LEUKEMIA & LYMPHOMA SOCIETY®
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February 5, 2018

Division of Dockets Management
US Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Pediatric Rare Diseases – A Collaborative Approach for Drug Development using Gaucher Disease as a Model, Guidance for Industry (FDA-2017-N-6476)

Dear Commissioner Gottlieb:

The Leukemia & Lymphoma Society (LLS) appreciates the opportunity to submit comments on the Food and Drug Administration's (FDA) draft guidance for industry on a collaborative approach for drug development in pediatric rare diseases. As the world's largest voluntary organization dedicated to the needs of blood cancer patients, LLS is a strong supporter of initiatives aimed at enhancing the efficiency of drug development in rare diseases, particularly for the pediatric population.

Each year, over 140,000 Americans are newly diagnosed with blood cancers, accounting for nearly 10 percent of all newly diagnosed cancers in the United States. Leukemia accounts for nearly 30 percent of all childhood malignancies and is the most common cancer in children. Approximately 15 percent of all children with leukemia have AML. Although survival rates have increased since the 1970s, approximately half of all childhood AML cases relapse despite intensive treatment. Additional therapies following relapse are often unsuccessful and can be especially difficult and damaging for children.[1]

LLS recognizes the inherent challenges in furthering the development of drugs for the pediatric population, and supports the FDA's proposed model. Specifically, we support the FDA's approach of multi-arm, multi-company clinical trials to drive critically needed treatments. LLS is very familiar with the challenges of this model as a result of our experience with our Master Protocol for Biomarker-Based Treatment of AML, the first collaborative clinical trial in a blood cancer, involving multiple medical institutions and drug companies.

LLS appreciates the FDA's commitment to working with us to advance our AML master protocol, and welcomes the opportunity to collaborate with the FDA on continued efforts to facilitate innovative models for drug development in pediatric rare diseases. In particular, LLS is pleased to see that the proposed model calls for relevant endpoints chosen based on mechanisms of action of the selected drug and consider heterogeneity of the patient population, long-term monitoring of primary and secondary endpoints, and age-specific cohorts. LLS agrees with the FDA's assessment that long-term follow-up is crucial to evaluating the long-term safety and

[1] "Acute Myeloid Leukemia." *National Cancer Institute, Office of Cancer Genomics,* 22 Jan. 2018, https://ocg.cancer.gov/programs/target/acute-myeloid-leukemia.

efficacy of treatment on disease manifestations in pediatric patients and we support the use of patient registries in monitoring efficacy and safety.

Maintaining Flexibility in Clinical Trial Design

LLS recognizes that this draft guidance includes specific recommendations regarding drug development for Gaucher disease only and that modified approaches may be proposed. LLS encourages the FDA to remain flexible with respect to clinical trial design, specifically with respect to the following study design features:

- "Double-blind, controlled, randomized" – LLS supports efforts to design smarter, patient-specific clinical trials geared to patients most likely to respond. In studies relying on validated biomarkers and personalized therapy, double-blind and randomized criteria may not be possible. While a double-blind, controlled, randomized trial is certainly an appropriate study design feature for Gaucher disease, when relying on biomarker-based selection criteria in hematologic malignancies, an active control arm may not be warranted.

- Synthetic control arms – LLS encourages the FDA to consider reliance on synthetic control arms in clinical trials for rare pediatric diseases. Although concurrently randomized controls remain the gold standard for evaluating investigational therapies, the use of historical controls may be more efficient and economical. Historical controls derived from a single clinical trial may contain biases, making it preferable to pull raw data from past studies to create unbiased control arms. By accessing databases of patient information, it is possible to create a synthetic control arm to minimize time, site, and study-specific bias.

- Focus on new therapies – Given that placebos are not utilized in oncology, LLS encourages the FDA to continue their efforts to endorse trials that focus on developing new therapies, not merely enhancing standard of care or minimizing the number of patients treated with placebo.

LLS would like to applaud the FDA for its continued efforts to facilitate drug development in pediatric rare diseases. We are happy to share lessons learned from convening our AML master protocol, and look forward to continuing our work with the FDA to improve the lives of all blood cancer patients.

Sincerely,

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