Concurrence Memorandum

June 7, 2021

From: Peter Stein, MD, Director, Office of New Drugs/CDER/FDA

BLA # 761178
Applicant: Biogen Inc.
Proprietary Name: Aduhelm
Established or Proper Name: Aducanumab-avwa

This memo documents support for the accelerated approval of aducanumab for the treatment of patients with Alzheimer's disease. Detailed discussion of the disease background and currently available treatments, and the substantial unmet needs in patients with Alzheimer's Disease (AD), are provided in the Summary decisional memo (from Drs. Buracchio, Yasuda, Bastings, and Dunn; referred to herein as Summary Review) and the Clinical Review by Dr. Krudys. As discussed further below, the review team for this BLA is aligned that the application should be approved, with the exception of the Office of Biostatistics, which does not support approval. This memo documents my concurrence with the accelerated approval of the BLA, including with the Office of Neuroscience's conclusion that the application contains substantial evidence of effectiveness on the surrogate endpoint of reduction in brain amyloid plaque and that the surrogate endpoint is reasonably likely to predict clinical benefit.

Briefly, AD is a neurodegenerative disorder leading to progressive, irreversible destruction of neurons and loss of cognitive function and memory. Over time, patients progress to severe dementia, loss of independence, and death. Over 6 million Americans, ages of 65 and above have AD; it is the 6th leading cause of death in the US. Unfortunately, at present, there are limited treatment options. The approved drugs provide some improvements in cognitive functioning, but do not target the underlying pathology, none are approved for the early stages of the disease, and none have been shown to alter the progressive and severe functional losses. Thus, there is a huge unmet need for new and effective therapies directed at the underlying pathology. Amyloid plaques are a hallmark—and a sine qua non—of AD. These form from beta-amyloid monomers which, in turn, form oligomers and fibrils, are deposited as plaques and then interact with tau fibrils, leading to formation of neuro-fibrillatory tangles (NFT). Targeting amyloid plaques is not a new approach, but one tried unsuccessfully, over the past decades. This point will be discussed later in this memo.

Aducanumab is a human IgG1 anti-amyloid beta (Aβ) antibody targeting amyloid aggregates. The drug is administered by IV infusion every 4 weeks. Binding of antibody is intended to lead to clearance of amyloid from the brain. The development program for this drug included 7 clinical studies in patients and one study in healthy volunteers. This memo will focus on the results of the Phase 2 dose-range finding study (Study 103) and the two Phase 3 studies (Studies 301 and 302). The details of the aducanumab development program are discussed in the Clinical Review by Dr. Krudys, the Office of Clinical Pharmacology (OCP) review, the statistical review by Dr. Massie, and in the Summary Review.

Study 103 evaluated the safety and tolerability of aducanumab and provided useful proof-of-concept and dose-range finding information. The study was a randomized, sequential cohort, double-blind study with a 12-month treatment period in patients with early AD (mild cognitive impairment [MCI] or mild AD dementia). The study included 4 fixed doses of aducanumab (1-, 3-, 6-, and 10 mg/kg every 4 weeks), and a titration cohort dosing up to 10 mg/kg, and placebo (with placebo patients randomized concurrently in each sequential cohort). Based upon this design, the placebo group includes patients non-concurrently

randomized to active treatment groups, limiting the robustness of comparisons of each dose cohort to the overall placebo group. Patients in this study underwent positron emission tomography (PET) brain amyloid imaging (using [18F]-florbetapir), and had pharmacokinetic and exploratory clinical endpoints collected (the Clinical Dementia Rating-Sum of Boxes (CDR-SB), the standard clinical trial endpoint in AD, and the mini-mental status examination (MMSE)). Overall, 197 patients were randomized into the 6 treatment groups (5 active and placebo). Results from this study showed a clear dose- and time-dependent reduction in amyloid plaques as measured by Standardized Uptake Value Ratio (SUVR) with PET imaging. Dose-related numerical reductions relative to placebo for CDR-SB and MMSE were observed that were nominally significant in the 10 mg/kg dose group (p=0.0464 and 0.0356, respectively). These results must be considered with caution given the small group sizes (~30 patients per active treatment group), and high drop-out rate (especially in the 10 mg/kg group), but the dose-related numerical reduction in plaque SUVR and in clinical endpoints is notable.

The sponsor then conducted two Phase 3 studies, Studies 301 and 302. Both were placebo-controlled, double-blind, randomized studies in patients 50 to 85 years of age with prodromal disease (MCI from AD) or mild AD dementia. Patients had to have evidence of brain Aβ pathology by PET imaging. A more complete discussion of the enrollment criteria and study design elements are provided in the reviews by Dr. Massie (Office of Biostatistics/CDER/FDA), Dr. Krudys, and the Summary Review. Both studies evaluated two doses of aducanumab (3 mg/kg and 10 mg/kg; dosing was initially based upon Apoε4 carrier status prior to a protocol amendment).

Both studies were stopped prior to completion by the independent data monitoring committee (IDMC) after meeting pre-specified futility criteria based upon an analysis of pooled study data (with approximately 57% of patients completing the 78-week treatment period). When the studies were unblinded, it was discovered that Study 302 had met criteria for statistical significance for the primary endpoint, while Study 301 showed no suggestion of an effect of drug on the primary endpoint. This unusual pattern of results from two essentially identically designed and conducted studies prompted discussions between the applicant and the Office of Neuroscience that led to a series of further analyses seeking to understand the conflicting study results. Based upon these further analyses, the applicant submitted a BLA for the treatment of patients with AD.

Complete descriptions of both Studies 301 and 302 are provided in the Statistical Review (Dr. Massie), Clinical Review (Dr. Krudys), and the Summary Review, so these will be discussed only briefly here. Study 302, the study that was considered by most on the review team as positive, will be discussed first.

Study 302 randomized 1643 patients with either MCI due to AD (82%) or mild AD dementia (18%). About 88% who could have completed the study (given the early termination) reached the study endpoint at Week 78, with a modest imbalance in patient discontinuations due to adverse events not favoring the active treatment groups. The primary endpoint, evaluating the high dose, was statistically significant with a CDR-SB change from baseline relative to placebo of -0.39 (p=0.0120); the low dose had a non-statistically significant numerical reduction (p = 0.0901). Based upon the prespecified sequence for statistical testing (testing the primary endpoint at the high then the low dose), formal statistical testing stopped based upon the non-significant low dose CDR-SB response; therefore, all other endpoint statistical assessments with p values < 0.05 would be considered only as nominally significant. Evaluation of these endpoints from Study 302 at Week 78 showed that several did meet nominal significance, including MMSE (p value of 0.0493), ADAS-Cog 13 (p value of 0.0097), and ADCS-ADL-MCI (p value of 0.0006). As noted, the statistical testing results on these endpoints was not controlled for multiplicity. The Summary Review makes the point that these secondary endpoints are only modestly correlated with CDR-SB, each applying different methods and distinct instruments, and each evaluating

some non-overlapping domains of cognitive, memory, or behavioral functioning. The fact that these endpoints are derived from separate and distinct approaches to the measurement of important clinical aspects of AD increases the potential relevance of these findings.

The study included a subset of patients (about 30%) who underwent PET scanning using the same methods as discussed above for Study 103 (^{18}F-florbetapir Aβ PET imaging, measured using composite SUVR) and found time- and dose-dependent decreases in amyloid plaque relative to baseline, with nominal p values of < 0.001 at both doses at Week 78. Notably, the baseline characteristics of patients in the PET subgroup in this study, and in Study 301, discussed below, were similar to the overall patient cohort in the respective studies.

Study 301 included 1647 patients with either MCI due to AD (80%) or mild AD dementia (20%) randomized 1:1:1 to the two aducanumab doses and placebo. Overall, 85.5% of patients who could have completed the study (given the early termination) reached the study endpoint, with a modest imbalance in patient discontinuation due to adverse events not favoring the active treatment groups. Baseline characteristics were balanced across treatment groups. Results showed no effect of aducanumab on the primary endpoint of CDR-SB compared to placebo at the 10 mg/kg dose (p of 0.8330). A small, non-significant numerical reduction in CDR-SB relative to placebo was seen at the lower dose of aducanumab. There was also no notable numerical difference in MMSE relative to placebo; other clinical endpoints evaluated (ADAS-Cog 13 and ADCS-ADL-MCI) showed modest numerical trends favoring aducanumab at both doses, none of which achieved nominal statistical significance. The study included a subset of patients (about 35%) who underwent PET scanning in whom time- and dose-dependent decreases in amyloid plaque (SUVR) relative to baseline were observed, with nominal p values of < 0.001 at both doses at Week 78.

The clinical team conducted additional exploratory analyses to try to understand the negative results of Study 301, given the statistically significant findings in Study 302. Several explanations were considered, including an imbalance in rapid progressors, with more in the high dose group, and the titration scheme that led to a reduced high dose in APOE4 carriers (6 mg/kg) prior to protocol amendment 4 which increased the dose in carriers to 10 mg/kg. Analyses presented by Dr. Krudys using propensity score matching to compare subgroups by number of doses received in the 10 mg/kg dosing cohort to placebo suggests that among those patients who received at least 8 doses (vs who only received 1-7 doses), the CDR-SB response to drug in Study 301 was consistent with that seen in Study 302. These analyses, however, must be viewed with caution since they are non-randomized comparisons, and raise the concern regarding differential responses in patients able to remain on study drug relative to patients with earlier discontinuation, and do not alter the importance of the primary observation that the study failed to find any response relative to placebo on CDR-SB with aducanumab treatment. Moreover, a similar pattern of greater response in the 10 mg/kg treatment group in patients who had at least 8 doses vs less than 8 doses was not seen in Study 302, further undermining the strength of this observation.

For further discussion of the limitations of these studies, I refer the reader to the detailed review by Dr. Massie. Briefly, as expected from studies stopped prematurely, there was extensive missing data at Week 78 relative to the planned sample. Moreover, analyzing studies after "failure" was declared from a pre-specified futility analysis raises concerns regarding appropriate control of alpha. In his review, Dr. Massie also suggests that the results of the high dose in Study 302 appears to be driven by the worse placebo response (in APOE+ stratum) that is seen in patients enrolled after implementation of protocol version 4. I find this argument problematic since it compares results from subsets of patients within a treatment group rather than from comparison between intact treatment groups. Further, as noted in the

Summary Review, the effect size on CDR-SB relative to placebo pre- and post-amendment 4 are very similar, not supporting the concern raised by Dr. Massie on this point.

In summary, the program includes a small Phase 2 safety and tolerability study with clinical endpoints assessed (CDR-SB and MMSE) that were nominally significant relative to placebo (using the combined placebo group) in the 10 mg/kg dose group and showed a notable numerical dose-related response relative to placebo for CDR-SB and MMSE; and included two Phase 3 studies, one of which was positive on the primary endpoint (with caveats discussed above of analyses conducted after a trial is stopped), with several secondary clinical endpoints with impressively low p values (even though not corrected for multiplicity, the p values are persuasive). Notably, these endpoints, as discussed above, reflect distinct evaluations of disease severity that have modest correlation with that from the primary endpoint (CDR-SB), elevating the potential clinical relevance of results from these endpoints. On the other hand, Study 301, a comparably designed and conducted study, was entirely negative on the primary endpoint with only numerical point estimates that were only modestly favorable for aducanumab seen on secondary endpoints. Although post-hoc analyses of Study 301 perhaps provide some potential explanations for the negative results, these are insufficient for us to dismiss the results from Study 301 as non-relevant to the assessment of aducanumab effectiveness.

I note that Dr. Krudys and the OCP team both recommended standard approval for aducanumab. This recommendation rests upon their views of the strength of evidence from Study 302 (with the explanations for the negative results in Study 301), the exposure-response (PK-clinical endpoint) relationship (see the OCP review for discussion of this relationship), and the relationship between changes from baseline in PET SUVR for amyloid plaque and CDR-SB. In addition, the OCP team conducted a probability analysis of the findings on efficacy endpoints in Studies 301 and 302 and report that the numerically favorable results observed would be highly unlikely to occur by chance alone. They conclude that these results support substantial evidence of effectiveness of aducanumab. This argument considers Study 302 as the single adequate and well controlled positive trial, and the other results, such as from Study 103, as confirmatory evidence, and frames Study 301 as essentially non-contributory (in either a positive or negative manner) to the decision.

Despite the reasonable arguments to support standard approval from Dr. Krudys and the OCP team, I agree with the Office of Neuroscience that the evidence is not sufficiently compelling or persuasive to meet the substantial evidence standard for standard approval. My assessment is based on the following reasons. First, both Phase 3 studies were stopped for futility and were revisited after analyses showed disparate effects in the two trials. Conclusions from studies stopped for futility must be viewed with some caution, given the limits on strong control of alpha from what are, in essence, post-hoc analyses. This is exacerbated, as Dr. Massie points out, by the large proportion of missing information (especially for Week 78). Second, even though the results of Study 302 appear to be generally believable and supportive of effectiveness of aducanumab with respect to clinical endpoints (acknowledging that the secondary endpoints at the high dose with p values < 0.05 are only nominally significant), we are still left with a negative Phase 3 study (Study 301), a similarly designed study that failed to substantiate the findings of Study 302. Independent substantiation is the gold-standard basis for generating confidence in any initial scientific study finding. The statistical review by Dr. Massie provides a detailed assessment of all three studies, raising numerous concerns, only some of which are noted above. I refer the reader to this review. My assessment, as noted above, is that with Phase 3 studies stopped for futility (and the consequent limitations) and the failure to substantiate the one positive study, there is not sufficient support for substantial evidence of effectiveness with respect to clinical benefits for aducanumab to support standard approval.

Nonetheless, I agree that the results discussed above strongly suggest that treatment with aducanumab may result in clinical benefit. It is difficult for me to believe that the findings discussed by Dr. Krudys and the OCP team from Studies 103 and 302 are entirely explained by the play of chance. Although there are limitations of the analyses conducted by OCP in an attempt to quantify the probability that aducanumab is effective with respect to clinical endpoints, I note that the analyses do not conclude that the drug is likely ineffective. FDA, then, is faced with a situation where the available evidence on the clinical endpoints is short of what we would require for standard approval of aducanumab. At the same time, patients with AD have a serious, progressive, ultimately fatal disease and are desperate for treatments that delay progression and prolong well-functioning survival.

The present situation—where there is residual uncertainty regarding the clinical benefit of aducanumab but there is substantial evidence of effectiveness on an endpoint that is reasonably likely to predict such benefit—means that consideration must be given to accelerated approval (AA). AA is an approval pathway that is intended to provide earlier access to drugs for serious diseases with unmet medical needs, yet where there is some uncertainty at the time of approval regarding the drug's ultimate clinical benefit. Drugs approved through the AA pathway must provide a meaningful advantage over available therapy and demonstrate an effect on an endpoint that is reasonably likely to predict clinical benefit. This endpoint can either be a surrogate or an intermediate clinical endpoint (a clinical endpoint that can be measured earlier than irreversible morbidity or mortality). With regard to the surrogate endpoint, FDA guidance (*Expedited Programs for Serious Conditions – Drugs and Biologics*, 2014) notes that "*determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship*." The guidance gives detailed information about how to consider whether a surrogate is reasonably likely to predict clinical benefit, noting that "*the extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome."* It is important to note that the standard of substantial evidence still applies to the accelerated approval pathway and that FDA has generally considered substantial evidence of effectiveness to be necessary to support licensure of a BLA. However, for AA, FDA must conclude that there is substantial evidence demonstrating the drug's effect on the surrogate endpoint.

I concur with the Office of Neuroscience's conclusion that this pathway is applicable and appropriate for the approval of aducanumab, and I will explain my rationale in the next paragraphs.

First, as already discussed, AD is a serious disease with important unmet medical needs. The drugs approved for AD provide some symptomatic benefit, but do not have the potential to alter the underlying pathology of disease and thereby alter disease progression, as does aducanumab. Second, the reduction in amyloid plaque by PET imaging can serve, as discussed in detail below, as a surrogate reasonably likely to predict clinical benefit (referred to as a "reasonably likely surrogate" for the purpose of this memorandum).

PET imaging results from both the Phase 2 and 3 studies (Study 103 and Studies 301 and 302) consistently, and persuasively (with very low p values), show that aducanumab reduces Aβ plaque (decrease relative to baseline and placebo in SUVR plaque), in relevant brain regions. These changes were time- and dose-dependent, and, as discussed by OCP in their review, there is an exposure-response relationship for plaque SUVR (see Figure 3, OCP review). Thus, there is substantial evidence based upon

results from two adequate and well-controlled (AWC) trials (Studies 301 and 302) and supported by findings from Study 103 that aducanumab reduces Aβ plaque in the brains of patients with AD.

The next issue is whether reduction in amyloid plaque is reasonably likely to predict clinical benefit. The conclusion that change from baseline in plaque is a reasonably likely surrogate is supported by two sources of evidence, the role of amyloid in the pathogenesis of AD and the strong group-level relationship between the change in amyloid plaque by PET imaging and the change from baseline in CDR-SB.

As discussed already, amyloid plaque is a hallmark of AD—it is a defining and required feature of the disease. Since the initial amyloid cascade hypothesis was described decades ago, research has shown that the role of amyloid and amyloid plaques in the pathogenesis of dementia is more complicated than originally thought. It is now clear that there are different types of amyloid fibrils that appear to have different pathological roles. Further, it is now clear that amyloid fibrils and plaques are a necessary but not sufficient condition for AD; tau fibrils must interact with amyloid fibrils and plaque to generate the NFT that are a key pathological mechanism of neuronal damage. However, it is reasonable to conclude that the essential role of plaque in the mechanism of AD supports the potential for benefit of a drug that reduces amyloid plaque by increasing plaque clearance.

Several different classes of agents that have targeted amyloid plaque, including amyloid-directed monoclonal antibodies, however, have failed to demonstrate clinical effectiveness. Although the prior negative studies of amyloid-directed antibodies may raise concern about the therapeutic value of targeting amyloid plaque in the treatment of AD, it is important to recognize that these previously studied antibodies were directed at different epitopes or types of fibrils (leading to different ability of the antibody to clear plaque), had different potency, and, most importantly, generally did not substantively reduce amyloid plaque by PET imaging. Moreover, the studies of these antibodies included patients who did not have amyloid plaques (and therefore did not have AD) or patients with AD at later stages of disease that may no longer have been responsive to treatment.

It is also worth noting that in the scientific literature of AD, there is not an overall strong correlation between the extent of amyloid plaque and the severity of dementia. This is, perhaps, not surprising given the heterogeneity of the disease (in onset, progression, underlying risk factors, etc.), the complex pathogenesis in the generation of neurofibrillary tangles, the many individual factors that modify the impact of neuronal loss on cognition and memory, along with variability in measurement of both PET and clinical scales. Moreover, if there is a threshold rather than linear relationship between plaque and clinical findings, the relationship may be more difficult to see in correlational analyses. Despite the lack of a close correlation of the extent of amyloid plaque and severity of cognitive loss, the established and central role of amyloid plaque in AD still supports the conclusion that reduction in amyloid plaque is reasonably likely to provide clinical benefit in patients with this disease.

The conclusion that reduction in amyloid plaque by PET imaging is reasonably likely to predict clinical benefit is strongly supported by analyses of the treatment group-level relationship between the change from baseline in amyloid plaque SUVR relative to the change from baseline in CDR-SB. The relationship is evident by treatment group within Study 103, and within Study 302, with the same trend seen in Study 301 for the low dose and placebo groups but obviously not with the high dose in Study 301. As presented in the OCP review, the correlation coefficient for all treatment groups (from Studies 103, 301, and 302) is 0.45, and omitting the outlier value of the high dose in Study 301, is 0.76. This relationship is even stronger within Study 103 alone (0.95) and within Study 302 alone (0.99), but is not seen within Study 301 based upon the results in the high dose treatment group. Recognizing the limitations of the results, such as missing data, the consistency of these findings across the studies still

supports a conclusion that the change in amyloid plaque is reasonably likely to predict clinical benefit. As summarized in the OCP review, "*…there appears to be a clear relationship between Aβ plaque reduction in brain and preserving clinical function in various dose arms for all efficacy and safety trials in the aducanumab development program.*" Overall, these findings provide support for the conclusion that the change from baseline in amyloid plaque (SUVR by PET imaging) is reasonably likely to predict clinical benefit.

Moving from the treatment group-level to the patient-level analyses, the relationship is weaker, but still present. As reported in Dr. Massie's review "*pooling studies 301 and 302, the correlations adjusted for baseline CDRSB and baseline cerebellum SUVR for high dose were 0.145 (p=0.0375) and 0.145 (p=0.376).*" Dr. Massie discusses the weaknesses of the individual patient-level correlation in detail. However, I am persuaded by the OCP review that outlines the limitations of such individual patient-level correlation analyses. They note that there are "*multiple confounders across different individual subjects and when multivariate analyses are conducted, it is extremely difficult to correctly adjust the imbalance of multiple confounders across individual patients due to potential nonlinear relationships and complex interactions*." As discussed in the OCP review, limitations of the individual patient relationship between amyloid plaque burden and CDR-SB include the biological variability of both measurements, the potential that the effect of change in plaque burden on CDR-SB may not be linear (there may be a threshold effect), and potentially many covariates that may impact the change observed in both variables at the individual level. The treatment group level analyses, by focusing on randomized groups, limits the impact of differences in these covariates.

This principle is nicely illustrated in the context of reviewing Thorough QTc studies including drugs, such as moxifloxacin, that are known to increase the QTc interval. Individual patient-level data from such studies show only a modest correlation of drug concentrations relative to change in QTc (and graphically looks like "scattershot"). Group level results, however, at specified drug concentrations or at specific timepoints, reveal a strong positive relationship. Similarly, evaluating the change from baseline in CDR-SB compared to the change from baseline in SUVR amyloid plaque using treatment group level results, rather than individual patient-level results, from the aducanumab program shows a strong relationship—save the outlier of the high dose treatment group in Study 302 (see Figure 4 in the OCP review).

The relationship seen in the aducanumab program has also been reported publicly for other monoclonal antibodies directed at increasing the clearance of amyloid plaque (with a range of effects on plaque, from antibodies with no notable decrease in plaque—referenced above—and others that did reduce plaque). In their review, OCP evaluated publicly available information for six other antibody development programs with a range of effects on plaque, and the aducanumab program results. Graphing the group-level by dose results for the change from baseline for amyloid plaque by PET imaging and for CDR-SB, the same prominent linear relationship as observed for aducanumab is seen (see Figures 5A and 5B in the OCP review).

Typically, AA is used when it may require several years, or longer, for AWC trials to detect an effect on a clinical benefit endpoint, whereas drug response on a surrogate endpoint that is reasonably likely to predict such benefit could be seen much sooner, providing the potential for earlier access to a potentially valuable therapy. The current situation veers from this more usual scenario. Here, we have two AWC studies that evaluated clinical benefit (using a standard and accepted endpoint to assess clinical benefit in AD, CDR-SB), with one study showing aducanumab efficacy and one study failing to show such benefit. As already pointed out, taken together these trials provided suggestive but not substantial evidence of effectiveness. Although this is an unusual circumstance in which to apply AA, the use of the AA pathway nonetheless is appropriate here, given that the situation satisfies the requirements for this pathway. When

drugs are approved using AA, even though there is substantial evidence of effectiveness with respect to the surrogate endpoint at the time of approval, there is a recognition that there remains residual uncertainty of clinical benefit, typically because the studies assessing clinical benefit are ongoing, but here because the results of the studies assessing clinical benefit strongly suggested but did not establish benefit.

In summary, with respect to the use of AA for aducanumab, the criteria set out in statute, regulations, and discussed in the above referenced guidance are met: the setting is appropriate (serious disease with unmet need), the drug has the potential to provide a meaningful advantage over available therapy, there is substantial evidence of effectiveness on the surrogate, and the surrogate is reasonably likely to predict clinical benefit. A key element in AA is that there remains residual uncertainty at the time of approval as to whether the drug will provide clinical benefit, specifically whether the reasonably likely surrogate accurately predicts this benefit. As a key expectation of AA, the clinical benefit must be confirmed post-approval by the applicant based on additional study.

The Summary Review and the memo by Dr. Branagan (and Dr. Trummer for Amyloid-related Imaging Abnormalities (ARIA)) provides extensive discussion of aducanumab safety. In considering accelerated approval, one common concern is that the safety exposure at the time of such approval is often limited in size and duration. As a consequence, even if there is substantial evidence on a surrogate reasonably likely to predict clinical benefit, the safety exposure may be insufficient to conclude that the drug is safe for its intended use. This is not the case for aducanumab where the safety exposure database includes 959 patients with at least 6 months exposure and over 600 patients with more than 18 months of exposure (per Dr. Branagan's memo, Table 7). The safety evaluation of aducanumab shows that ARIA is the most important safety concern. ARIA with effusion or edema (ARIA-E) is a common finding in patients treated with aducanumab, occurring in 35% of patients at the 10 mg/kg dose. The majority of ARIA-E events occurred within the first 8 doses of the drug, and once detected, the finding resolved in most patients within 20 weeks (and 99% resolved overall). ARIA associated with hemorrhage also occurred more frequently with aducanumab; however, as Dr. Buracchio discusses in the Summary Review, there was no imbalance in hemorrhage greater than 1 cm in size between aducanumab and placebo. Clearly, ARIA is an adverse drug reaction that requires careful monitoring and appropriate management if detected.

Summary and Conclusions, and Benefit Risk Considerations

As already discussed, AD is a serious disease with progressive, unrelenting loss of cognitive function and memory resulting in lost independence and ultimately death. Even in patients with earlier clinical stages of disease, loss of brain function over 3-4 years is evident and irreversible and results in lost quality of life with deterioration in work, family, and social life. FDA has heard the voices of many patients afflicted with AD who express a desperate desire for an effective treatment. Although there are approved symptomatic treatments, there is no drug that reduces disease progression. In summary, the medical need for new therapies to treat AD, especially ones that target the underlying disease pathology, is substantial and urgent.

The Phase 2 study (Study 103) provided early and promising results with a clear dose-response in reducing amyloid plaque and exploratory clinical endpoints that showed dose-related improvements on both MMSE and CDR-SB. The two large Phase 3 studies were abruptly stopped by the IDMC for futility; subsequent analysis provided evidence of benefit on the primary endpoint from one study, but no evidence of benefit on the primary endpoint in the other study. Additional analyses from the single positive study, including detailed review of secondary clinical endpoints that are distinct measures of

disease severity relative to the primary endpoint, strengthened the argument for clinical benefit for aducanumab. We are left with conflicting information that is not readily resolved. We are also left with differing scientific perspectives from different members of the application review team. Having reviewed and considered the relevant information, I agree with the Office of Neuroscience that the totality of evidence supports the view that there is a reasonable likelihood of benefit from aducanumab, but does not provide substantial evidence of effectiveness on the clinical benefit endpoint (CDR-SB).

As discussed above, FDA has the statutory authority to approve drugs using AA; the current situation with aducanumab fits well into this approach which was, in fact, intended to support approval at a time when the drug has been demonstrated to be effective with respect to certain endpoints but when there remains residual uncertainty regarding clinical benefit. As reviewed above, the effect of the drug in reducing amyloid plaque was established in the Phase 3 trials, supported by the Phase 2 study. Thus, there is substantial evidence that aducanumab reduces amyloid plaque. Results from the development program for aducanumab demonstrate a convincing relationship between the reduction in amyloid plaque by PET imaging and the improvement in clinical function (as measured by CDR-SB), supporting the conclusion that it is "reasonably likely" to predict clinical benefit; a similar relationship between the changes from baseline in amyloid plaque and CDR-SB was noted in publicly available information from other amyloid plaque-directed monoclonal antibody programs reviewed by OCP. Consistent with the requirements for AA, clinical benefit must be confirmed post-approval, and the applicant will conduct a large, placebo-controlled, double-blind randomized trial for this purpose.

In considering the benefit and risk balance for aducanumab, an accelerated approval permits access to a drug that is reasonably likely to provide an important clinical benefit to patients with early AD, addressing the underlying pathological process, and potentially delaying progression. These are highly important clinical benefits to patients with a serious progressive disease with few treatment options and none that addresses the progressive loss of brain function. However, these benefits, although reasonably likely to be provided by the drug, have not yet been established by sufficient trial evidence—that is, there remains residual uncertainty. On the risk side, some ARIA events can be severe, although this risk is monitorable and remediable when these events are detected, and information provided in labeling can help to mitigate this risk. In clinical practice, the extent of this risk could be greater given the likelihood of more variable monitoring and management than may occur in the setting of a well-controlled clinical investigation. In addition, since aducanumab is an intravenously administered drug, patients will face the inconvenience and discomfort that such a route of administration entails.

It is important to also consider the alternative, a complete response for this BLA, with subsequent completion of an additional trial (assuming the sponsor chose to conduct and submit such a trial). If this subsequent trial were positive, an approval decision at that timepoint could be the potential outcome. Given the time required to complete such a trial, any approval decision would occur after a multiple year delay relative to the current accelerated approval. Since AD is a progressive disorder, years delay in access would mean that patients eligible for treatment with this drug under AA could suffer irreversible loss of brain neurons and cognitive function and memory. Moreover, there may be a "window" for benefit, so that patients progressing to later stages of the disease over the next several years may no longer be eligible for treatment, if it is confirmed to provide clinical benefit, since the drug will be indicated for patients relatively early in the clinical course. This benefit-risk balance is typical with AA since approval using this pathway requires a tradeoff: patients and physicians who choose to use the drug must be willing to accept some residual uncertainty regarding clinical benefit – and therefore be willing to take a drug that may ultimately prove ineffective – along with the risks of the drug, in order to gain earlier access to a potentially valuable treatment. FDA staff has heard from patients that many would consider

this a reasonable tradeoff and would opt to accept the uncertainty and risks for a drug that is likely, but not confirmed, to provide clinical benefit, potentially slowing the progression of their disease. Based upon this, I agree with the Office of Neuroscience that the benefit-risk balance for aducanumab is positive given the potential for important clinical benefit in the absence of treatment options that target the underlying disease, and with manageable risks, even considering the remaining uncertainty of clinical benefit.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILIOS A PAPANASTASIOU
06/06/2021 09:58:33 PM

PETER P STEIN
06/07/2021 07:16:34 AM