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

RE: The FDA's reckless decision to approve aducanumab for treating Alzheimer's disease

Dear Secretary Becerra:

Public Citizen is writing to express its outrage over the Food and Drug Administration's (FDA's) indefensible decision to approve Biogen's aducanumab (Aduhelm) for treatment of Alzheimer's disease despite the lack of evidence that the drug provides any meaningful clinical benefit plus the fact that the drug has a well-documented risk of potentially serious brain injury.

The FDA's decision to approve aducanumab for anyone with Alzheimer's disease, regardless of severity, showed a stunning disregard for science, eviscerated the agency's standards for approving new drugs, and ranks as one of the most irresponsible and egregious decisions in the history of the agency. The primary beneficiaries of the agency's action are Biogen and its shareholders, who undoubtedly are ecstatic about their soon-to-be-reaped windfall profits from sales of the company's exorbitantly priced but ineffective drug. The damage caused by the FDA's reckless approval of aducanumab to the agency's credibility as a science-based regulatory agency and to public health — and potentially to the financial sustainability of the Medicare program — cannot be overstated.

Public Citizen therefore calls on you to immediately request the resignations or seek the removal of the three officials most responsible for the agency's aducanumab approval decision: Acting FDA Commissioner Janet Woodcock, Center for Drug Evaluation and Research (CDER) Director Patrizia Cavazzoni, and CDER's Office of Neuroscience (ON) Director Billy Dunn.

The litany of flaws in the FDA's review and decision-making process for aducanumab is lengthy and includes the following, among other mistakes: (1) the unprecedented, inappropriately close collaboration between the FDA and Biogen in the analysis of data from the key clinical trials of the drug that dangerously compromised the independence and objectivity of the agency's review of the drug; (2) basing approval on an unvalidated surrogate endpoint — reduction of amyloid-beta plaques in the brain — and incorrectly claiming that this reduction is expected to lead to a reduction in the clinical decline of Alzheimer's disease despite abundant currently available evidence showing no correlation between changes in this endpoint and changes in clinical measures of cognitive function; (3) failure to adequately integrate the thoughtful, science-based input and recommendations of the agency's Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee into the approval decision and to seek additional advice from the

committee before utilizing the Accelerated Approval pathway, which Dr. Dunn explicitly stated at the November 6, 2020, PCNS Drugs Advisory Committee meeting was not being considered for the drug; and (4) approving the drug for *all* types of Alzheimer's disease patients despite the fact that the safety and effectiveness of the drug were assessed in clinical trials that enrolled only patients with *mild* Alzheimer's disease.

The following is a detailed discussion of each of these flaws.

Unprecedented and inappropriate close collaboration between the FDA and Biogen

As we explained in detail in our April 1 letter to you¹ and our December 9, 2020, letter to the Department of Health and Human Services (HHS) Office of Inspector General (OIG),² there was unprecedented close collaboration between the FDA and Biogen before and after the submission of the company's biologics license application (BLA) for aducanumab for treatment of Alzheimer's disease.

Such close collaboration — which was made fully transparent in press releases and presentation documents issued by Biogen and in the unprecedented joint briefing document prepared by the FDA and Biogen for the FDA's PCNS Drugs Advisory Committee meeting on November 6, 2020 — dangerously compromised the independence and objectivity of senior staff and clinical reviewers in the agency's ON in CDER's Office of New Drugs during the agency's review of Biogen's BLA for aducanumab and key data from the two identical pivotal phase 3 clinical trials of the drug. ON Director Dunn supervised the FDA team conducting this review and likely played a key role in the close FDA–Biogen collaboration.

The FDA's unbridled enthusiasm for aducanumab documented in the PCNS Drugs Advisory Committee meeting joint briefing document and echoed in Dr. Dunn's presentation at the November 2020 advisory committee meeting was unsupported by any objective review of data from the pivotal phase 3 clinical trials, which had been terminated early because a planned prespecified interim analysis showed the trials were unlikely to yield evidence that the drug was effective for treating Alzheimer's disease.

Accelerated Approval based on an unvalidated surrogate endpoint

The FDA approved aducanumab for treatment of Alzheimer's disease under its Accelerated Approval pathway based on an unvalidated surrogate endpoint — reduction of amyloid-beta plaques in the brain. In her June 7, 2021, statement announcing the FDA's approval decision, Dr. Cavazzoni asserted that “reduction in [brain amyloid-beta] plaques — a hallmark finding in the brain of patients with Alzheimer's — is expected to lead to a reduction in the clinical decline of this devastating form of dementia.”³ However, the currently available evidence — including evidence from the clinical trials of aducanumab itself — fails to show a correlation between changes in this surrogate endpoint and changes in clinical measures of cognitive function.

¹ <https://mkus3lurbh3lbztg254fzode-wpengine.netdna-ssl.com/wp-content/uploads/2575.pdf>.

² <https://mkus3lurbh3lbztg254fzode-wpengine.netdna-ssl.com/wp-content/uploads/2660.pdf>.

³ <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease>.

Like the prior 22 unsuccessful experimental drugs targeting amyloid-beta that were pursued as potential treatments for Alzheimer's disease over the past two decades, use of aducanumab is predicated on the still-unproven "amyloid hypothesis," which was introduced in the early 1990s and posits that deposition of amyloid-beta plaques in the brain causes the neuronal degeneration seen in Alzheimer's disease.⁴ None of these drugs was shown to be efficacious for treating Alzheimer's disease and many caused serious harm, including worsening of cognition in some cases.⁵

No test to measure amyloid-beta plaques in the brains of living patients was available until the FDA in 2012 approved florbetapir F18 injection for positron-emission tomographic (PET) imaging.⁶ (Note that utility and validity of florbetapir F18 PET imaging for measuring amyloid-beta plaques in the brain has been challenged by some experts in nuclear medicine imaging.⁷) Thus, for drugs targeting amyloid-beta that were being developed as potential treatments for Alzheimer's disease prior to 2012, there was no in vivo test that allowed researchers to assess whether these drugs reduced the accumulation of amyloid-beta plaques in the brains of clinical trial subjects.

Since 2012, clinical testing of several drugs that targeted amyloid-beta in the brain — including the anti-amyloid-beta monoclonal antibodies bapineuzumab⁸ and gantenerumab⁹ and the amyloid-beta antigen CAD 106,¹⁰ — found that the drugs either prevented further accumulation of amyloid-beta in the brain or reduced the amount of amyloid-beta plaques in the brain based on florbetapir F18 PET imaging. But for each drug, there was no evidence that the drugs were effective in preventing cognitive decline.

Most importantly, although the clinical trials of aducanumab demonstrated amyloid-beta reductions that were greater than those observed for bapineuzumab, gantenerumab, and CAD 106, data from the two phase 3 clinical trials of aducanumab also found no correlation between the reductions in amyloid-beta plaques in the brain and changes in the primary clinical measure for cognitive function in subjects with Alzheimer's disease.¹¹

⁴ Alavi A, Barrio JR, Werner TJ, et al. Suboptimal validity of amyloid imaging-based diagnosis and management of Alzheimer's disease: why it is time to abandon the approach. *Eur J Nucl Med Mol Imaging*. 2020;47(2):225–230.

⁵ Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15(2):73–88.

⁶ Yang L, Rieves D, Ganley C. Brain amyloid imaging — FDA approval of florbetapir F18 injection. *N Engl J Med*. 367(10):885–887.

⁷ Alavi A, Barrio JR, Werner TJ, et al. Suboptimal validity of amyloid imaging-based diagnosis and management of Alzheimer's disease: why it is time to abandon the approach. *Eur J Nucl Med Mol Imaging*. 2020;47(2):225–230.

⁸ Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):322–333.

⁹ Ostrowitzki, S, Lasser RA, Dorflinger E, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther*. 2017;9(1):95.

¹⁰ Vandenberghe R, Riviere ME, Caputo A, et al. Active A β immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. *Alzheimers Dement*. 2016;3(1):10–22.

¹¹ <https://www.fda.gov/media/143504/download>. PDF page 66.

Failure to adequately integrate the scientific input of the PCNS Drugs Advisory Committee and to reconvene the committee for advice on use of the Accelerated Approval pathway

In the discussions that followed presentations made by Biogen and the FDA's Dr. Dunn at the November 2020 meeting of the PCNS Drugs Advisory Committee that was convened to consider whether aducanumab should be approved, several committee members voiced critical comments and pointed questions that reflected deep skepticism about the post hoc analyses of the two key phase 3 clinical trials of the aducanumab that had been conducted collaboratively by Biogen and the FDA.

During the subsequent discussion of the eight questions that the FDA asked the advisory committee members to address, the advisory committee members unleashed a torrent of appropriately harsh criticism of the post hoc analyses of the aducanumab clinical trial data; the nature and organization of the questions posed by the FDA; the FDA's collaborative review process; and the one-sided briefing document that had been jointly written by Biogen and the FDA (see our December 9, 2020, letter to the HHS OIG for details¹²).

Ultimately, in a near unanimous vote (10 of 11 members, with one member expressing uncertainty), the advisory committee members concluded that there was not sufficient evidence that aducanumab was effective based on the primary clinical outcome measure for cognitive function used in the two phase 3 clinical trials of the drug.

During the November 2020 advisory committee meeting, in response to a question from one advisory committee member about the lack of correlation between the observed changes in amyloid-beta plaques in the brain on the florbetapir F18 PET imaging and changes in measures of cognitive function in the clinical trials of aducanumab, Dr. Dunn explicitly stated that the agency was "not using amyloid as a surrogate [endpoint] for efficacy."¹³ Likewise, at a later point in the meeting during further discussion of this lack of correlation, FDA clinical reviewer Kevin Krudys stated that "it's not like changes in beta-amyloid are being used as a surrogate [endpoint] here."¹⁴

These statements by Dr. Dunn and Dr. Krudys signaled to the advisory committee members that the FDA did not intend to use the Accelerated Approval pathway to approve aducanumab and were highly pertinent to the committee's deliberations given that some committee members highlighted the lack of correlation between the observed changes in amyloid-beta plaques in the brain and changes in cognitive function in the clinical trials of aducanumab. For example, one committee member noted the following:

But in the larger context of the discussion today, particularly with relevance to the impact of aducanumab and slowing some of disease progression, the question is whether lowering of brain amyloid burden as evidenced by PET imaging results in a clinical benefit. I think those are very distinct questions, but I think one follows the other very logically.

¹² <https://mkus3lurbh3lbztg254fzode-wpengine.netdna-ssl.com/wp-content/uploads/2660.pdf>.

¹³ <https://www.fda.gov/media/145691/download>. PDF page 140.

¹⁴ <https://www.fda.gov/media/145691/download>. PDF page 236.

With regard to this question, I think the data are far less compelling. I would point to slide 20 of the FDA statistical reviewer's presentation, where you examine the relationship between change in global brain amyloid burden at week 78 in individuals exposed to high-dose aducanumab and change in the CDR sum of box scores [the primary clinical outcome measure for cognitive function]. There really appears to be no relationship either in Study 302 or [Study] 301 [the two phase 3 clinical trials of aducanumab], and this appears to be the case even when the analysis is restricted to only individuals exposed to the [high] 10-mg per kilogram dose.

I think there are some larger implications of these findings which we are not tasked with discussing today. One of the larger questions relevant to these observations is whether lowering brain amyloid burden is in fact the correct target in Alzheimer's disease, but like I said, I think that's beyond the remit of the discussion today.

Despite (1) the advisory committee's overwhelming opposition to FDA approval of aducanumab because the available evidence showing a lack of substantial evidence that the drug provided clinically meaningful benefit based on cognitive function measures and (2) the agency's explicit signal to the advisory committee members that it did not have any intention of using the Accelerated Approval pathway to approve the drug, the FDA nevertheless seven months later approved the drug under the Accelerated Approval pathway based on an unvalidated and highly suspect surrogate outcome.

Before making the momentous, unwarranted decision to approve aducanumab for treating Alzheimer's disease patients under the Accelerated Approval pathway, the FDA should have convened another public meeting of the PCNS Drugs Advisory Committee to obtain further independent expert input on whether the reduction in brain amyloid-beta plaques seen in the clinical trials was an appropriate surrogate outcome to justify such action. The committee also should have been asked whether approval of the drug under such circumstances — assuming there was a sound rationale for doing so — should have been limited to a subset of Alzheimer's disease patients, such as those with mild Alzheimer's disease.

Instead, it appears that the FDA's decision to approve aducanumab was preordained and that the agency had no interest in seeking further input from the advisory committee because of the potential for a further rebuke of the agency's assessment of the drug and another advisory committee vote opposing approval.

The FDA's utter disregard for the advisory committee's expert input demonstrates an abject failure of the agency to adequately integrate the scientific input and recommendations of the PCNS Drugs Advisory Committee into the agency's review and decision-making process. The agency's obvious disdain for the advisory committee's input prompted three members to publicly announce their resignations from the committee last week. One of these resigning committee members — Dr. Aaron Kesselheim, Professor of Medicine at Brigham and Women's Hospital and Harvard Medical School — eloquently explained his reasons for leaving the committee in his scathing resignation letter as follows:

But after my experience on this Advisory Committee for both the eteplirsen [a drug for Duchenne muscular dystrophy that was approved by the FDA in 2016 under the Accelerated Approval pathway] and now the aducanumab discussions, it is clear to me that FDA is not presently capable of adequately integrating the Committee's scientific recommendations into its approval decisions...

For both eteplirsen and aducanumab, the decisions by FDA administrators to ignore the Advisory Committee's clear recommendations led to their approval of two highly problematic drugs that offered little evidence that they would meaningfully benefit patients suffering from these devastating conditions. This will undermine the care of these patients, public trust in the FDA, the pursuit of useful therapeutic innovation, and the affordability of the health care system.

For these reasons, I feel I can no longer make a useful contribution as a member of this Advisory Committee. The aducanumab and eteplirsen debacles demonstrate that the agency needs to reassess its decision-making processes, including how drug candidates are selected for [Advisory Committee] review, which questions are put to the Committee and how those questions are worded, how anecdotal patient experience with drugs is presented to the committee, and how Committee recommendations are used (or ignored) by FDA officials. When clear [Advisory Committee] recommendations against a drug are overruled by FDA administrators, as occurred in both these instances, the agency owes it to the nation to provide a detailed justification.

In the future, reforms in these areas could allow outside experts to be better able to provide meaningful input into the FDA approval process. Should this occur, I would look forward to the possibility of rejoining a committee if and when it becomes clear that our input as experts will be fairly sought and help support appropriate decision-making that is truly in patients' best interests.¹⁵

Approving aducanumab for *all* types of Alzheimer's disease patients

Aducanumab was initially tested in a phase 1 clinical trial that exposed 53 subjects with mild-to-moderate Alzheimer's disease to single doses of aducanumab (ranging from 0.3 to 60 milligrams/kilogram (mg/kg)) and a phase 1b randomized, placebo-controlled trial that tested aducanumab at fixed dosages ranging from 1 to 10 mg/kg every four weeks for 14 doses in 196 subjects with prodromal Alzheimer's disease (the very early form of the disease) or mild Alzheimer's disease dementia. Biogen subsequently launched two identical phase 3, randomized, placebo-controlled clinical trials to evaluate the safety and efficacy of two dosing regimens of aducanumab in subjects with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia.¹⁶

¹⁵ <https://pbs.twimg.com/media/E3jKN4GWYAUGj9U.png>.

¹⁶ <https://www.fda.gov/media/143502/download>. PDF page 22.

Thus, the safety and efficacy of serial monthly doses of aducanumab were evaluated only in subjects with very early or mild Alzheimer's disease, not subjects with moderate or severe disease.

Yet the FDA inexcusably approved aducanumab “for the treatment of Alzheimer's disease,”¹⁷ meaning Biogen can market the drug for use in any patient with Alzheimer's disease, regardless of disease severity, despite the complete absence of any evidence that the drug is safe and effective for patients with moderate or severe Alzheimer's disease. Such an action by the agency was not evidence-based and defied reason given that patients with moderate or severe Alzheimer's disease plausibly could be more susceptible to the adverse brain effects caused by the drug than patients with mild Alzheimer's disease.

Conclusions

The correct decision regarding Biogen's BLA for aducanumab for treating Alzheimer's disease was obvious: The FDA should have rejected the drug and required that the company conduct another large, placebo-controlled clinical trial *before* giving any further consideration to approving aducanumab to treat Alzheimer's disease.

Approving aducanumab despite the lack of evidence of effectiveness has raised false hope for millions of Alzheimer's disease patients and their families, threatens to bankrupt the Medicare program because of the drug's exorbitant price (not to mention the additional costs of serial MRI scans that will be needed to monitor for the drug's adverse effects on the brain), and will impede for years the development of other experimental treatments for this devastating disease.

The FDA's non-evidence-based decision to approve aducanumab ultimately represents the pinnacle of the agency's egregious disregard for science. Under the leadership of Dr. Woodcock over the past three decades, the relationship between the FDA's CDER and the pharmaceutical industry has grown ever cozier — resulting in regulatory capture of the agency by the industry — and the agency's standards for approving new drugs have gradually eroded. The approval of aducanumab sets the bar for ensuring the safety and effectiveness of new drugs at a dangerous new low, not just for future Alzheimer's disease drugs but also for future drugs for a wide array of other diseases. The FDA no longer is the world's gold standard for drug approval and safety.

As HHS Secretary, you must take immediate action to mitigate the damage caused by the FDA's approval of aducanumab to the agency's credibility as a science-based regulatory agency and to public health and to avoid potentially catastrophic impacts to the financial sustainability of the Medicare program and our health care system more broadly.

We therefore urge you to immediately request the resignations or seek the removal of the three individuals most responsible for the agency's aducanumab approval decision: Acting FDA Commissioner Janet Woodcock, CDER Director Patrizia Cavazzoni, and CDER's ON Director Billy Dunn. New leadership of the FDA and CDER is a prerequisite for restoring the agency's

¹⁷ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf.

credibility and reversing the slide in the agency's standards for ensuring the safety and effectiveness of new drugs.

You should direct the next Acting FDA Commissioner to consider whether the agency's approval of Biogen's BLA for aducanumab should be withdrawn.

Finally, we reiterate our April 1, 2021, request for you to ask the HHS OIG to initiate a thorough investigation of the unprecedented close collaboration between the FDA and Biogen that occurred before and after the submission of Biogen's BLA for aducanumab for treatment of Alzheimer's disease. Fully understanding the extent to which that close collaboration undermined the integrity and independence of the FDA's review of aducanumab will be essential to rebuilding public trust in the agency.

Thank you for your attention to these urgent public health issues. We would welcome an opportunity to meet with you or your senior staff to discuss these issues. Please contact me at 202-588-7781 or mcarome@citizen.org if you have any questions.

Sincerely,



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

cc: The Honorable Rachel Levine, Assistant Secretary for Health, HHS