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RE: FDA-2024-N-1869 Response for BLA 761248

Dear Dr. Buracchio:

1. Background

The FDA has called a meeting where presentations will be heard, viewed, captioned, and recorded through an online teleconferencing and/or video conferencing platform. The Committee will discuss biologics license application 761248 for donanemab solution for intravenous infusion, submitted by Eli Lilly and Co., for treating early symptomatic Alzheimer's disease.

The FDA is inviting Interested persons to present data, information, or views on issues pending before the committee, orally or in writing. FDA is establishing a docket for public comment on this meeting. The docket number is FDA-2024-N-1869.

This document is our submission in response to the FDA invitation, highlighting the scientific rationale for not only rejecting the biologics license application 761248 but also declaring that unless proof of substantial antibody exposure into the brain is established, future INDs may not be allowed.

2. Introduction

Causality aside, all neurodegenerative disorders end up with autoimmune responses attacking rogue proteins, along with brain tissue, leading to all known symptoms. Antibodies that can selectively remove rogue proteins were an obvious choice, but after decades of efforts, two antibodies to treat Alzheimer's disease were approved, and dozens were tested clinically; one, aducanumab, was withdrawn, and the other, donanemab, is now subject to review by the FDA, whether it should be approved. Other antibodies bapineuzumab, solanezumab, crenezumab, gantenerumab, lecanemab (approved), continue struggling to demonstrate their efficacy. However, this outcome should have been evident since their passage across the blood-brain barrier (BBB) is severely restricted. The INDs issued for these products were unjustified and tantamount to human abuse (1).

More relevant to donanemab that is intended for early Alzheimer's disease treatment is the FDA guidance, "Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry" issued in March 2024 (2) to assist sponsors in the clinical development of drugs for the treatment of the stages of sporadic Alzheimer's disease (AD) that occur before the onset of overt dementia (i.e., Stages 1 through 3). Historically, clinical criteria that defined later stages of AD, after the onset of overt dementia, were used for enrollment in clinical trials. This guidance allows enrollment of subjects with AD at earlier stages of the disease, in which there may be minimal or no detectable abnormality on clinical assessments. The diagnostic criteria are well defined based on true biological presence of AD rather than criteria based on syndromic or other definition.

3. Perspective

Neurodegenerative diseases (NDs) are complex disorders with multifactorial pathology that result in progressive damage to neuronal cells and loss of neuronal connectivity, ultimately leading to impaired mobility and cognition. Protein aggregation due to misfolding and oligomerization gives rise to extracellular or intracellular inclusions, a common hallmark for many NDs. Further spreading, such as those of amyloid aggregates in the nervous system, are like prion-based infections; hence, a prion-like mechanism is often considered a significant element in the etiology of NDs (3).

In the past few decades, many of the genetic and biochemical causes underlying NDs associated with protein aggregation were uncovered, leading to the distinction between rarer familial forms, where disease-causing mutations are genetically inherited, and the more common sporadic forms, where genetic and environmental risk factors drive the pathogenesis (4). In both cases, the affected proteins are found enriched in pathological aggregates, highlighting their importance in the manifestation of the disease.

In AD, two different types of deposits are observed. The aberrant cleavage products of the transmembrane protein Aβ precursor protein (APP) form extracellular plaque deposits in the temporal and parietal brain regions. In contrast, the protein tau (MAPT) accumulates intracellularly in neurofibrillary tangles (5).

In Parkinson's disease (PD), the primarily affected brain area is the substantia nigra (SN), where α-synuclein (α-syn; SNCA) aggregates are found to accumulate in dopaminergic neurons (6).

In ALS, cellular aggregates of superoxide dismutase 1 (SOD1), RNA-binding protein FUS (FUsed in Sarcoma), and TAR-DNA–binding protein 43 (TDP-43) have been identified in motor neurons of the primary motor cortex, brainstem, and spinal cord (7).

However, despite the accumulated knowledge and the many clinical, no therapeutic strategy has proven successful to cure any of the NDs. This led many scientists even to question whether protein aggregation is central to ND etiology or a manifestation of other underlying causes (8, 9). However, despite failures, the developers keep repeating the testing of similar drugs, even when the failures are apparent, perhaps due to the lack of other options and the need to have an active portfolio for one of the most lucrative markets for new drugs.

4. Current Status

There are 141 drugs being tested in clinical trials for the treatment of Alzheimer's disease. More than three-fourth of these drugs are designed to try and slow down how quickly the disease progresses (10). More recently, monoclonal antibodies have been introduced to treat NDs without any delivery support to enhance their transmission across the blood-brain-barrier (BBB).

Antibody bioavailability in the brain is low, often cited to be around 0.1% of circulating serum concentrations (11). Multiple groups have observed that CNS exposure for circulating biologics is limited to 0.1 to 0.4% of corresponding serum concentrations (12-14), although some estimates for transporting immunoglobulins into neural tissue are far lower (15). Consequently, the maximal brain concentration for peripherally dosed large molecules will always be insufficient to achieve the target engagement required for a therapeutic response (16, 17). Administration methods such as intracranial, intrathecal, or intraventricular injections and chemical BBB disruption may facilitate higher brain concentrations for some drugs. Still, these approaches are invasive and incompatible with repeat dosing regimens (18-20).

In the past, several antibody candidates have failed to meet clinical endpoints. *Bapineuzumab* (the humanized version of the murine 3D6) was the first anti-Aβ antibody that entered clinical trials. It binds to the N-terminal end (amino acid 1-5) and thus binds all forms of Aβ (21). Despite showing reductions of Aβ plaques, *bapineuzumab* studies were terminated because it lacked treatment effects in two phase 3 trials. Side effects related to vascular Aβ were also raised as a concern (22). Clinicaltrials.gov lists around 250 interventional studies that treat NDs involving antibodies (23).

Despite the well-established barriers to crossing the BBB, in 2021, the FDA conditionally approved the first such therapy, *Aducanumab*, Aduhelm®)(24). This human IgG1 monoclonal antibody targets amyloid-beta plaques. However, the decision was controversial (25). It was made under an accelerated approval process (26, 27) where the cognitive decline was only slowed in one of two studies at the highest dose (28); soon after the approval, it was discontinued, effective 2024, without reasons (29).

A second therapeutic antibody, *lecanemab* (Leqembi®), was recently granted the same type of approval (January 2023) by the FDA. *Lecanemab* is the humanized version of murine mAb158 with high selectivity for soluble protofibrils (30)). The approval was based on phase 2 clinical data that lecanemab reduced Aβ-plaque load(31). However, results in the phase 3 study slowed overall cognitive decline by 27%. They had positive outcomes on biomarkers and secondary endpoints, further providing evidence of aggregated Aβ as a viable target for treatment in AD (32) (33). The FDA approved Lecanemab in January 2023 but halted further progress on Lecanemab after the withdrawal of aducanumab.

Donanemab is also under development to treat AD (34). In the clinical trials of donanemab among participants with early symptomatic Alzheimer's disease and amyloid and tau pathology, it was claimed to significantly slow down clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology

population (34). In this randomized clinical trial that included 1736 participants with early symptomatic Alzheimer's disease and amyloid and tau pathology, the least-squares mean change in the integrated Alzheimer Disease Rating Scale score (range, 0-144; lower score indicates more significant impairment) at 76 weeks was −6.02 in the donanemab group and −9.27 in the placebo group for the low/medium tau population and −10.19 in the donanemab group and −13.11 in the placebo group in the combined study population, both of which were significant differences. This study does not conclude that the patients will have a lower incidence later in the stage or that the observed difference is sufficient to infer a prospective indication of donanemab (34).

Cinpanemab is one of several α-synuclein antibodies being investigated for PD (35) It is intended to treat ALS and was recalled due to lack of efficacy (36, 37).

For AD treatment, there are also clinical trials MEDI1814, ADEL-Y01, TB006, PF-04360365, and LY2062430, among others.

Other antibodies for PD include ABBV-0805, MEDI1341, LU AF82422, and prasinezumab (https://www.alzforum.org/therapeutics/cinpanemab).

One suggestion to increase the dose is risky as it increases the risk of side effects. The main side effect of anti-Aβ antibodies is “amyloid-related imaging abnormalities” or ARIA, identified by MRI, classified into two subtypes, ARIA-E (edema) and ARIA-H (hemorrhage) (38).

There has been variation in the ability of the monoclonal anti-Aβ antibodies studied in large-scale AD trials to lower insoluble brain Aβ levels (PET-detectable). However, PET is not able to distinguish between parenchymal and vascular amyloid. Therefore, while data showing how much anti-Aβ monoclonal antibodies have decreased PET-detectable Aβ in clinical trials probably primarily reflect these antibodies' effects on neuritic plaques, the data are not exclusive to neuritic plaques as there may also have been some clearance of diffuse plaques and/or CAA-associated Aβ.

A recent meta-analysis reports thirty-three randomized controlled trials with 21,087 patients involving eight mAbs. Despite immunotherapies significantly increasing the risks of adverse events and ARIA, the data suggest that mAbs can effectively improve the cognitive function of patients with mild and moderate AD. According to the NMA, aducanumab was the most likely to achieve significant improvements in different cognitive and clinical assessments (statistically improved MMSE and CDR-SB), followed by donanemab (statistically improved ADAS-Cog and PET-SUVr) and lecanemab (statistically improved ADCS-ADL) (39).

5. Alternate Solutions

Since it is the VH and VL portions of antibodies that bind, shorter forms of antibodies can prove just as effective such as scFv-CH (single-chain variable fragment), Single-chain variable fragment (scFv), scFV-CH3 (Minibodies), Diabody, sdAb (Single Domain Antibody), F(ab)2 Fragments, F(ab) Fragment, Reduced IgG (rIgG), Bispecific antibodies (BsAbs), and Multi-specific Antibodies.

Antibodies produced in llamas and other camelids (such as camels and alpacas) are known as "VHH" antibodies or "nanobodies." These are unique because they are smaller and simpler than conventional antibodies. While the conventional antibodies are made up of two heavy chains and two light chains, the camelid antibodies can exist in a simpler form with only heavy chains, naturally devoid of light chains. This variable is called a nanobody. Nanobodies are approximately 12-15 kDa in size, making them much smaller than conventional antibodies (about 150 kDa). Nanobodies are highly stable, resistant to extreme conditions such as high temperatures and low pH and can be easily produced in microbial systems. They have a strong binding affinity and can recognize unique epitopes that conventional antibodies might not be able to bind. The smaller size of nanobodies gives them a slight advantage over conventional antibodies in crossing the blood-brain barrier (BBB), although their passive diffusion is still limited. So far, no nanobody has been tested in humans to treat any ND, a possibility that should encouraged and promoted by the FDA.

It is worthwhile noting that if the size of an antibody is too small, it will be cleared fast through kidneys, making it less effective. There is also no assurance that just being small is sufficient to ensure transit across the BBB. However, there remains uncertainty that can be overcome by capitalizing on the transcytosis of antibodies and their fragments that occur through several mechanisms, including receptor-mediated transcytosis (RMT), adsorptive-mediated transcytosis, and cell-mediated transcytosis (40, 41). One of the most exploited receptors for RMT is the transferrin receptor (TfR), which naturally facilitates iron transport into the brain. Antibodies designed to target the TfR can hitch a ride across the BBB through this mechanism. Another example is the insulin receptor, which has also been targeted for RMT to deliver antibodies into the brain.

Antibodies can be engineered to bind to TfR directly or through transferrin. When engineering the antibody, it should preferably bind to a different epitope than Tf on the TfR to avoid interference with the endogenous process of iron delivery to the brain. Many TfR-antibodies bind the apical domain of TfR (42, 43). It should have a moderate affinity for TfR in the nanomolar range (44). High affinity might result in a lower ability of the antibody to dissociate from TfR, which leads to sorting into lysosomes for degradation (45). The dissociation constant might be more critical than the association constant (44). Too low affinity might lead to poor ability of the antibody to bind TfR at the BBB and, consequently, poor brain delivery (46). Affinity can be pH-dependent, so the antibody binds TfR well at physiological pH but dissociates at lowered pH in the early endosome (47).

The first attempt for in vivo binding is the monovalent anti-TfR conjugate based on Roche’s “brain shuttle” technology applied to gantenerumab (Trontinemab) (RG6102), shows an 8-fold higher CSF-to-serum ratio than standard gantenerumab. This Fab fragment binds to the transferrin receptor and is attached to the gantenerumab monoclonal antibody's effector (Fc) domain. This leads to its endocytosis and release of antibodies into the brain parenchyma (48). However, this approach has several drawbacks. First, the binding with transferrin in vivo will always be unpredictable, subject, and highly subjective. Second, the binding nature is specified by the structure of the Fab, which can only be based on natural linkers available in the body. These noncleaving linkers result in exocytosis as the

conjugate inside the cell binds to the receptor and thus returns to general circulation. This property reduces the therapeutic efficacy. While it is anticipated that the Fab binding to transferrin still allows iron binding, this cannot be ensured, possibly affecting the iron transport cycle. As discussed below, the linker between the antibody and its fragment must be cleavable, so upon entering the brain, the linker is broken, blocking the antibody's or the fragment's exocytosis.

Conjugating with transferrin offers the best option of all the choices available for RMT. There are several considerations in designing this conjugate. The linkers should be pH-sensitive and break within the brain environment to prevent exocytosis. Modeling exercises show the stability of aducanumab in Table 1 and donanemab in Table 2.

Table 1. The binding properties of donanemab conjugates.

[NEED TO ADD A PARAGRAPH EXPLAINING THESE VALUES AND HOW WE CONCLUDE THAT BINDING WITH TRANSFERRIN DOES NOT ALTER THE BINDING WITH AMYLOID?]

Protein-protein complex	ΔG (kcal mol^{-1})	K_d (M) at ℃	ICs charged-charged	ICs charged-polar	ICs charged-apolar	ICs polar-polar	ICs polar-apolar	ICs apolar-apolar	NIS charged	NIS apolar
Aducanumab-Abeta	-18.1	$5.10E^{-14}$	22	20	64	1	19	29	21.2	40.1
Transferrin-(G4S)-Aducanumab-Abeta	-21.3	$2.60E^{-16}$	39	27	83	1	18	43	28.5	35.5
Transferrin-$(G4S)_3$-Aducanumab-Abeta	-29.2	$4.10E^{-22}$	32	33	136	7	38	79	28.9	35.7

6. Recommendations

NDs represent one of the most critical disorders that remain untreated; as a result, billions of dollars are spent in finding their treatment modalities; since the target is an antigen, antibodies make a logical choice, but having established unequivocally that these large molecules cannot enter brain in sufficient quantity to be therapeutically effective, there is need for the FDA to make it clear to developers that human studies will not be allowed unless the target product can accumulate in sufficient quantity within the brain. Additionally, the accumulation will be at the binding site, not at the parenchymal level. The inefficiencies of animal models to demonstrate efficacy also need to be reconstituted due to their poor ability to emulate human response. Fortunately, several logical solutions are now available including the use of antibody fragments that are further transported across the BBB through RMT. Further engineering the conjugates to break down in the brain ensures prevention of exocytosis. In our opinion, all antibodies listed above can be made safer and effective by applying these technologies; testing these technologies is a low-cost exercise. Additionally, we recommend exploiting mRNA technology to deliver conjugated antibody-transferrin molecules, that will significantly reduce the development time and cost of development.

7. Conflict of Interest

The submitter of the recommendations made above are a developer of mRNA-based treatments of NDs and own US patents on RMT-based delivery of multiple antibody treatments [www.therarna.com].

Best Wishes.

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