



VIA ELECTRONIC DELIVERY

July 5, 2023

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Patient-Focused Drug Development (PFDD): Incorporating Clinical Outcome Assessments (COA) Into Endpoints for Regulatory Decision-Making; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; Availability
Docket No. FDA- 2023-D-0026**

CLL Society appreciates the opportunity to submit its comments on the Food and Drug Administration's (FDA's) above-referenced draft guidance to industry related to methods, standards, and technologies for collecting and analyzing COA data (the "Draft Guidance").

CLL Society is dedicated to addressing the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) community through patient education, advocacy, support, and research. We are the largest nonprofit focused exclusively on the unmet needs of patients living with CLL and SLL.

Our patients live with a chronic rare cancer of the immune system. We strive to fulfill our primary mission of ensuring that patients have access to safe and effective treatment options, which includes informing patients and caregivers about the therapeutic landscape. We also stress the importance of clinical trials to those in our community, build and support patient networks, engage in research, and educate patients and their caregivers.

CLL Society appreciates FDA's considerable efforts to engage patient advocacy organizations and other stakeholders throughout the complex process of producing the four Patient-Focused Drug Development (PFDD) guidance documents. Patient engagement is critical in CLL and other conditions where, as more fully discussed below, product development is essential to address significant unmet needs. We are hopeful that FDA will continue to expand the role patients and their advocacy organizations have in FDA's drug development processes, including those related to approval, as well as determinations initiated to withdraw approval or modify a product's label.

FDA's PFDD initiatives are particularly important to our patient communities given that CLL is not an ideal disease state from a research perspective. Delays associated with the wait required to



obtain overall survival data have already dampened research efforts and slowed patient access to potentially life-saving therapies. In addition, while we advocate for crossover in clinical trials to save lives, the strategy inherently compromises the “purity” of survival data. The question remains whether those with CLL will continue to have access to PI3K inhibitors as a remaining treatment option after both a BTK and BCL2 inhibitor have failed them and is one illustration of the inherent difficulties associated with studying this disease. It not only highlights the heightened risk manufacturers must weigh when pursuing new therapeutic candidates, but it also underscores the perspective that patients at varying stages of a disease can have on their own preferred outcomes, their varying degrees of tolerance for uncertainty, and the delicate balance between potential risks versus benefit of a drug.

Background

CLL/SLL is a chronic blood cancer of the white blood cells known as B-lymphocytes where there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common type of adult leukemia in the United States, with around 21,000 cases diagnosed annually. It is classified as both a type of leukemia and a type of non-Hodgkin’s Lymphoma (NHL). SLL is simply a different manifestation of the same disease and is best understood as a stage of CLL where there are not yet a significant number of cancer cells located in the bloodstream. We, therefore, refer to the disease state collectively as CLL.

CLL is extremely heterogeneous, meaning each person’s disease course and progression can vary considerably. Some patients have an aggressive form of the disease, experience rapid deterioration, and survive for as little as two years. Others have a less aggressive form of the disease, may never need treatment, and can expect to have a normal life expectancy.

Targeted therapies such as BTK inhibitors and the BCL2 inhibitor known as venetoclax offer substantial efficacy against CLL and have transformed care for our patient community. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. They can take continuous daily oral therapy with a BTK inhibitor (with or without the addition of a monoclonal antibody) until their disease progresses. Alternatively, patients can choose a short-term time-limited treatment approach that combines venetoclax and a monoclonal antibody. The latter approach allows for drug discontinuation until active monitoring reveals that another treatment is needed.

Although most CLL patients can expect a response to initial therapy, nearly all current treatment options are palliative and not curative. Most patients will experience one or more relapses during the course of their disease, and many are forced to either change treatments, take a “drug



holiday,” or adjust dosing due to drug intolerance. For patients with relapsed or refractory disease (or drug intolerance), treatment decisions are highly individualized based on prior therapies, prior response, the reason for discontinuation of previous therapy, comorbidities, biomarker characteristics, patient preference, and therapeutic goals. Patients can experience serial relapses, and many will be treated with all available agents at some point during the course of their disease.

For now, patients with a CLL diagnosis can expect to live the rest of their lives with cancer. This means that endpoints demonstrating the potential for patients to live treatment-free for months, years, or longer can be particularly meaningful.

CLL Society appreciates that the four guidance documents in FDA’s PFDD series offer sponsors a relatively detailed roadmap toward integrating the patient voice in drug development efforts. Our specific comments in response to the draft guidance are below.

Specific Comments and Recommendations

CLL Society appreciates that the draft guidance includes a detailed discussion on endpoint selection that recommends setting a research objective that takes the disease’s natural history into account. Given that CLL is a chronic blood cancer, treatment value from the patient perspective might turn more towards durability of response (time to progression requiring another line of treatment), tolerability, treatment protocol (e.g., staying on a drug continuously until disease progression vs. only taking a drug for a limited amount of time), whether the treatment constitutes an entirely new class of treatment or if it is a new option within an existing drug class, and many other factors.

One example of COA within the context of CLL product development is the emerging use of measurable residual disease (MRD). A recent review on the use of MRD in CLL clinical trials¹ concluded that, “[m]easurable residual disease (MRD) status in chronic lymphocytic leukemia (CLL), assessed on and after treatment, correlates with increased progression-free and overall survival benefit.” For patients, adoption of COAs capturing MRD has multiple advantages, which includes providing an additional objective measure of treatment effect that is likely to indicate clinical benefit. This would not only improve the breadth of data available to FDA but could significantly improve patient and clinician understanding of the treatment effects of emerging CLL product candidates. We expect that FDA acceptance of MRD data would also increase real-world use of

¹ Fisher A, Goradia H, Martinez-Calle N, Patten P, Munir T. The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. *Front Oncol.* 2023 Feb 22;13:1130617. doi: 10.3389/fonc.2023.1130617. PMID: 36910619; PMCID: PMC9992794.



MRD tools to guide and improve patient treatment plans, eventually enabling more patients to live longer while potentially spending less time and money treating their cancer.

With respect to our specific feedback on FDA's draft guidance, we:

- Agree that COA should reflect a meaningful aspect of patient health and support an inference of treatment effect.
- Appreciate FDA's acknowledgement that some conditions may require multiple baseline assessments and longer or shorter baseline periods.
- Ask that FDA acknowledge that while "the most straightforward analysis will be a comparison of randomized groups with respect to the follow-up score(s) after adjusting for the baseline value (e.g., with a linear model to compare average follow-up scores)," ***use of historical controls or other comparators are appropriate for patient populations in which randomized controlled trials are not feasible.***
- Agree that sample sizes are calculated based on the primary endpoint and that COA are frequently used for secondary endpoints. CLL Society, however, is concerned that FDA's subsequent statement that, "Incorporating COA into clinical studies would necessitate a larger sample size to ensure sufficient statistical power" will discourage use of COA due to the resultant increase in research costs. We recommend that this statement be removed from the FDA's final guidance.
- Recommend that FDA reconsider its position that COA scores obtained at screening should not be used as the patient's baseline value and that a pre-randomization assessment should be performed to establish the patient's baseline value. Some COA (e.g., MRD, organ function laboratory studies) are unlikely to introduce substantial concerns of regression to the mean or other types of bias. The potential for intervening bias is particularly irrelevant in single-arm studies.
- Recommend that the FDA include, within its discussion of the need to obtain COA scores periodically, a clarification that there are circumstances in which repeat assessments are unnecessary and inappropriate. For example, repetitive imaging to assess for enlarged lymph nodes and organomegaly (enlarged spleen and/or liver) with CT scans should be avoided for those with CLL.
- Appreciate that the FDA specifically emphasizes the importance of minimizing participant burden and demonstrating respect for patients and caregivers. Encouraging early



discussions that include FDA, sponsors, and the patient community will maximize the extent to which clinical trials are able to increase the convenience and value of participation. Patients are also in the best position to determine how the location and timing of assessments impact both the burden and accuracy of COA.

Conclusion

CLL Society once again appreciates the opportunity to contribute the CLL patient perspective as CMS implements the DPNP. We remain hopeful that the Agency will take our comments and recommendations into account as it implements the DPNP, and we welcome the opportunity to discuss our comments and/or the experience of those living with CLL more generally.

If you have any questions, please feel free to contact Saira Sultan, CLL Society's Director of Government Affairs and Public Policy at ssultan@cllsociety.org.

Sincerely,

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Co-Founder, Chief Medical Officer, & Executive Vice President
CLL Society