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

June 27, 2024

Docket No. FDA–2013–D–0077 re: Early Alzheimer's Disease: Developing Drugs for Treatment; Draft Guidance for Industry

To whom it may concern,

Thank you for this opportunity to provide a public comment on the March 2024 draft guidance "Early Alzheimer's Disease: Developing Drugs for Treatment." We appreciate FDA's efforts to increase clarity for Sponsors conducting clinical trials in Early Alzheimer's Disease.

Our feedback is centered on the special population of adults with Down syndrome who have or are at risk of Down syndrome-associated Alzheimer's disease (DS-AD), for whom we represent. People with Down syndrome have a 90% risk of developing Alzheimer's disease, with initial signs and symptoms that could present as early as in their forties, and on average receive their diagnosis at age 54, decades before the general population. Alzheimer's disease currently is associated with 70-80% of deaths in adults with Down syndrome (Fortea, 2021). In addition, to date no one with Down syndrome has been included as a participant in a clinical trial of any anti-amyloid antibodies, approved or not. The patient with DS-AD and the caregiver community believe that the cognitive disability associated with Down syndrome should not be a barrier to inclusive and equitable drug development practices.

As FDA considers revisions to this guidance, we hope FDA will address inclusion of the DS population in early AD clinical development programs. The guidance revisions are a critical opportunity to remove the regulatory uncertainty for Sponsors interested in conducting clinical trials in the DS population and help rectify the exclusion of our population from clinical trials. In furtherance of this goal to explicitly recognize DS-AD as being included within the sporadic AD indication, we hope that FDA will consider the following suggested revisions:

1) It is our understanding that FDA considers DS-AD and sporadic AD the same condition, such that an approval for a sporadic AD indication subsumes DS-AD even though DS-AD is not explicitly mentioned in product labeling; we appreciate that it is not possible, nor appropriate, for FDA to list out all possible subpopulations in approved labeling; however, there is uncertainty amongst Sponsors developing drugs for sporadic AD and/or DS-AD as to whether the Agency views these as distinct conditions; we kindly request that FDA address this in its guidance to provide certainty to all stakeholders;
2) In the draft guidance please add Stage 0 (at line 103) to represent the full continuum of progression of AD in accordance with the recently issued draft AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease

guidelines; we would request that DS-AD be used an example of a Stage 0 population that is highly enriched for assessment in this early stage; and

Further, we recognize that explicit inclusion of the DS-AD population in this guidance may raise questions for Sponsors and Agency personnel as to what differences in general clinical development approaches are appropriate when DS-AD patients are included in trials or in trials specific to DS-AD patients. For example, here are three important factors to consider:

- The stages of eligibility (lines 101-133) would require clinical consensus specific to the DS-AD population given cognitive differences relative to the general sporadic AD population (as noted by FDA in 2021 LuMind-IDSC-convened Critical Path Innovation Meeting, or CPIM) and such a consensus-building project is ongoing and is expecting completion sometime in 2025 (see https://lumindidsc.org/down-syndrome-research-in-action/policy).
- The biomarker staging cut-points for DS-AD will need to be established. Work for that is currently ongoing.
- Different clinical endpoints will be needed to measure a clinically meaningful change in treatment of AD in people with Down syndrome (as was also a topic of much discussion at the 2021 CPIM).

We believe it is appropriate to acknowledge these limitations in guidance, while also encouraging Sponsors to include DS-AD patients in their development programs, and denoting that Sponsors are encouraged to meet with FDA to discuss such inclusive programs.

We thank the FDA for considering these comments, which are intended to reduce barriers to clinical trials in DS-AD and even encourage such development. We are available as a resource in the consideration of these comments, including to answer any questions.

Best regards,

Hampus Hillerstrom

President & CEO, LuMind IDSC Foundation

References

de Graaf G, Buckley F, Skotko BG. People living with Down syndrome in the USA: BIRTHS AND POPULATION. Factsheet updated: May 7, 2022 | https://go.dselink.net/us-population-factsheet .

Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. Lancet Neurol. 2021 Nov;20(11):930-942. doi: 10.1016/S1474-4422(21)00245-3. PMID: 34687637; PMCID: PMC9387748.

AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: https://aaic.alz.org/diagnostic-criteria.asp .

Kyprianou N, Hendrix J, Hillerstrom H, Grimm R, Kirova AM, Rubenstein E. Caregivers' perception of adults with Down syndrome willingness to participate in research. J Intellect Disabil Res. 2023 Apr;67(4):352-361. doi: 10.1111/jir.12999. Epub 2022 Dec 21. PMID: 36543755; PMCID: PMC11079918.