July 27, 2023

The Honorable Xavier Becerra
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

Dear Secretary Becerra and Administrator Brooks-LaSure:

We are physicians, public health researchers, and health policy experts (some of whom are former MEDCAC chairs, former FDA employees, former HHS employees, and former Congressional staff) committed to improving the health and safety of patients. Specifically, we are writing regarding the plans of the Center for Medicare and Medicaid Services (CMS) to provide broader coverage of Leqembi (lecanemab) and other similar treatments for Alzheimer's disease through one or more registries, following the Food and Drug Administration's (FDA) traditional approval of the drug on July 6.

We support the need for additional information about the safety and efficacy of Leqembi, since the data that served as the basis of FDA approval raise many essential questions about the drug's safety and efficacy. While randomized clinical trials are the best way to establish that meaningful clinical benefit will outweigh the harms, we are optimistic that evidence gathered in patient registries will provide important information about these questions. In requiring registries for this new class of treatments, we recognize the importance of minimizing burden on clinicians and patients while still protecting patient safety; however, CMS's primary goal must be to gather the evidence needed to determine whether FDA-approved monoclonal antibodies for the treatment of Alzheimer's disease are reasonable and necessary for the Medicare population. That goal thus requires that all critical data be included in publicly accessible registries as a condition of coverage.

Toward realizing this goal and maximizing the benefit of the registry for CMS as well as patients, clinicians, and researchers, we are writing now to share our collective expertise.

- Most importantly, we support CMS' plan for its Leqembi registry because the data from the registry will be available for CMS to analyze, and it is our understanding that FDA and outside researchers will also have access to independently statistically analyze the data. However, we are very concerned that Leqembi registries developed by medical societies, medical centers, nonprofit organizations, or other non-governmental entities may limit access to their respective population-level data, potentially making it difficult

for CMS and other researchers to conduct independent analysis of the data. Since Medicare coverage for Leqembi is dependent on participation in a registry, with the goal of answering important questions about the benefits and risks of this drug for the Medicare population, coverage should not be provided for registries that fail to appropriately share data. More specifically, as a condition of coverage, CMS should require that population-level data from any and all registries be made available to CMS (and preferably other researchers as well) to be independently statistically analyzed, and that all registries, whether government-sponsored or privately maintained, obtain a baseline level of information.

- We are also concerned about the potential for lack of consistency of data collected in different registries. Using the same measure of cognitive impairment, for example, is essential to make sense of the results of the registry. If different measures are used by different registries, and those registries also vary in terms of the diversity of patients or other variables studied, it will be difficult if not impossible to draw conclusions about the impact of Leqembi on the primary endpoint of interest, which is cognitive impairment, or other essential endpoints pertaining to safety.

- We also strongly recommend that the CMS registry and any other Alzheimer's treatment registries include information regarding patients who are homozygous for a genetic mutation known as APOE ε4 or who are taking anti-platelet or anti-coagulation blood thinners. Given the well-established concerns regarding those types of patients, in addition to the boxed warning on the Leqembi label and the post-market requirements that the FDA has recently made public, those data are necessary to ensure that the registry data will provide essential information about the patients that are likely to be most at risk for harm from Leqembi. The failure of the CMS registry or any other Alzheimer's treatment registries to not include that information would raise serious ethical questions.

As you are well aware, Alzheimer's is a complex disease and our understanding of its causes, progression and symptoms is continually evolving. Leqembi is specifically approved for very early Alzheimer's and mild cognitive impairment caused by Alzheimer's, either of which would be diagnosed based on amyloid beta plaques on the brain. However, mild cognitive impairment is a common condition that is not necessarily caused by Alzheimer's disease, even when amyloid beta plaques are present on the brain; this can therefore result in a misdiagnosis. In fact, many people with amyloid plaques have no evidence of Alzheimer's disease,[1] and there are numerous studies indicating that mild cognitive impairment can be reversed with changes in medication (such as reducing the use of antihistamines, sleeping aids, and anti-anxiety medications), and

[1] Penn Medicine News. (2019). Measuring the brain's amyloid buildup less effective in identifying severity, progression of Alzheimer's disease compared to other imaging methods. https://www.pennmedicine.org/news/news-releases/2019/august/measuring-brains-amyloid-buildup-less-effective-alzehimers-disease-compared-imaging-methods

improvements in social interactions, sleeping habits, diet, and exercise.[2,3,4] As a result, CMS and researchers' access to this information from all Leqembi registries is needed to determine the risks and benefits of Leqembi for Medicare patients.

In closing, we would appreciate the opportunity to speak with you or your designee regarding the registries to be used for Leqembi in the near term and we look forward to working together to support patients with Alzheimer's disease.

Thank you in advance,

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[2] Shimada, H., Doi, T., Lee, S. et al. (2019). Reversible predictors of reversion from mild cognitive impairment to normal cognition: a 4-year longitudinal study. *Alzheimer's Research & Therapy.* 11, 24. https://doi.org/10.1186/s13195-019-0480-5

[3] Montero-Odasso, M., Zou, G., Speechley, M., et al. (2023). Effects of exercise alone or combined with cognitive training and vitamin D supplementation to improve cognition in adults with mild cognitive impairment: a randomized clinical trial. *JAMA Network Open.* 2023;6(7):e2324465. doi:10.1001/jamanetworkopen.2023.24465

[4] Petersen, R., Lopez, O., Armstrong, M. et al. (2018). Practice guideline update summary: Mild cognitive impairment report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology;*90:126-135. https://n.neurology.org/content/neurology/90/3/126.full.pdf, see page 128 for information on reverting from MCI.

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