MARAC Statement: Temporary Suspension of Clinical Trials

March 1, 2021 - The Sickle Cell Disease Association of America's Medical and Research Advisory Committee (MARAC) is aware of the announcement on February 16, regarding the temporary suspension of bluebird bio clinical trials of **LentiGlobin Gene Therapy for Sickle Cell Disease** and the pause of all commercial use of bluebird bio European gene therapy.

Additionally, on February 22, the National Heart, Lung, and Blood Institute (NHLBI) temporarily suspended their unrelated gene therapy trial—**Pilot and Feasibility Study of Hematopoietic Stem Cell Gene Transfer for Sickle Cell Disease** at Boston Children's Hospital. The NHLBI stated that this temporary suspension was, "out of an abundance of caution" despite having no indications of harm.

On February 23, another gene therapy trial, **Gene Transfer for Patients with Sickle Cell Disease**, was also paused by the sponsor Aruvant.

MARAC has investigated the situation and met with bluebird bio to discuss the information available to the public. In the bluebird bio study, two patients developed blood cancer, and a third patient is under investigation for a related problem called myelodysplastic syndrome. The details of these patients are being examined by their doctors and the bluebird bio sponsors. Investigations are trying to determine whether the blood cancer can be linked to the gene therapy vector, the chemotherapy preparation for gene therapy, or damage of the host stem cell. No events occurred in the other clinical trials.

We value patient trust and patient concerns. SCDAA tries to express the voice of people living with sickle cell disease (SCD), and MARAC supports this mission with biomedical expertise. MARAC is monitoring developments and will continue to communicate findings to the SCD community. Nearly all the members of MARAC are involved in research to help those with SCD, and some who participated in developing this advisory statement are gene therapy investigators. The MARAC members with a potential conflict of interest due to their involvement in gene therapy clinical trials are listed on the following page.

MARAC acknowledges that there has been a history of clinical investigations that were unethical, including the infamous Tuskegee syphilis study, but this past week's events highlight that clinical research is no longer in that era. The modern safeguards for clinical research are working. Preplanned "stopping rules" triggered a "pause" of enrollment by bluebird bio when unusual and concerning events occurred. The Data Safety and Monitoring Board for the NHLBI gene therapy study followed "out of an abundance of caution," as did the Aruvant study. There were public announcements, and an intensive investigation is now underway to gather more information. The participants in the studies are being notified and are receiving appropriate medical care from the investigators.

Clinical research has been and continues to be the path for progress to improved SCD survival and quality of life. MARAC celebrates the decades of clinical research studies on which the progress in sickle cell care that we have today has been built — including penicillin, hydroxyurea, stroke screening and new medications.

SCDAA honors the SCD warriors who volunteer in clinical research. They have given their time so that others may benefit from new future treatments and cures. We pay tribute to all of those who have been lost to SCD, and we know many have died too young.

Dsiclosures:

Gene therapy study sponsor	Investigators	Other roles
bluebird bio	Julie Kanter, M.D. Raffaella Colombatti, M.D. Lakshmanan Krishnamurti, M.D.	Biree Andemariam, M.D., consultant Andrew Campbell, M.D., co-investigator, 2019 advisory board Baba Inusa, funded for ASCAT conference Elizabeth Klings, M.D., consultant on pulmonary function Sophie Lanzkron, M.D., chair of adjudication committee Kim Smith-Whitley, M.D., co-investigator Ahmar Zaidi, consultant/Honoraria
Aruvant		Biree Andemariam, M.D., consultant (past) Lewis Hsu, M.D., Data Safety Monitoring Board
NHLBI		Julie Kanter, M.D., protocol committee for BMTCTN-2001 Marsha Treadwell, Ph.D., consultant for Data Strategy Consortium
Vertex / CRISPR Therapeutics		Miguel R. Abboud, M.D., Data Safety Monitoring Board Biree Andemariam, M.D., consultant Kim Smith-Whitley, M.D., co-investigator

SCDAA Medical and Research Advisory Committee Members

continued on next page

continued on next page