real-World Evidence Initiative, and other ASH programs to help inform CMMI's continued work on the model.

As you know and we have noted throughout this letter, SCD is a complex disease and there are so many factors and intricacies to consider in the CGT Access Model. We believe structuring the CGT Access Model as a comprehensive care framework will be the most effective in providing the highest quality care to individuals with SCD. While we are excited that CMMI is developing the CGT Access Model, we also want to emphasize the importance of comprehensive care for all SCD patients and

urge CMMI to develop a SCD comprehensive care model that is appropriate for those who do and those who do not elect to pursue CGT.

ASH appreciates the opportunity to provide these comments. Please use ASH Manager for Health Care Access Policy, Carina Smith (*casmith@hematology.org* or 202-292-0264), as your point of contact if you have any questions or if we can provide additional information.

Sincerely,

Robert Brodsky, M.D
ASH President