Summary Memorandum

Date	June 7, 2021
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Subject	Summary Memorandum
BLA #	761178
Applicant	Biogen Inc.
Date of Submission	July 7, 2020
PDUFA Goal Date	June 7, 2021
Proprietary Name	Aduhelm
Established or Proper Name	aducanumab-avwa
Dosage Form(s)	Solution for injection
Applicant Proposed Indication(s)/Population(s)	To delay clinical decline in patients with Alzheimer's disease
Applicant Proposed Dosing Regimen(s)	10 mg/kg as an intravenous infusion every four weeks
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Alzheimer's disease

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. In general, the average survival is 4 to 8 years after a diagnosis of dementia due to AD. It is estimated that 6.2 million Americans age 65 and older are currently living with AD dementia, and AD is the sixth leading cause of death in the United States. Currently approved treatments for AD include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. These drugs provide modest benefits to patients with AD, but it is unclear if these drugs slow or prevent neurodegeneration in patients with AD. There is an urgent and unmet medical need for effective treatments for AD, and a particular unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with drugs that target the underlying pathophysiology of AD in an effort to fundamentally affect the course of the disease an important focus of development.

Aducanumab-avwa is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta (Aβ). Extracellular deposits of Aβ, referred to as amyloid plaques, are one of the pathologic hallmarks of AD, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain has been proposed to be the primary driver of the disease process and precedes the accumulation of tau pathology and neural degeneration.

Studies 301 and 302 were identically-designed, randomized, double-blind, placebo-controlled studies each comparing two doses (low dose and high dose) of aducanumab to placebo over 18 months in patients at the early stages of symptomatic Alzheimer's disease. The two studies were terminated before their planned completion date based on an interim analysis that suggested futility; however, the collected data from each study was analyzed according to the prespecified statistical analysis plan (SAP).

Study 302 demonstrated a statistically significant treatment benefit (smaller increase in CDR-SB[1]) for aducanumab 10 mg/kg, compared to placebo (-0.39 [-22%], p = 0.0120). Statistically significant treatment effects in favor of aducanumab 10 mg/kg were observed for all three ranked secondary clinical endpoints (MMSE, ADAS-Cog 13, and ADCS-ADL-MCI) and the tertiary endpoint (NPI-10).[2] These endpoints are only modestly correlated, assess different domains that patients have stated are important to them (e.g., maintaining independence in activities of

[1] Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), which measures cognitive and functional impairment in AD.

[2] Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale - 13 -item version (ADAS-Cog 13), Alzheimer's Disease Cooperative Study-Activities of Daily Living – MCI, Neuropsychiatric Inventory - 10-item version (NPI-10)

daily living), and contribute largely independent support for the effect of aducanumab. There was some evidence of dose response with the low dose having a non-statistically significant numerical reduction on CDR-SB. The primary results on clinical endpoints were robust to numerous sensitivity analyses and explorations of prespecified subgroups. The effect of aducanumab on clinical endpoints was supported by robust and highly statistically significant dose- and time-dependent reductions of markers of brain amyloid beta plaques, and dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration. The changes on measures of Aβ were correlated with changes on clinical outcomes.

Supportive data is provided from Study 103, a smaller randomized, double-blind, placebo-controlled, sequential cohort, dose-finding study for aducanumab in AD. Study 103 was conducted in a similar population and used many of the same endpoints that were used in Studies 301 and 302. The results on clinical endpoints (CDR-SB and MMSE) at the highest dose studied (10 mg/kg) were nominally significant and consistent with the positive results observed in Study 302, though because of the sequential cohort design, non-concurrent randomization is a factor in active vs. overall placebo comparisons. Nonetheless, there was a notable dose-related numerical reduction relative to placebo for CDR-SB and MMSE. There was a clear dose- and time-dependent reduction of markers of brain amyloid beta plaques. The dose-response relationship for Aβ reduction in Study 103 provides support for the reduction in amyloid observed findings on Study 302, and is consistent with the dose-response relationship observed in Study 302 for CDR-SB and MMSE.

Study 301 is a negative study and does not contribute to the evidence of effectiveness on clinical outcomes for aducanumab; however, the study does contribute to a conclusion that aducanumab reduces amyloid beta plaques, as the PET subset demonstrated statistically significant time- and dose-dependent decreases in amyloid beta plaques. Study 301 also contributes to the understanding of the relationship between change from baseline in reduction in brain Aβ and the estimate of the treatment effect for CDR-SB.

Study 301 and Study 302 had discordant results on the primary endpoint, with one study (301) being negative for the high dose, but the second (302) being positive for the high dose, with persuasive results on secondary endpoints; the two studies had similar but non-significant findings for the low dose. In order to achieve a maximum understanding of the data, exploratory analyses were conducted to investigate the discordance between the studies. These analyses suggested that demographic and baseline characteristics, the possibility of functional unblinding, and differences in placebo response between the two studies did not contribute to the discordant results. Analyses of differences in the proportion of rapidly progressing patients in the two studies and of dosing differences between the two studies suggested a contribution of each of these differences to the discordant results. The analyses of rapid progressors suggested that small imbalances in the number of rapid progressors can have a relatively large impact on the magnitude of the primary and secondary endpoints, and the high-dose arm in Study 301 was disproportionately affected by such an imbalance in rapid progressors. The analyses of dosing differences indicated that dosing is an important consideration for interpretation of the efficacy results in Studies 301 and 302, and patients in Study 301 with higher exposure to the 10 mg/kg dose had treatment effects similar to patients in Study 302 with comparable dose exposure. Lower exposure to the target dose of 10 mg/kg in Study 301 appears to be a small but contributing factor to the differences in results of Study 301 and Study 302. These findings are exploratory and resulted from analytical approaches with varied strengths and weaknesses. Although they are informative, the fundamental issue that Study 301 did not demonstrate the effect on the high dose that was demonstrated in Study 302 remains and clearly introduces

residual uncertainty that would not be present had Study 301 demonstrated a similar effect as Study 302.

In short, Study 103, a sequential cohort study that was primarily intended to assess safety and tolerability along with pharmacodynamic dose finding, but which included a rigorous design with regard to blinding and assessment, showed a notable dose-related numerical reduction in clinical decline relative to placebo for CDR-SB and MMSE, with nominal significance for both CDR-SB and MMSE at 10 mg/kg, along with a clear and persuasive dose- and time-dependent reduction of amyloid beta plaques. Study 302 and Study 301, though prematurely terminated, when analyzed using data collected per protocol and according to the prespecified analytical plan, show discordant results. Study 302 demonstrated a statistically significant treatment benefit on CDR-SB at 10 mg/kg, and particularly persuasive statistically significant treatment effects for several secondary clinical endpoints that are only modestly correlated with each other and with the primary outcome, since there are many non-overlapping domains assessed, and the approach to assessments are distinct, increasing the relevance of their results; along with some evidence of dose response, and clear and persuasive highly statistically significant dose- and time-dependent reductions of amyloid beta plaque, accompanied by dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration. The changes on measures of Aβ were correlated with changes on clinical outcomes. Study 301 did not demonstrate an effect on the primary endpoint, but did show clear and persuasive highly statistically significant dose- and time-dependent reductions of amyloid beta plaque. Analyses of Study 301 and 302 indicate that the primary findings of Study 302 were robust and suggest that differences between the trials (as discussed above) could have contributed to the lack of observed effect in Study 301, but these are exploratory and do not eliminate the residual uncertainty created by the primary results of Study 301 when considering the overall data.

The primary clinical review argues primarily for standard approval. Despite the early termination of Study 302, Dr. Krudys considers the data submitted to be interpretable and capable of providing evidence for the effectiveness of aducanumab for AD. He considers Study 302 to be a robust and exceptionally persuasive study that provides the primary evidence of effectiveness to support approval. He bases this conclusion on a treatment effect demonstrated on a clinically meaningful endpoint, and reinforced by effects on secondary endpoints, biomarkers, and in relevant subgroups. Dr. Krudys also considers that Study 103, with design features consistent with Study 302, provides support for the findings of Study 302. Dr. Krudys notes that Study 301 is a negative study and does not contribute to the evidence of effectiveness on clinical outcomes; however, he feels that the results of the exploratory analyses contribute to an overall understanding of Study 301 and do not detract from the persuasiveness of Study 302. Dr. Krudys has concluded that the applicant has provided substantial evidence of effectiveness to support approval of aducanumab for AD.

Dr. Krudys has also reviewed the evidence to support accelerated approval and concludes that reduction in brain amyloid as measured by PET is reasonably likely to predict clinical benefit. He also notes that the time- and dose-dependent effect of aducanumab on reduction of brain amyloid beta plaques observed across Studies 103, 301, and 302 meets the standard for substantial evidence of effectiveness in this context. In this setting, where the evidence supporting clinical benefit is strong but associated with the residual uncertainty conveyed by the clinical endpoint results of Study 301 (and the associated contribution of those results to the premature termination of both studies), Dr. Krudys concludes that the accelerated approval pathway is supported by the data.

The primary statistical review does not recommend approval. Dr. Massie notes that the only valid analyses of Study 301 and Study 302 are the prespecified randomization supported analyses. This results in a conflict between one positive study and one negative study. The statistical review notes that exploratory analyses cannot take the place of a prespecified primary analysis supported by randomization, arguing that the overall prespecified final analysis of 301 is the only valid analysis of that study and that explorations of the data in Study 301 cannot result in definitive conclusions of the same weight as the prespecified final analysis. Numerous explorations of the data are contained in the statistical review in support of a negative result for Study 301. Additional exploratory analyses are described to suggest that increased placebo progression post-PV4 may account for the treatment effect observed in Study 302. Dr. Massie also argues that Study 103, a smaller study with a sequential cohort design not intended to primarily assess efficacy, should not be weighted more strongly than a large, randomized, parallel group, placebo-controlled study. That statistical review argues that there is no compelling correlation between effects on amyloid beta plaques and effects on CDR-SB at the patient level.

The clinical pharmacology review recommends approval. The clinical pharmacology team finds that four primary findings contribute to the evidence of effectiveness of aducanumab. 1) Positive findings for the high dose group from Study 302. 2) The dose-response relationship observed in Study 103. 3) Positive exposure-response relationships for CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI from Studies 301 and 302. 4) Exposure-SUVR and SUVR-clinical endpoint relationships observed in Studies 301, 302, and 103. In addition, the clinical pharmacology review discusses two important supportive analyses that further increase the persuasiveness of the primary findings. 1) The review team concluded that the relationship between brain amyloid reduction and CDR-SB for aducanumab was consistent with the relationship observed for other compounds targeting amyloid beta based on a review of publicly available information, including compounds for which the reduction in amyloid beta plaque ranged from minimal to a similar extent as that seen with aducanumab. 2) Based on extensive clinical trial simulations, the review team concluded that the probability of the high dose group in Study 302 being a false positive is very low, and the high dose group in Study 301 is likely a chance finding driven by the pre-PV4 subgroup. Also, the probability of observing the overall positive findings from Studies 103, 301, and 302 under the null assumption that aducanumab is the same as placebo was extremely low. The clinical pharmacology review team notes that it is practically impossible to observe the overall pattern of results in these three studies if aducanumab is similar to placebo.

In summary, regarding the evidence of effectiveness of clinical benefit, data from an early phase study (103) showed a notable dose-related numerical reduction in clinical decline relative to placebo for CDR-SB and MMSE, with nominal significance for both CDR-SB and MMSE at 10 mg/kg. Further data are provided by two identically-designed late phase studies (302 and 301) that, though prematurely terminated, provide interpretable efficacy results. When analyzed using data collected per protocol and according to the prespecified analytical plan, these studies show discordant results for the 10 mg/kg arms. Study 302 demonstrated a persuasive statistically significant treatment benefit on the primary endpoint at 10 mg/kg, and particularly persuasive statistically significant treatment effects for several secondary clinical endpoints that are only modestly correlated with each other and with the primary outcome, along with some evidence of dose response. Study 301 did not demonstrate an effect on the primary endpoint. Analyses of Study 301 and 302 indicate that the primary findings of Study 302 were robust and suggest that differences between the trials could have contributed to the lack of observed effect in Study 301, but these analyses are exploratory and do not eliminate the residual uncertainty regarding clinical benefit created by the primary results of Study 301 when

considering the overall data. These clinical findings are supported by clear and persuasive highly statistically significant dose- and time-dependent reductions of amyloid beta plaque across all three studies, which were correlated with changes on clinical outcome, and dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration.

The primary clinical review and the clinical pharmacology team's review have resulted in a conclusion that substantial evidence has been provided for the clinical benefit of aducanumab and both recommend standard approval. These recommendations are described above and are predicated on the strength of the evidence provided by Study 302, felt by both Dr. Krudys and the entire clinical pharmacology team to be robust and exceptionally persuasive, and the supportive evidence provided by Study 103, with further support from extensive exploratory and sensitivity analyses, dose-response and exposure-response relationships, and SUVR-clinical endpoint relationships observed across all three studies. Further, both reviews note the consistency of aducanumab's relationship between brain amyloid reduction and CDR-SB with the relationship observed for other compounds targeting amyloid beta. Finally, Dr. Krudys and the clinical pharmacology team both note, for the reasons above, and based on extensive clinical trial simulations performed by the clinical pharmacology team, that the probability of the high dose group in Study 302 being a false positive is extremely low , and the high dose group in Study 301 is likely a chance finding, a Type II error – a false negative, driven by the pre-PV4 subgroup of that treatment arm. Dr. Krudys notes that Study 301 is a negative study and does not contribute to the evidence of effectiveness on clinical outcomes; however, he feels that the results of the exploratory analyses contribute to an overall understanding of Study 301 and do not detract from the persuasiveness of Study 302. The clinical pharmacology team agrees with the clinical and statistical reviews that Study 301 was a negative study on its primary endpoint, but notes the contributions of exposure-response relationships for CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI from Studies 301 and 302, and the exposure-SUVR and SUVR-clinical endpoint relationships observed in Studies 301, 302, and 103, to establishing evidence of effectiveness. The statistical review does not agree that substantial evidence has been provided for the clinical benefit of aducanumab and does not recommend approval for the reasons noted above. Fundamentally, the recommendation is based on the conflict between Study 301 and Study 302 on the prespecified randomization supported analyses. Numerous explorations and analyses are included in the statistical review (see the review for details) to reinforce this concern. The statistical review also argues that Study 103 should not be weighted more strongly than a large, randomized, parallel group, placebo-controlled study.

There is common ground here concerning Study 301. All three reviews agree that Study 301 is negative, and that it is critical to consider its impact. All three reviews recognize and address the uncertainty created by the primary high dose result of Study 301. The statistical review notes that exploratory analyses and the results of a small early phase study cannot replace or eliminate the results of Study 301. The clinical and clinical pharmacology reviews agree with this stance. The clinical and clinical pharmacology teams present thoughtful and reasonable arguments in support of approval, based, in part, upon analyses intended to address this uncertainty. Ultimately, Dr. Krudys feels that the results of the exploratory analyses contribute to an overall understanding of Study 301 and do not detract from the persuasiveness of Study 302, and the clinical pharmacology team feel that the overall data, including data from Study 301, support a positive effect of aducanumab.

That there is uncertainty introduced by the findings of Study 301 is clear. Indeed, it is self-evident that the overall findings of Study 302 and Study 103, should they have been the only results being considered, would not be affected by such uncertainty and it might then be reasonable

and appropriate to view the results of Study 103 as confirmatory evidence in support of the positive results of Study 302. It is in that spectrum of uncertainty that the various recommendations for and against approval reside.

Dr. Krudys, in recognition of the presence of this uncertainty, has discussed the relevance of the accelerated approval pathway to the data at hand. As discussed above, he concludes that the accelerated approval pathway is supported by substantial evidence of the effect on aducanumab on reduction in amyloid beta plaques.

The accelerated approval pathway is intended to provide a path to approval for drugs in certain situations where there is some uncertainty at the time of approval regarding the drug's ultimate clinical benefit. Accelerated approval is based on an outcome that is reasonably likely to predict clinical benefit, rather than on the clinical benefit itself. These outcomes predictive of benefit are generally surrogate markers of disease of some sort, but may also be an intermediate clinical endpoint that can be measured earlier than the outcome of ultimate clinical importance. Substantial evidence of effectiveness is required on such an endpoint to support accelerated approval, just as it is required for an endpoint supporting standard approval. Accelerated approval (AA) is intended for serious conditions where the drug provides a meaningful advantage over available therapies.

Alzheimer's disease is a serious condition, and aducanumab, unlike other approved therapies, is targeted at an underlying, fundamental, and defining pathophysiological feature of the disease, with the potential to alter the inescapable and relentless progression of this disease. The clinical data that exist suggest that an alteration in such progression, assessed as a reduction in clinical decline over a prolonged period of time, is an anticipated benefit of aducanumab. Finally, a surrogate outcome for which there is substantial evidence of effectiveness, reduction in amyloid beta plaques on PET imaging, has been assessed in the aducanumab development program, and is reasonably likely to predict clinical benefit, as demonstrated in the reviews discussing the relationship of amyloid plaque reduction to clinical outcome.

When residual uncertainty exists about the clinical benefit of a drug, it is important to address that uncertainty, and accelerated approval provides an opportunity to address the uncertainty associated with a surrogate outcome that is reasonably likely to predict clinical benefit by requiring a post-approval study to verify the clinical benefit predicted by the effect on the surrogate. Thus, accelerated approval provides an appropriate approval pathway, in a population and situation for which the pathway is intended, that will be accompanied by a requirement to address the residual uncertainty discussed above.

A key issue is whether substantial evidence of effectiveness exists for amyloid beta plaque reduction. Clearly, for the reasons discussed above, it does. Treatment with aducanumab results in clear and persuasive highly statistically significant dose- and time-dependent reductions of amyloid beta plaque in all studies. Studies 301 and 302 were adequate and well controlled late-stage large studies of conventional design. Study 103 is an early-stage smaller study of rigorous design and conduct (e.g., placebo control, blinded assessments, prespecified analytical plan) that represents another adequate and well controlled study for the assessment of the highly objective endpoint of amyloid beta plaque measurement. There is substantial evidence that aducanumab reduces amyloid beta plaque.

An equally important issue is whether that effect, for which substantial evidence exists, is reasonably likely to predict benefit. Again, for reasons discussed above, this is the case. There are several reasons why this is so.

First, amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of the disease. Although the role of amyloid and its relationship to other pathophysiological features of AD, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in AD, including early in the disease. Mutations causing abnormalities in amyloid that result in autosomal dominant AD further reinforce its fundamental role. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit.

Second, a strong group-level relationship has been established for the change from baseline in amyloid beta plaque SUVR-change from baseline in CDR-SB clinical endpoint in Studies 301, 302, and 103, as shown and discussed in the clinical and clinical pharmacology reviews. This relationship is evident for all studies in all arms except, as expected, for the high dose arm of Study 301. This overall finding strongly supports the reasonable likelihood that reduction in amyloid beta plaque by aducanumab predicts clinical benefit.

It is important to recognize that patient-level correlations are weaker (but still present), and the statistical review argues in some detail that there is no compelling correlation between effects on amyloid beta plaques and effects on CDR-SB at the patient level. The clinical pharmacology review provides a thorough discussion of the confounded nature of individual-level correlation assessment for patients that were randomized at the group-level, and does not recommend this approach.

Third, the overall findings of Study 302 and Study 103, in the context of the lowering of amyloid beta plaque in those studies, contribute to a reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

Fourth, the clinical pharmacology review team concluded that the relationship between amyloid beta plaque reduction and CDR-SB for aducanumab was consistent with the relationship observed for other compounds targeting amyloid beta. This relationship exists across a range of plaque reduction. The clinical pharmacology team found that there was a clear relationship between reduction of amyloid beta plaque burden in brain and preservation of clinical function in the aducanumab program, which was consistent across all 6 other available programs of anti-amyloid beta antibodies under development over the past decade based on a review of publicly available information. A larger reduction of amyloid plaque levels in brain was clearly associated with a better maintenance of function as measured by CDR-SB. In contrast, compounds at the tested doses with no/minimal changes in amyloid beta plaque levels consistently failed to demonstrate superiority over placebo in slowing the disease progression in clinical studies with treatment duration of 1.5 to 2 years. This finding across various programs of evidence consistent with the primary findings regarding aducanumab supports a reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

Fifth, aducanumab's robust and highly statistically significant dose- and time-dependent reductions of markers of brain amyloid beta plaque was accompanied by dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration.

These additional findings of an effect on other critical aspects of Alzheimer's pathophysiology at doses of aducanumab associated with reduction in amyloid beta plaque and correlated with evidence of clinical benefit contribute to a reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

Sixth, preliminary data from an ongoing redosing study suggest that patients in Study 302 treated with aducanumab 10 mg/kg who achieved a greater degree of amyloid beta plaque reduction (an SUVR <1.1, the value reported to discriminate between a positive and negative amyloid PET scan) had more stable results upon entry into the redosing study on the Study 302 primary and secondary clinical measures that were assessed upon entry into the redosing study than patients who did not achieve that degree of amyloid plaque reduction. This observation provides further support to the relationship between amyloid beta plaque reduction and clinical benefit.

There are therefore multiple lines of evidence establishing a reasonable likelihood that reduction of amyloid beta plaques will be associated with clinical benefit, and there is substantial evidence that aducanumab reduces amyloid beta plaques. Accordingly, for the reasons discussed above, the criteria for accelerated approval are met.

It is important to note a somewhat less common aspect of these data in the context of accelerated approval. More commonly, accelerated approval is envisioned in a circumstance when the effect on a surrogate is available much sooner than a clinical outcome of ultimate interest. Enquiries from sponsors are often made when studies do not succeed in establishing evidence of clinical benefit, such as proposals to assess effectiveness using an alternative endpoint from the same studies instead (e.g., change in a biomarker of some sort that was measured in the study). In such situations, there are typically little to no data suggesting clinical benefit of the drug, and, not uncommonly, the proposed biomarker is nonspecific or not well understood with regard to the disease under investigations. Under such circumstances, efforts to rescue, or salvage, a failed study via the accelerated approval pathway are typically inappropriate, for a variety of reasons. The character of the biomarker is often insufficient to establish reasonable likelihood to predict clinical benefit, substantial evidence of an effect on the biomarker is often lacking, and the clinical data that exist in the study under question provide no evidence of benefit. The circumstances here are fundamentally different, as discussed above.

It is also important to mention that there have been multiple studies of agents targeting amyloid beta, and they are frequently grouped together as "anti-amyloid" therapies and tend to be viewed as a class. The multiple prior failures of drugs in this space, including monoclonal antibodies, are frequently cited as diminishing confidence in the value of this therapeutic strategy. The clinical review discusses several factors that are relevant to this issue. Different mechanisms characterize these therapies, including various attempts to limit production or enhance clearance of amyloid beta. The character of these investigational drugs can vary widely, and not all are monoclonal antibodies. Dr. Krudys describes a variety of factors that may contribute to previous failures, including insufficient dosing, unknown target engagement, off-target effects, and inclusion of individuals in trials without evidence of brain amyloid beta pathology (i.e., patients without Alzheimer's disease) or at later stages of Alzheimer's disease. Amongst anti-amyloid beta monoclonal antibodies specifically, there are differences due to effector function, binding at different epitopes, and selectivity for amyloid beta variants. For these reasons, as Dr. Krudys notes, previous late-stage failures of anti-amyloid beta therapies do not constitute a demonstrated "class failure" and are not particularly informative for the assessment

of the effectiveness of aducanumab. Dr. Krudys describes how the aducanumab development program in many ways stands apart from these previous failures. The pivotal trials of aducanumab included patients with evidence of brain amyloid beta pathology who were early in the disease process. An early trial, Study 103, demonstrated target engagement and confirmed reduction of amyloid beta plaque burden. Accordingly, aducanumab may more appropriately be grouped with agents which have also demonstrated plaque reduction at appropriate dosages with some early evidence suggesting favorable effects on clinical endpoints. In short, the spectrum of results seen with prior agents is not of consistent relevance to the aducanumab findings. Prior failures do not necessarily diminish the reasonable likelihood that amyloid beta plaque reduction with aducanumab treatment will result in clinical benefit, and, in fact, the most relevant and informative information from monoclonal antibody agents which have also demonstrated plaque reduction at appropriate dosages contribute further to a reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

The safety of aducanumab has been well characterized in a safety database of adequate size. The safety reviews, including a general review of safety by Dr. Branagan and a focused review of ARIA by Dr. Trummer, show that ARIA is the most important safety concern. Aducanumab can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA (-E and/or -H) was observed in 41% of patients treated with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo. ARIA-E was observed in 35% of patients treated with 10 mg/kg, compared to 3% of patients on placebo. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers (42% and 20%, respectively). The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of 10 mg/kg who had ARIA-E, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients. Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. 10% of all patients who received 10 mg/kg had more than one episode of ARIA-E. ARIA-H in the setting of ARIA-E associated with the use of 10 mg/kg was observed in 21% of patients treated with 10 mg/kg, compared to 1% of patients on placebo. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between aducanumab and placebo. There was no imbalance in hemorrhage greater than 1 cm between aducanumab and placebo. Clinical symptoms were present in 24% of patients treated with 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 5% of patients on placebo. The most common symptom in patients treated with 10 mg/kg with ARIA was headache (13%). Other frequent symptoms were confusion/delirium/altered mental status/disorientation (5%), dizziness/vertigo (4%), visual disturbance (2%), and nausea (2%). Serious symptoms associated with ARIA were reported in 0.3% of patients treated with 10 mg/kg. Clinical symptoms resolved in the majority of patients (88%) during the period of observation. In addition, hypersensitivity reactions of angioedema and urticaria occurred in 1 patient in the placebo-controlled clinical trials.

In summary, with regard to the evidence of effectiveness supporting accelerated approval on the basis of a reduction in amyloid beta plaque, the requirements are met. Alzheimer's disease is a serious and life-threatening condition with a tremendous unmet medical need. This unmet need is not only well recognized by the Agency and the scientific community, but is clearly articulated by the voices of Alzheimer's disease patients and their caregivers who leave no doubt of the urgent need for an effective treatment. Even given the residual uncertainty with respect to its clinical benefits, patients and caregivers have clearly stated their desire for a drug that is likely to be effective. This is exactly the

situation for which accelerated approval exists – where the evidentiary criteria for accelerated approval are met, it can provide earlier access to a promising drug to patients with unmet needs. There is substantial evidence that aducanumab reduces amyloid beta plaques, and this reduction is reasonably likely to result in clinical benefit for patients. Accelerated approval provides an opportunity to both accelerate the availability of a promising new treatment and address residual uncertainty by requiring the conduct of an additional study to verify clinical benefit.

ARIA is the primary risk associated with the use of aducanumab. It is usually asymptomatic, and when symptomatic, it is rarely serious, though serious asymptomatic (i.e., radiographic) and symptomatic cases can occur. It will receive a warning in labeling describing the risk along with monitoring and dosing recommendations. The applicant will provide a structured educational program for clinicians involved with aducanumab treatment, and will be identifying and characterizing cases of ARIA when used clinically. Aducanumab will be used initially in specialized centers familiar with Alzheimer's disease patients, testing, and monitoring. It is possible that the character of ARIA will be different in clinical practice than in clinical studies. Enhanced pharmacovigilance will be performed to more fully characterize ARIA in the practice setting. A hypersensitivity reaction occurred in a patient in the clinical trials. It will receive a warning in labeling. There are no safety issues that preclude approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. • Clinical symptoms include difficulty remembering recent conversations, names or events, impaired communication, disorientation, confusion, poor judgment, behavioral changes, and ultimately, difficulty walking, speaking, and swallowing. • Alzheimer's disease exists on a continuum from biological changes in the brain, to subtle problems with memory and thinking, and ultimately difficulties that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise. • After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. • An estimated 6.2 million Americans age 65 and older are currently living with Alzheimer's disease. • Alzheimer's disease is the sixth leading cause of death in the United States. • Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue which imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer's disease dementia is expected to increase significantly in the next few decades.
Current Treatment Options	• FDA-approved therapies include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine. • Treatment effects are modest. • Antipsychotics are commonly prescribed to treat behavioral symptoms but are not approved for the treatment of Alzheimer's disease and are associated with increased mortality in older patients.	There is an urgent and unmet medical need for effective treatments for Alzheimer's disease. In addition to the general need for more effective treatments, there is a particular unmet need for effective treatments to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Benefit	• Study 302 demonstrated a statistically significant treatment benefit (smaller increase in CDR-SB) for aducanumab 10 mg/kg, compared to placebo (-0.39 [-22%], p = 0.0120)
	  • Statistically significant treatment effects in favor of high-dose aducanumab were observed for all three secondary clinical endpoints: MMSE (mean difference from placebo 0.6; p=0.049), ADAS-Cog 13 (mean difference from placebo -1.4; p<0.01), and for ADCS-ADL-MCI (mean difference from placebo 1.7; <0.001).
	  • Results were robust to several sensitivity analyses.
	  • Favorable trends were also observed for low dose aducanumab for all endpoints, suggesting the presence of a dose-response relationship
	  • Change from baseline in brain amyloid signal relative to placebo as measured by SUVR was similar in the low-dose and high-dose groups at Week 26, -0.075 (p<0.0001) and -0.082 (p<0.0001), respectively due to similar dosing during titration. At Week 78, the adjusted mean change from placebo was -0.179 (p<0.0001) and -0.278 (p<0.0001) in the low-dose and high-dose groups, respectively, indicating time- and dose-dependent relationships.
	  • Statistically significant reductions in p-Tau and t-Tau were also observed.
	
	• Study 301 did not demonstrate a benefit of aducanumab on clinical endpoints; however, the study does contribute data to support the effects of aducanumab on amyloid reduction.
	  • Change from baseline in brain amyloid signal relative to placebo, as measured by composite SUVR, was similar in the low-dose and high-dose groups at Week 26, -0.065 (p<0.0001) and -0.066 (p<0.0001), respectively (dosing was similar in both groups during titration). At Week 78, the adjusted mean change from placebo was -0.167 (p<0.0001) and -0.232 (p<0.0001) in
		There are uncertainties about the effectiveness of aducanumab on clinical outcomes, due to Study 301 being a negative study. However, there is substantial evidence for a robust treatment-related reduction in brain amyloid plaque, as measured by PET imaging in the three clinical trials (Studies 103, 301, and 302). There is also extensive scientific evidence of amyloid's role in AD. Based on the available clinical data, and the current understanding of the pathophysiology of Alzheimer's disease, the reduction in amyloid identified in aducanumab clinical studies is reasonably likely to predict clinical benefit in AD, and supports the accelerated approval of aducanumab.
		
		A requirement to conduct a clinical trial to confirm the benefits of aducanumab in AD will be issued as a post-marketing requirement (PMR)

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	the low-dose and high-dose groups, respectively, indicating time- and dose-dependent relationships.
	
	• Study 103 was a smaller study that provides support for the effectiveness of aducanumab.
	  • Aducanumab 10 mg/kg fixed-dose showed a statistically significant reduction, as compared to placebo, in the change from baseline in CDR-SB and MMSE (CDR-SB: -1.26, 95% CI -2.356, -0.163; MMSE: 1.9, 95% CI 0.06, 3.75).
	  • Significant reductions in brain amyloid were achieved in the 3 mg/kg, 6 mg/kg and 10 mg/kg fixed-dose treatment groups at Week 26, and all aducanumab treatment groups at Week 54. The adjusted mean change from baseline at Week 26 and Week 54 for the fixed-dose 10 mg/kg treatment arm were -0.202 ($p<0.0001$) and -0.263 ($p<0.0001$), respectively.
	
	Uncertainties
	• Study 301 did not demonstrate a benefit of aducanumab on clinical endpoint
	• Although the population enrolled in Studies 103, 301, and 302 did not include patients at either end of the Alzheimer's disease continuum, it is plausible that patients across the continuum may benefit from aducanumab, especially early in the course of a progressive disease.	

Risk and Risk Management	• The safety database includes 3,078 subjects exposed to at least one dose of aducanumab, including 834 subjects treating mild dementia or mild cognitive impairment due to Alzheimer's disease for at least 6 months, and 551 subjects treated over 12 months at the proposed dose. • The most common TEAEs in the Phase 3 controlled trials that were the primary sources of evidence of effectiveness (at least 2% and at least 2% greater than placebo) were related to ARIA-E (up to 35%), ARIA-microhemorrhages and hemosiderin deposits (up to 19%),	The safety database fulfills minimum ICH guidance. Risk management can be achieved through clear product labeling and monitoring for ARIA, as described in the label. A Warnings and Precautions Section 5.1 of the prescribing information will alert prescribers to

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	superficial siderosis of the central nervous system (up to 15%), headache (up to 21%), fall (up to 15%), diarrhea (up to 9%), and confusion/delirium/altered mental status/disorientation (grouped terms, up to 8%), in the aducanumab 10 mg/kg arm.
	• ARIA (-E and/or -H) was observed in 41% of patients treated with aducanumab 10 mg/kg, compared to 10% of patients on placebo in pooled Studies 301 and 302.
	• Clinical symptoms were present in 23% of patients treated with aducanumab 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 4% of patients on placebo. The most common symptom in patients with ARIA treated with aducanumab 10 mg/kg was headache (12%), confusion, delirium, altered mental status, or disorientation (4%) Dizziness or vertigo (4%), visual disturbance (2%), and nausea (2%) were reported in patients treated with aducanumab and none on placebo in patients who experienced ARIA.
	  • ARIA-E was observed in 35% of patients treated with aducanumab 10 mg/kg, compared to 3% of patients on placebo. Among patients treated with aducanumab 10 mg/kg who had ARIA-E, the maximum radiographic severity was mild in 30%, moderate in 57%, and severe in 13% of patients. The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses). After detection, resolution occurred in 57% of patients by 12 weeks, 89% by 20 weeks, and 99% overall. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers (42 and 20%, respectively).
	  • ARIA-H in the setting of ARIA-E associated with the use of aducanumab 10 mg/kg was observed in 21% of patients treated with aducanumab 10 mg/kg, compared to 1% of patients on placebo. There was no imbalance in isolated ARIA-H. There was no imbalance in hemorrhage greater than 1 cm between aducanumab and placebo.
	• Hypersensitivity - One subject developed the serious adverse reactions of angioedema and urticaria. There was no imbalance overall in hypersensitivity reactions.
		the risk of ARIA and its symptoms when they occur. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing will be provided in Section 2.3 and 2.4 of the prescribing information. MRI prior to the 7th infusion will identify asymptomatic ARIA that has occurred by the end of the titration period and MRI prior to the 12th infusion will identify asymptomatic ARIA on a stable dose of 10 mg/kg. Enhanced clinical vigilance is recommended with additional guidance for considerations regarding continued treatment. ARIA will also be addressed in the Medication Guide.
		
		Prescribers will be made aware of the risk of serious hypersensitivity reactions in Section 5.2 of Warnings and Precautions. This will also be addressed in the Medication Guide.
		
		Requested postmarketing vigilance will further characterize the uncertainties related to safety of aducanumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Uncertainties • Patients with moderate or severe dementia were excluded from the key studies analyzed for review of safety; therefore, safety outcomes in these patients is unknown. • The optimal timing and frequency of MRI monitoring as a tool for mitigating ARIA is unknown. • The safety of treating patients through episodes of asymptomatic ARIA is unknown. • The safety of concomitant use of medications that increase bleeding risk is unknown, as is the risk in patients otherwise at risk for bleeding.	

2. Background

This application under review is for aducanumab (previously BIIB037), proposed for the treatment of Alzheimer's disease (AD). Aducanumab is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody administered by intravenous (IV) infusion that targets aggregated soluble and insoluble forms of amyloid beta. It is a new molecular entity (NME) containing no previously approved active ingredient (including any ester or salt of the active ingredient) and is not currently marketed in the United States for any indication.

AD is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans age 65 and older are currently living with Alzheimer's disease dementia, and the number is projected to reach over 12 million by 2050, in the absence of interventions to prevent or slow the disease (Alzheimer's Association, 2021).

The pathologic hallmarks of AD are extracellular deposits of β-amyloid (Aβ), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain is generally thought to be the primary driver of the disease process, and precedes the accumulation of tau pathology and neurodegeneration. The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of Aβ may begin 20 years or more before symptoms arise (Vermunt et al., 2019). Based on these findings, National Institute on Aging—Alzheimer's Association (NIA-AA) research criteria have been recently developed for the diagnosis and staging severity of AD, based on neuropathologic biomarker-based findings of the presence or absence of amyloid, tau, and evidence of neurodegeneration (Jack et al., 2018). The 2018 FDA Guidance, "Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry", also utilizes a biomarker-based framework along with the presence of clinical signs or symptoms (from asymptomatic to overt dementia) to define stages of AD to inform guidance for drug development programs.

Currently approved AD treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, that are purported to address cholinergic deficits in AD by increasing acetylcholine levels in the central nervous system (CNS), and the N-methyl-D-aspartate antagonist memantine. Memantine was approved in 2003, and is the most recently approved novel medication for AD; it is postulated to work by binding preferentially to N-methyl-D-aspartate (NMDA) receptor-operated cation channels to block persistent activation by the excitatory amino acid glutamate. These drugs provide modest benefits to patients with AD, but it is unclear whether these drugs slow or prevent neurodegeneration in patients with AD. There remains a tremendous unmet need for therapies in AD that slow, halt, reverse, prevent, or cure the disease, with drugs that target the underlying pathophysiology of AD in

an effort to fundamentally affect the course of the disease an important focus of development efforts.

Therapies to inhibit Aβ production or enhance Aβ clearance have been investigated in an attempt to slow or halt the disease process. There have been several anti-Aβ monoclonal antibodies studied in AD that have had negative studies in Phase 3 development; however, differences in enrollment criteria, study design, and trial endpoints make it difficult to compare them to the aducanumab program. There are also significant differences between anti-Aβ monoclonal antibodies related to binding at different epitopes, and selectivity for different Aβ variants (e.g., monomers, soluble oligomers, aggregated forms) (Linse et al. 2020). Some anti-Aβ monoclonal antibodies, including aducanumab, have been associated with the occurrence of amyloid-related imaging abnormalities (ARIA) that require special attention with respect to dosing and monitoring. ARIA covers a spectrum of findings detected on brain magnetic resonance imaging (MRI), including ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H).

In this BLA, the Applicant has submitted data from two identically-designed Phase 3 randomized, double-blind, placebo-controlled, parallel group studies (Studies 301 and 302) to support the efficacy and safety of aducanumab in AD. The two studies were terminated before their planned completion date based on an interim analysis that suggested futility; however, the collected data from each study was analyzed according to the prespecified statistical analysis plan (SAP). Additional supportive data is provided from Study 103, a randomized, double-blind, placebo-controlled, dose-finding study for aducanumab in AD.

3. Product Quality

The technical lead on the Office of Pharmaceutical Quality (OPQ) review was Dr. Haoheng Yan (Dr. Yan's review lists the entire OPQ team that was involved with the review of this application).

Aducanumab-avwa is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody targeting aggregated soluble and insoluble forms of amyloid beta. It is expressed in a Chinese hamster ovary (CHO) cell line.

Aduhelm (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution for intravenous infusion after dilution. It is supplied in single-dose vials available in concentrations of 170 mg/1.7 mL (100 mg/mL) or 300 mg/3 mL (100 mg/mL).

The following summary is extracted from the OPQ review:

"The OPQ assessment of manufacturing has identified that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The

manufacturing process is robust for inactivation and removal of adventitious agents. The BLA is recommended for approval from product quality and sterility assurance perspectives. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of aducanumab-avwa at concentrations presented in the patient samples. ADAs were not assessed for neutralizing activity. The BLA assessment team concluded neutralizing antibody analysis was not necessary for approval of the BLA because the treatment emerging ADA positive rate is extremely low in the clinical studies and there was no observation of effect on ADA positivity on exposure or efficacy."

OPQ has identified 4 product quality related and 1 immunogenicity assay-related issues to be further assessed as post marketing commitments (PMCs). For each of these items, the information submitted in the BLA has provided sufficient level of assurance that these are not an approvability issue, but additional studies will provide further assurance for consistently producing high quality product or if further revisions are needed for the assay that will be used in the required confirmatory trial.

OPQ has determined that the data submitted in this application are adequate to support the conclusion that the manufacture of aducanumab-avwa is well-controlled and leads to a product that is pure and potent. OPQ recommends approval of the application under conditions specified in the package insert.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. David Hawver, with Dr. Lois Freed performing a secondary review.

The key findings from the nonclinical review are summarized below:

Pharmacology:

- Aducanumab (and/or a chimeric murine version, ch12F6A) demonstrated specific binding to aggregated forms of human Aβ peptides (plaques, fibrils, protofibrils, and oligomers) that resulted in significant reductions in insoluble Aβ and amyloid plaques in the brain of aged Tg2576 mice (mouse model for AD that overexpress a mutant form of Amyloid Precursor Protein).

Toxicology

- The toxicology of aducanumab was adequately assessed in general toxicity studies in monkey and Tg2576 mouse.
- In the pivotal repeated-dose study in monkey, administration of aducanumab (0, 10, 100, or 300 mg/kg/week IV) for 4 weeks resulted in no adverse effects.

- A pivotal 13-week repeated-dose study in Tg2576 mouse with IV administration of ch12F6A (0, 10, 70, or 500 mg/kg/week) demonstrated increased incidence and/or severity of meningeal and/or cerebral vascular inflammation, thrombosis, and/or hemorrhage at the mid and high doses. There was also an associated slight exacerbation of the cerebral amyloid angiopathy that increases with aging in this mouse model. These vascular effects were similar to the drug-related ARIA reported on brain MRI in clinical studies of aducanumab. However, in a pivotal 6-month study of ch12F6A (0, 10, 40, or 250 mg/kg/week IV) in Tg2576 mouse, there were no clear drug-related adverse effects observed. Dr. Hawver notes in his review that the inconsistent results between the 13-week and the 26-week studies may be related to the difference in the age of the animals at initiation of dosing (79-80 and 69-73 weeks-old, respectively).

Reproductive and developmental toxicology

- There were no adverse effects on fertility and early embryonic development, embryofetal development, or pre- and postnatal development in studies of aducanumab (0, 100, 300, and 1000 mg/kg/week IV) conducted in rat.

Genotoxicity

- Genotoxicity studies were not conducted because antibodies are generally unable to interact with genetic material.

Carcinogenicity

- Carcinogenicity studies were not conducted because the target, aggregated Aβ, is not present in wild-type rodents. The effect of aducanumab administration on the risk of malignancy in humans is unknown.

Dr. Hawver and Dr. Freed have concluded that the nonclinical data are adequate to support the approval of aducanumab for the treatment of AD.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Gopichand Gottipati, Ph.D. (the primary reviewer), Vishnu Sharma, Ph.D., Michael Bewernitz, Ph.D., Hao Zhu, Ph.D., Atul Bhattaram, Ph.D., and Sreedharan Sabarinath, Ph.D. The final OCP signatories were Yaning Wang, Ph.D., and Mehul Mehta, Ph.D.

Following are the key findings of the OCP review:

- **Absorption:** Since aducanumab is administered intravenously, absorption is not relevant. Tmax is considered to be the end of infusion.
- **Elimination:** Mean terminal elimination half-life is 25 days.
- **Distribution:** The volume of distribution of aducanumab is 9.6 liters.

- **Metabolism and Excretion:** Aducanumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Monoclonal antibodies typically do not undergo metabolism by the cytochrome P450 system and are unlikely to be affected by drug transporters.
- **Intrinsic/Extrinsic Factors:** No dose adjustments are needed based on age, race, sex, renal or hepatic impairment, food-intake, or drug/transporter mediated interactions.
- **Food Effects:** Since aducanumab is administered intravenously, food effects are not relevant.

Dosing:
The applicant has proposed a maintenance dosing regimen of 10 mg/kg IV once every 4 weeks following an initial titration period (1 mg/kg every 4 weeks for 2 doses, 3 mg/kg every 4 weeks for 2 doses, and 6 mg/kg every 4 weeks for 2 doses). Based on a review of the available clinical data and exposure-response analyses, OCP agrees with the proposed dosing regimen.

Pharmacometrics analyses to support effectiveness of aducanumab:
OCP's conclusion regarding the evidence of effectiveness of aducanumab is informed by the following:

- Clear exposure-efficacy relationships across multiple clinical endpoints in Studies 301 and 302, even though the magnitude of drug effect on disease progression slopes were different, and evidence of dose-response for exploratory endpoints in Study 103
- Consistent pharmacodynamic effect in clinical studies, and clear relationship between brain Aβ plaque reduction and treatment effect on CDR-SB across Studies 103, 301, and 302
- Similar relationship between Aβ plaque reduction and CDR-SB reported for other agents targeting the Aβ pathway
- Extremely low probability of observing the overall positive findings from Studies 302, 301, and 103 under the null assumption that aducanumab is the same as placebo

When evaluating the relationship between SUVR and CDR-SB, the OCP review team advises using placebo-corrected, baseline-adjusted values to account for differences between studies. Such an approach has been employed in regulatory submissions previously. The reviewers caution against interpreting relationships assessed at the individual level because of potential imbalances in baseline characteristics of patients. Based on their analyses, OCP concludes that there is a clear relationship between Aβ plaque reduction and preserving of clinical function in the aducanumab development program and that the relationship is consistent with the hypothesized mechanism of action.

This relationship was supported by an analysis of 7 anti-amyloid antibodies, including 3 antibodies that specifically target aggregated forms of Aβ (donanemab, BAN2401, and aducanumab). The database included publicly reported, randomized, placebo-controlled, double-blind Phase 2 and Phase 3 studies investigating biomarkers and clinical outcomes for

at least a 12-month period. The relationship between clinical outcomes and reduction in brain amyloid as measured by SUVR or Centiloids, depending on data availability, was investigated. OCP concludes that a larger reduction of brain amyloid is associated with less change on the CDR-SB (i.e., clinical benefit). Compounds with no or minimal change in brain amyloid consistently failed to demonstrate superiority over placebo in slowing the disease progression as measured by CDR-SB.

The OCP review team recommends approval of the BLA.

6. Clinical/Statistical- Efficacy

Kevin Krudys, Ph.D., was the clinical reviewer for this application. Tristan Massie, Ph.D., was the reviewer for the Office of Biostatistics (OB) with concurrence from Kun Jin, Ph.D., Team Leader, Sue Jane Wang, Ph.D., Deputy Director, and James (Hsien-Ming) Hung, Ph.D., Division Director.

The applicant conducted two identically-designed Phase 3 clinical efficacy trials, Study 301 (221AD301) and Study 302 (221AD302), which serve as the primary basis for this application. Additional supportive data is provided from Study 103, a randomized, double-blind, placebo-controlled dose-finding study for aducanumab in early AD. The design and results of these studies will be described below.

Studies 301 (221AD301) and 302 (221AD302)

Study 301 (221AD301) and Study 302 (221AD302) were identically-designed Phase 3, multicenter, double-blind, placebo-controlled, parallel-group studies to assess the efficacy and safety of aducanumab in patients with AD. The stage of the disease at the time of enrollment was mild cognitive impairment (MCI) due to AD or mild dementia due to AD. Patients were randomized 1:1:1 to two different dosages of aducanumab ("low dose" and "high dose", further described below), or placebo, administered monthly. The studies included a 78-week placebo-controlled treatment period, followed by an 18-week safety follow-up period after the final dose. Randomization was stratified by site and by ApoE ε4 carrier status (carrier or non-carrier), and enrollment was monitored such that approximately 80% of the population included patients with a baseline clinical stage of MCI due to Alzheimer's disease. Patients who completed the placebo-controlled period had the option to enter a 5-year, dose-blind, long-term extension (LTE) study. Patients randomized to aducanumab in the placebo-controlled period continued in the same treatment group for the LTE period, and patients randomized to placebo in the placebo-controlled period were switched to receive aducanumab (high-dose or low-dose as randomized at study entry).

The studies enrolled patients age 50 to 85 years who fulfilled clinical criteria for either MCI due to Alzheimer's disease or mild Alzheimer's disease dementia, as defined by the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) framework (Albert et al., 2011), with evidence of brain Aβ pathology by visual read of a positron emission tomography (PET) scan. Patients were also required to have a Clinical Dementia Rating Scale global score of 0.5,

Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive), and a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score of 85 or lower, and at least 6 years of education or work experience. Patients were excluded for clinically significant, uncontrolled medical, neurologic, or psychiatric conditions other than AD, history of bleeding disorders, or use of antiplatelet or anticoagulant therapies other than aspirin at ≤325 mg daily. Patients were also excluded if a brain MRI performed at screening showed evidence of acute or sub-acute hemorrhage, prior macrohemorrhage, or prior subarachnoid hemorrhage (unless finding was not due to an underlying structural or vascular hemorrhage), greater than 4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis, or history of diffuse white matter disease.

The primary efficacy endpoint was the change in the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), which measures cognitive and functional impairment in AD. The following secondary and tertiary clinical endpoints were also assessed:

- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale–Cognitive Subscale - 13 -item version (ADAS-Cog 13)
- Alzheimer's Disease Cooperative Study-Activities of Daily Living - MCI
- Neuropsychiatric Inventory - 10-item version (NPI-10) (tertiary endpoint)

Key pharmacodynamic endpoints included:

- Change from baseline in amyloid signal, as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR), in a subset of sites and patients (approximately 400) at Week 26 and Week 78.
- Change from baseline in CSF levels of Aβ1-42, Aβ1-40, phosphorylated tau at residue 181 (p-Tau), and total tau (t-Tau) at Week 78 in a subset of patients.
- Change from baseline in tau PET, as measured by 18F-MK-6240 PET and quantified by a composite SUVR at the Week 78 or end-of-treatment visit, in a subset of patients.
- Change in brain volume (whole brain, whole cortex, hippocampus, and lateral ventricle), as measured by MRI at Week 30 and Week 78.

The two aducanumab dosage levels ("low dose" and "high dose") were selected to balance dose-dependent Aβ reduction and occurrence of amyloid-related imaging abnormalities (ARIA), based on findings in Study 103. The incidence of ARIA was found to be dose- and ApoE ε4 carrier-dependent in Study 103. It was hypothesized by the Applicant that dose titration would minimize the incidence of ARIA in Studies 301 and 302. For these reasons, dosing was initially dependent on ApoE ε4 carrier status, with ApoE ε4 carriers titrated to lower doses (3 mg/kg low dose and 6 mg/kg high dose) than ApoE ε4 non-carriers (6 mg/kg low dose and 10 mg/kg high dose). IV infusions of aducanumab or placebo were administered every 4 weeks over 76 weeks, for a total of 20 doses. The titration period lasted 8 or 24 weeks (2 to 6 doses), depending on the target dose.

In parallel with the initiation of Study 302, the applicant added a cohort to Study 103 to assess the impact of titration to 10 mg/kg in ApoE ε4 carriers on the incidence and severity of ARIA. The incidence of ARIA and discontinuations from study treatment due to ARIA in this cohort appeared to be reduced compared to ApoE ε4 carriers who received a fixed dose of 10 mg/kg throughout the study. Following this analysis, the sponsor submitted a protocol amendment (Version 4) to increase the high dose (after titration) for ApoE ε4 carriers from 6 mg/kg to 10 mg/kg. After implementation of protocol Version 4, subjects assigned to the ApoE ε4 carrier high-dose arm that were enrolled under prior protocol versions were titrated to 10 mg/kg following receipt of at least 2 doses of 6 mg/kg.

The dosing scheme is illustrated in Table 1, copied from Dr. Krudys's review.

Table 1: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status

Dose (Week)		0	4	8	12	16	20	24 to 76
Treatment Group		Dose (mg/kg)						
ApoE ε4 carrier	Low Dose	1	1	3	3	3	3	3
	High Dose (Protocol Version 1-3)	1	1	3	3	3	3	6
	High Dose (Protocol Version ≥4)	1	1	3	3	6	6	10
	Placebo		Saline					
ApoE ε4 non-carrier	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo		Saline					

Adapted from Table 12 in the Study 302 protocol.

Dose modifications/discontinuation for ARIA: The occurrence of certain ARIA events during the titration period required additional monitoring to continue through completion of the titration period, and created a potential for functional unblinding of investigators, patients, and caregivers. In order to mitigate this potential for unblinding, the treating healthcare provider (HCP) was not allowed to discuss AEs, including occurrence of ARIA, with the independent rating HCPs. If treatment was suspended due to ARIA during dose titration prior to the subject reaching the maximum dose, additional monitoring was performed, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding. For the LTE period, study site staff and patients were blinded to dose level.

Dose modification criteria were established to account for the expected occurrence of ARIA. Dose reduction, suspension, or termination were dependent on the radiographic severity of ARIA, as detected by MRI, the presence or absence of clinical symptoms, and the severity of symptoms, if present. Please refer to Dr. Krudys's review for a detailed description of the Dose Modification/Discontinuation Rules for ARIA.

Statistical Analysis Plan:
The Statistical Analysis Plan (SAP) was finalized on September 11, 2018. The SAP included an interim futility analysis (described below) based on a pooled analysis of Studies 301 and 302

when the studies had reached 50% completion. Using a data cut-off of December 26, 2018, futility was declared on March 21, 2019. Between the data cut-off of December 26, 2018, and the declaration of futility on March 21, 2019, the studies continued with per-protocol collection of data. Analysis of the complete set of data collected up to March 20, 2019, using the prespecified primary analysis method yielded results that appeared to show a statistically significant effect for the high dose in one of the two trials (Study 302), but not the other (Study 301). The Applicant met with the Division in a series of meetings to discuss the appropriate path forward, including the potential for additional analyses to support a marketing application. Based on these analyses, the Division agreed that the results of Study 301 and Study 302 are interpretable and suitable for additional consideration. An SAP addendum was added on November 4, 2019, prior to database lock, and after Division feedback and concurrence.

Primary analysis

A mixed model repeated measures (MMRM) model was used to analyze change from baseline CDR-SB using fixed effects of treatment, time (categorical), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). For the MMRM analysis, missing data were assumed to be missing at random. Different assumptions for missing data were explored as part of sensitivity analyses.

Analyses of secondary/tertiary endpoints

MMRM models with fixed effects specific to each endpoint were used to analyze the MMSE, ADAS-Cog 13, ADCS-ADL-MCI, and NPI-10.

Amyloid PET analysis

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. The SUVR was calculated for the following target brain regions of-interest (ROIs): composite ROI, frontal cortex, parietal cortex, lateral temporal cortex, sensorimotor cortex, anterior cingulate cortex, posterior cingulate cortex, medial temporal cortex, occipital cortex, striatum, and statistical ROI normalized to reference region activity. Additionally, SUVR ROIs including pons and deep subcortical white matter, which are believed to be least affected by amyloid pathology, were also evaluated. The composite ROI comprises major cortical regions of the frontal, parietal, lateral temporal, sensorimotor, anterior, posterior cingulate, and occipital cortices to serve as a summary measure of global cerebral amyloid burden. The statistical ROI is a region of interest consisting of the posterior cingulate cortex, precuneus, and medial frontal cortex that has been demonstrated to yield optimal group separation between subjects with low and high amyloid burden across different reference regions. A negative change from baseline in composite ROI SUVR indicates a reduction in amyloid burden and a negative treatment difference (aducanumab minus placebo) favors aducanumab. The composite ROI will serve as the ROI of primary focus.

The following reference regions will be employed: cerebellum, cerebellum cropped, cerebellar white matter, cerebellar grey matter, deep subcortical white matter, pons,

cerebellum + pons, cerebellar white matter + pons, deep subcortical white matter + cerebellum, deep subcortical white matter + pons and deep subcortical white matter + cerebellum + pons. Cerebellum will serve as the reference region of primary focus.

The composite ROI SUVR using cerebellum as the reference region was used as the primary endpoint for amyloid PET analysis.

The ^{18}F-florbetapir Amyloid PET Analysis Population was defined as all randomized subjects who received at least one dose of study treatment, used ^{18}F-florbetapir ligand for their amyloid PET scan, and had an evaluable amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

Change from baseline in brain amyloid signal, as measured by SUVR, was analyzed with an MMRM model with fixed effects of treatment group, visit, treatment group-by-visit interaction, baseline SUVR, baseline SUVR-by-visit interaction, baseline MMSE, ApoE ε4 status, and baseline age.

Sample Size

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a standard deviation (SD) of 1.92, and a drop-out rate of 30%.

Adjustment for Multiplicity

A sequential (closed) testing procedure was used to control the overall Type I error rate for the primary endpoint according to the following order: high-dose aducanumab versus placebo, and low-dose aducanumab versus placebo. All comparisons after the initial comparison with $p > 0.05$ were not to be considered statistically significant. Secondary endpoints were rank prioritized according to the following order: MMSE, ADAS-Cog 13, ADCS-ADL-MCI. To control for Type I error for each of the secondary endpoints, a sequential (closed) procedure, including both the order of the secondary endpoints and treatment comparisons was to be used. If statistical significance was not achieved for 1 or 2 treatment comparisons (i.e., high dose or low dose), all endpoints of a lower rank would not be considered statistically significant for that 1 or 2 treatment comparisons, respectively.

Dr. Massie notes in his review that "The closed testing for each of the secondary endpoints suggests that if the low dose is not significant, the following tests and p-values for the high dose for lower endpoints in the hierarchy would not be allowable without inflating type I error. It seems that the plan was slightly ambiguous unless one interpreted it with the presumption that strong control of type I error over all key hypotheses is a requirement. The sponsor argued in their response to appendix 2 of the advisory committee briefing package that if the high dose was significant on the primary then it could be tested on the secondary regardless of the primary result for the low dose. However, the plan is not consistent with

testing all key endpoints for the high dose before testing any key endpoints for the low dose. Type I error is not strongly controlled and could be as high as .0975 across all key hypotheses involving both doses and multiple endpoints if testing of the high dose could proceed regardless of the low dose result on the primary endpoint under the weak null, e.g., if the null hypothesis was false on the primary for one dose but true for the other dose and true for both doses on the secondaries then the chance of one or more type I errors in this scenario could be as high as .0975 if significance on the primary allowed further testing for the same dose regardless of the primary result for the other dose. For this reason strong control is needed."

Dr. Krudys notes that "The Type I error was controlled at a level of 0.05 for the primary endpoint. The family-wise Type I error for the secondary endpoints was controlled at a maximum of 0.1. After accounting for correlation of endpoints, the applicant calculated the family-wise Type I error for secondary endpoints to be 0.09 (i.e., a 4.5% probability for a false positive result)."

The OCP review also discusses this issue and makes similar observations, noting that "For the primary endpoint, a more strict type I error rate of 0.05 (2.5% chance of falsely concluding the drug is better than placebo based on the primary endpoint if the drug is not different from placebo) was planned while a less strict type I error rate of 0.1 (5% chance of falsely concluding the drug is better than placebo based on any secondary endpoint if the drug is not different from placebo) was planned for the secondary endpoints. After accounting for the correlation between MMSE and CDR-SB, the actual type I error rate for the secondary endpoints was updated to be 0.09 (4.5% chance of falsely concluding the drug is better than placebo based on any secondary endpoint if the drug is not different from placebo)."

Interim analysis for Futility

An interim analysis for futility was planned to occur after approximately 50% of the subjects had the opportunity to complete the Week 78 visit for both Studies 301 and 302. The analysis was performed by an independent data monitoring committee (IDMC) that was not involved in the conduct of the study after unblinding. Following review of the unblinded results of the interim analysis, the IDMC was to make a recommendation to the Applicant based on pre-specified criteria.

The futility criteria were based on conditional power, which was defined as the chance that the primary efficacy endpoint analysis would be statistically significant in favor of aducanumab at the planned final analysis, given the data considered for the futility analysis. Conditional power assumed that the future unobserved treatment effect would be equal to an estimate based on pooled observed data from Studies 301 and 302. The studies were to be considered futile if both studies had a conditional power for the primary efficacy analysis that was less than 20% in both the high-dose and low-dose treatment groups. Given insufficient knowledge of aducanumab's potential effects on various functional/cognition endpoints or in certain subgroups at the planning time, the SAP specified that other data in addition to the pre-specified criteria could also be considered by the IDMC. In the interim

analysis, data from patients who were enrolled in the study but had not had the opportunity to complete the Week 78 visit were not included in the analysis, although this criterion was not described in the SAP for the interim analysis.

Subgroup Analyses

Subgroup analyses for CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI were conducted for the following pre-defined groups:

- Laboratory ApoE ε4 status (carrier or non-carrier)
- Baseline clinical stage (MCI due to Alzheimer's disease or mild Alzheimer's disease)
- Use of Alzheimer's disease concomitant medication at baseline (yes or no)
- Baseline MMSE (MMSE ≤26 or MMSE ≥27)
- Region (United States, Europe/Canada/Australia, Asia)
- Age (≤64, 65-74, ≥75)

Subgroup analyses for PET SUVR in the ^{18}F-florbetapir amyloid PET analysis population were prespecified for groups defined by laboratory ApoE ε4 status, baseline clinical stage, and baseline SUVR value in quartiles. Additional subgroup analyses were performed for all of the factors in the list above, except for region.

SAP Addendum

The SAP addendum (submitted on November 4, 2019) specified that the primary analysis, using the previously specified MMRM model, would be conducted in the intent-to-treat (ITT) population, excluding data collected after March 20, 2019 (prior to the futility declaration on March 21, 2019).

The SAP described the following analysis populations:

Intent-to-Treat (ITT) Population: all randomized subjects who received at least one dose of study treatment, excluding data collected after March 20, 2019.
Opportunity-to-Complete (OTC) analysis: The MMRM model for the primary analysis was to be repeated in the OTC population, defined as the ITT population that has had the opportunity to complete Week 78 by March 20, 2019.

Results

Early Termination of Studies 301 and 302

The Applicant announced the termination of Studies 301 and 302 on March 21, 2019, based on the pre-specified interim futility analysis that pooled data from the two studies. Pooling of the data assumed that the treatment effect would be similar in the two studies. At the interim data cutoff date of December 26, 2018, 57% of participants from Study 301, and 49% of participants from Study 302 had the opportunity to complete the Week 78 visit. Between the data cut-off of December 26, 2018, and the declaration of futility on March 21, 2019, the studies continued with per-protocol collection of data, as planned, as the studies were active

and continuing with an expectation of proceeding to conclusion, as is standard for the conduct of futility analyses. Analysis of the complete set of data collected up to March 20, 2019, using the prespecified primary analysis methods yielded results that appeared to show a statistically significant effect for the high dose in one of the two trials (Study 302) but not the other (Study 301). During a Type C Meeting on June 14, 2019, the applicant and the Division agreed that it would have been more appropriate if futility had not been declared, and the Division recommended that further analyses of the available data be conducted to understand the effect of early termination of the studies on the interpretability of the data and to address the partially conflicting results for Study 301 and Study 302.

The applicant initially sought advice from the Agency about the appropriate interpretation of the data and next steps. Recognizing the unique and complex circumstances, the Division recognized that it was premature to provide specific guidance to the applicant on interpretation without a maximized understanding of the data that exceeds that which could be achieved in a single meeting with only a high-level summary presentation of results and issues. Given the tremendous unmet need in AD and the potential importance of these findings, plans for an ongoing analytical dialogue were initiated to maximally understand the findings from Study 301 and Study 302, in order to fully inform advice on appropriate next steps. The analyses were intended to understand the discordance between the studies, and there was no a priori hypothesis that aducanumab was or was not effective for the treatment of AD, or that one study had the "right" results and the other study had the "wrong" results. The findings could have concluded that there was evidence of bias, or study conduct issues that render either study uninterpretable. However, hypotheses were developed regarding potential sources of discordance, that were predetermined to the maximum extent possible, to guide the exploratory analyses. The Applicant had a series of further meetings with the Agency to discuss additional analyses of the data and consider advice on next steps (please refer to Dr. Krudys's review for a description of the meetings). As an initial aspect of further consideration, virtual completion of the studies using modeling and simulation was used to explore the range of plausible outcomes, had the studies been run to completion. At a Type C meeting on October 21, 2019, it was agreed that the early termination of the aducanumab program did not compromise the interpretability of the efficacy results of Studies 301 and 302, and that the data were suitable for additional consideration. It was also agreed that it would be appropriate to conduct the pre-specified primary analysis specified on the more complete ITT dataset that includes assessments collected before March 21, 2019. The Applicant submitted an SAP addendum on November 4, 2019, prior to database lock, and after Division feedback. The results described below are based on the final datasets from Studies 301 and 302, and on analyses that were agreed upon by the Agency.

Results of Study 301

A total of 6173 patients were screened for the study, and 1653 patients were randomized. Table 2 shows the key baseline demographics for Study 301. Demographic characteristics were well-balanced across the treatment arms, and generally representative of the patient population, except for an under-representation of African American and Hispanic patients. The mean age at baseline was 70 years, with a range of 50 to 85. The study included 80%

patients with MCI due to AD and 20% with mild Alzheimer's dementia, and 56% of the overall population was receiving concomitant AD medication at baseline. A total of 46% of the patients enrolled were in the United States. The most common reason for study discontinuation was the administrative decision to terminate the study. Among those with the opportunity to complete the study by March 20, 2019, 85.5% completed the study. The percentage of patients who discontinued the study due to adverse events was low (4.6% in low dose, 5.0% in high dose, and 2.9% in placebo).

Table 2: Study 301 Baseline Demographics (ITT Population)

Demographic Parameters	**Placebo** (N=545) n (%)	**Treatment Group**		
		Aducanumab Low Dose (N=547) n (%)	**Aducanumab High Dose** (N=555) n (%)	**Total** (N=1647) n (%)
Sex				
Male	258 (47.3%)	263 (48.1%)	263 (47.4%)	784 (47.6%)
Female	287 (52.7%)	284 (51.9%)	292 (52.6%)	863 (52.4%)
Age				
Mean years (SD)	69.8 (7.7)	70.4 (7.0)	70.0 (7.7)	70.1 (7.5)
Median (years)	70.0	71.0	71.0	71.0
Min, max (years)	50, 85	51, 85	50, 85	50, 85
Baseline Clinical Stage				
MCI due to AD	443 (81.3%)	440 (80.4%)	442 (79.6%)	1325 (80.4%)
Mild AD	102 (18.7%)	107 (19.6%)	113 (20.4%)	322 (19.6%)
Laboratory ApoE ε4 Status				
Carrier	376 (69.0%)	391 (71.5%)	378 (68.1%)	1145 (69.5%)
Homozygote	104 (19.1%)	101 (18.5%)	104 (18.7%)	309 (18.8%)
Heterozygote	272 (49.9%)	290 (53.0%)	274 (49.4%)	836 (50.8%)
Non-carrier	167 (30.6%)	156 (28.5%)	176 (31.7%)	499 (30.3%)
Undetermined	2 (0.4%)	0	1 (0.2%)	3 (0.2%)
Concomitant AD medication				
Any AD medication at baseline	299 (54.9%)	317 (58.0%)	313 (56.4%)	929 (56.4%)
Only cholinesterase inhibitors	242 (44.4%)	257 (47.0%)	264 (47.6%)	763 (46.3%)
Baseline CDR-SB	545	547	554	1646
Mean (SD)	2.40 (1.01)	2.43 (1.01)	2.40 (1.01)	2.41 (1.01)
Median	2.50	2.50	2.50	2.50
Min, Max	0.5, 7.0	0.5, 8.0	0.5, 5.5	0.5, 8.0
Baseline MMSE	545	547	555	1647
<24	3 (0.6%)	1 (0.2%)	1 (0.2%)	5 (0.3%)
≥24 - <27	284 (52.1 %)	282 (51.6%)	302 (54.4%)	868 (52.7%)
≥27 - ≤30	258 (47.3%)	264 (48.3%)	252 (45.4%)	774 (47.0%)
Region				
United States	251 (46.1%)	260 (47.5%)	252 (45.4%)	763 (46.3%)
Rest of the World				

Demographic Parameters	Placebo (N=545) n (%)	Treatment Group		
		Aducanumab Low Dose (N=547) n (%)	Aducanumab High Dose (N=555) n (%)	Total (N=1647) n (%)
Europe/Canada/Australia	242 (44.4%)	236 (43.1%)	243 (43.8%)	721 (43.8%)
Asia	52 (9.5%)	51 (9.3%)	60 (10.8%)	163 (9.9%)

Source: Table 14, 16, 17, 49, and Table 59 in Study 301 CSR

Primary Endpoint

The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 78, did not show a difference in the aducanumab high-dose treatment arm compared to placebo (0.03 [2%], p = 0.8330). A numerical difference of -12% in favor of the aducanumab low-dose treatment arm, compared to placebo, was observed; however, this was not statistically significant. These results were verified by the clinical and statistical reviewers.

Table 3: Study 301 Primary Endpoint Analysis (ITT population)

	Placebo	Aducanumab Low Dose	Aducanumab High Dose
Baseline CDR-SB			
n	545	547	554
Mean	2.40	2.43	2.40
Change from Baseline in CDR-SB at Week 78			
n	333	331	295
Adjusted mean (standard error)	1.56 (0.108)	1.38 (0.108)	1.59 (0.111)
Difference from placebo (%)		-0.18 (-12%)	0.03 (2%)
95% CI for difference		(-0.469, 0.110)	(-0.262, 0.326)
p-value (compared with placebo)		0.2250	0.8330

Source: Table 22 from Study 301 CSR

Secondary Endpoints

A summary of the analysis results for the secondary endpoints is provided in Table 4.

Table 4: Study 301 Secondary Endpoint Analysis (ITT population)

	Placebo	Aducanumab Low Dose	Aducanumab High Dose
Baseline MMSE			
n	545	547	554
Mean	26.4	26.4	26.4
Change from Baseline in MMSE at Week 78			
n	322	334	297
Adjusted mean (standard error)	-3.5 (0.21)	-3.3(0.21)	-3.6 (0.21)
Difference from placebo (%)		0.2 (-6%)	-0.1 (3%)
95% CI for difference		(-0.35, 0.74)	(-0.62, 0.49)
p-value (compared with placebo)		0.4795	0.8106
Baseline ADAS-Cog 13			
n	542	547	553
Mean	22.48	22.52	22.40
Change from Baseline in ADAS-Cog 13 at Week 78			
n	331	332	294
Adjusted mean (standard error)	5.14 (0.38)	4.56 (0.38)	4.55 (0.38)
Difference from placebo (%)		-0.58 (-11%)	-0.59 (-11%)
95% CI for difference		(-1.58, 0.42)	(-1.61, 0.43)
p-value (compared with placebo)		0.2536	0.2578
Baseline ADCS-ADL-MCI			
n	541	546	553
Mean	43.0	42.9	42.9
Change from Baseline in ADCS-ADL-MCI at Week 78			
n	331	330	298
Adjusted mean (standard error)	-3.8 (0.35)	-3.1 (0.35)	-3.1 (0.35)
Difference from placebo (%)		0.7 (-18%)	0.7 (-18%)
95% CI for difference		(-0.19, 1.64)	(-0.25, 1.61)
p-value (compared with placebo)		0.1225	0.1506

Sources: Tables 92, 104 and 116 in Study 301 CSR

Tertiary Clinical Endpoint

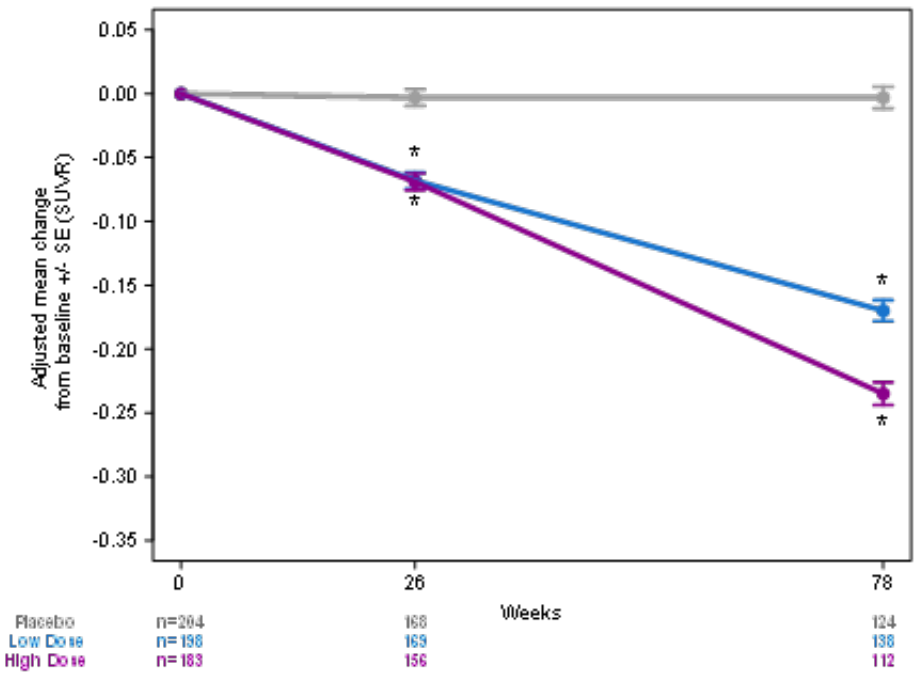
The adjusted mean change from baseline in NPI-10 at Week 78, compared to placebo, was 0.1 (8%, p = 0.9071) for aducanumab high dose, and -1.0 (-83%, nominal p=0.046) for aducanumab low dose.

Pharmacodynamic Endpoints

Amyloidβ Pathology

An Aβ PET sub-study enrolled approximately 35% of the ITT population in Study 301. In the ^{18}F-florbetapir Aβ PET analysis population (n=585; 198 low dose, 183 high dose, and 204 placebo), aducanumab treatment produced dose- and time-dependent reductions in brain amyloid beta plaque. Change from baseline in brain amyloid signal relative to placebo, as measured by composite SUVR, was similar in the low-dose and high-dose groups at Week 26, -0.065 ($p<0.0001$) and -0.066 ($p<0.0001$), respectively (dosing was similar in both groups during titration). At Week 78, the adjusted mean change from placebo was -0.167 ($p<0.0001$) and -0.232 ($p<0.0001$) in the low-dose and high-dose groups, respectively, indicating time- and dose-dependent relationships (Figure 1). Consistent findings were observed for other brain regions and when using additional reference regions. Adjusted mean changes from baseline in brain amyloid for all subgroups of interest demonstrated significant reduction in SUVR relative to placebo with larger reductions for the high-dose treatment arm compared to the low-dose treatment arm. In addition, a statistically significant, dose-dependent increase in CSF $A\beta_{1-42}$ levels was observed at Week 78 for the high-dose group as compared to placebo ($p=0.0006$).

Figure 1: Study 301 Change from Baseline in Aβ PET Composite SUVR



Created by reviewer from Table 23 in Study 301 CSR
* $p<0.0001$

Continued reduction in brain amyloid as measured by SUVR was observed in patients who remained on aducanumab treatment throughout the placebo-controlled and LTE periods. The mean change from baseline in SUVR (95% CI) was -0.234 (-0.2509, -0.2162) at Week 78, and -0.290 (-0.3148, -0.2670) at Week 132 for the high dose, and -0.171 (-0.1871, -0.1554) at Week 78, and -0.209 (-0.2306, -0.1783) at Week 132, for the low dose.

Tau Pathology and Neurodegeneration

CSF biomarker longitudinal assessments were conducted in small subsets of participants (approximately 3% of the ITT population) in Study 301.

In a subset of 53 patients (20 low dose, 18 high dose, and 15 placebo), a numerical decrease relative to placebo in CSF-p-Tau levels of similar magnitude was observed for the low dose (-11.27 pg/mL, p=0.2726) and the high dose (-10.95 pg/mL, p=0.3019). In a subset of 50 patients (19 low dose, 17 high dose, and 14 placebo), aducanumab produced a numerical decrease in CSF t-Tau levels relative to placebo at Week 78 (-12.83 pg/mL, p=0.8453 for low dose, and -69.25 pg/mL, p=0.3098 for the high dose).

Conclusion of Study 301

Study 301 did not demonstrate effectiveness on its prespecified clinical outcomes. The study showed a statistically significant time- and dose-dependent effect on reduction of Aβ plaques. Effects on tau proteins numerically favored aducanumab but were not statistically significant. The change on measures of Aβ plaques were highly persuasive. Study 301 also contributes to the understanding of the relationship between change from baseline in reduction in brain Aβ and the estimate of the treatment effect for CDR-SB (see Figure 6 and associated text, below).

Results of Study 302

A total of 6757 patients were screened for entry into the study and 1638 patients were randomized. Table 5 shows the key baseline demographics for Study 302. Demographic characteristics were balanced across the treatment arms and generally representative of the patient population, except for an under-representation of African American and Hispanic patients. The mean age at baseline was 71 years, with a range of 50 to 85. The study included 82% patients with MCI due to AD, and 18% with mild Alzheimer's dementia; 52% of the overall population was receiving a concomitant AD medication at baseline. A total of 40% of the patients enrolled were in the United States. The most common reason for study discontinuation was the administrative decision to terminate the study. Among those with the opportunity to complete the study by March 20, 2019, 87.6% completed the study. The percentage of patients who discontinued the study due to adverse event was low (2.4% in low dose, 3.7% in high dose, and 1.8% in placebo).

Table 5: Study 302 Baseline Demographics (ITT Population)

Demographic Parameters	Placebo (N=548) n (%)	Treatment Group		
		Aducanumab Low Dose (N=543) n (%)	Aducanumab High Dose (N=547) n (%)	Total (N=1638) n (%)
Sex				
Male	258 (47.1%)	274 (50.5%)	263 (48.1%)	795 (48.5%)
Female	290 (52.9%)	269 (49.5%)	284 (51.9%)	843 (51.5%)
Age				
Mean years (SD)	70.8 (7.4)	70.6 (7.5)	70.6 (7.5)	70.7 (7.4)
Median (years)	71.0	72.0	72.0	72.0
Min, max (years)	50, 85	50, 85	50, 85	50, 85
Baseline Clinical Stage				
MCI due to AD	446 (81.4%)	452 (83.2%)	438 (80.1%)	1336 (81.6%)
Mild AD	102 (18.6%)	91 (16.8%)	109 (19.9%)	302 (18.4%)
Laboratory ApoE ε4 Status				
Carrier	368 (67.2%)	362 (66.7%)	365 (66.7%)	1095 (66.8%)
Homozygote	92 (16.8%)	97 (17.9%)	77 (14.1%)	266 (16.2%)
Heterozygote	276 (50.4%)	265 (48.8%)	288 (52.7%)	829 (50.6%)
Non-carrier	178 (32.5%)	178 (32.8%)	181 (33.1%)	537 (32.8%)
Undetermined	2 (0.4%)	3 (0.6%)	1 (0.2%)	6 (0.4%)
Concomitant AD medication				
Any AD medication at baseline	282 (51.5%)	281 (51.7%)	285 (52.1%)	848 (51.8%)
Only cholinesterase inhibitors	235 (42.9%)	230 (42.4%)	228 (41.7%)	693 (42.3%)
Baseline CDR-SB				
Mean (SD)	2.47 (1.00)	2.46 (1.01)	2.51 (1.05)	2.48 (1.02)
Median	2.50	2.50	2.50	2.50
Min, Max	0.5, 6.0	0.5, 5.5	0.5, 5.5	0.5, 6.0
Baseline MMSE				
<24	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
≥24 - <27	296 (54.0%)	314 (57.8%)	296 (54.1%)	906 (55.3%)
≥27 - ≤30	252 (46.0%)	228 (42.0%)	250 (45.7%)	730 (44.6%)
Region				
United States	218 (39.8%)	218 (40.1%)	216 (39.5%)	652 (39.8%)
Rest of the World				
Europe/Canada	287 (52.4%)	287 (52.9%)	291 (53.2%)	865 (52.8%)
Asia	43 (7.8%)	38 (7.0%)	40 (7.3%)	121 (7.4%)

Source: Tables 14, 16, 17, 49, and 59 Study 302 CSR

Primary Endpoint

The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 78, demonstrated a statistically significant treatment effect in the aducanumab high-dose treatment arm, compared to placebo (-0.39 [-22%], p=0.0120) (Table 6). The low-dose

treatment arm demonstrated a numerical advantage compared to placebo (-0.26 [-15%]), p=0.0901.

Table 6: Study 302 Primary Endpoint Analysis (ITT population)

	Placebo	Aducanumab Low Dose	Aducanumab High Dose
Baseline CDR-SB			
n	548	543	547
Mean	2.47	2.46	2.51
Change from Baseline in CDR-SB at Week 78			
n	288	290	299
Adjusted mean (standard error)	1.74 (0.115)	1.47 (0.116)	1.35 (0.115)
Difference from placebo (%)		-0.26 (-15%)	-0.39 (-22%)
95% CI for difference		(-0.569, 0.041)	(-0.694, -0.086)
p-value (compared with placebo)		0.0901	0.0120

Source: Table 22 from Study 302 CSR

Several SAP-defined and post hoc sensitivity analyses were performed for the primary endpoint. Results from these analyses were supportive of the primary analysis and demonstrated that the statistically significant results for the primary endpoint were not sensitive to departures from the missing at random assumption. Notably, an analysis of the CDR-SB at Week 78 remained statistically significant in the OTC population (n=953) for the high dose, 95% CI = [-0.70, 0-.02], p=0.0368.

The estimate of the treatment effect favored aducanumab across all prespecified subgroups of interest.

ApoE ε4 status. It is of particular interest whether ApoE ε4 carriage had an impact on efficacy because it is the most relevant known genetic risk factor for the development of sporadic Alzheimer's disease and is thought to affect disease pathogenesis via both amyloid-dependent and amyloid-independent mechanisms. As noted by Dr. Massie in the statistical review, there was a trend for a lower response in ApoE ε4 non-carriers on the CDR-SB (ITT analysis). Analyses of dosing in the study show that non-carriers received a higher dose than carriers throughout the study, but did not show a better response. Dr. Massie interprets this to suggest that there may be no or little effect of aducanumab in ApoE ε4 non-carriers. However, additional analyses using the OTC and uncensored datasets question the robustness of this finding. Dr. Krudys notes in his review that in the OTC dataset, which by definition only includes patients who have had the opportunity to receive all doses, the percent decline versus placebo for CDR-SB was -23% for ApoE ε4 carriers and -19% for ApoE ε4 non-carriers. In the uncensored ITT population, the percent decline versus placebo for CDR-SB was -26% for ApoE ε4 carriers and -20% for ApoE ε4 non-carriers. Also, brain amyloid is similarly reduced in ApoE ε4 carriers and ApoE ε4 non-carriers, suggesting the underlying

pharmacodynamic effect is similar in the two populations. Dr. Krudys concludes that the data suggest a treatment effect exists for both ApoE ε4 carriers and ApoE ε4 non-carriers, although it is possible that the effect may be smaller in ApoE ε4 non-carriers. Given that non-carriers constituted only approximately 30% of the study population, and considering the number of patients who did not have complete 78-week data due to early termination, a definitive conclusion about the treatment effects and ApoE ε4 status cannot be made based on the current data, but the breadth of evidence that is available suggests that an effect of the drug is present regardless of ApoE ε4 status.

Impact of Protocol amendment, Version 4. Dr. Massie also conducted exploratory analyses to look at the impact of the protocol amendment (Version 4 [PV4]) that increased the high dose for ApoE ε4 carriers to 10 mg/kg on the treatment effect for the CDR-SB. Based on his analyses, Dr. Massie concludes that Study 302 may be positive because of a worse placebo response in the post-PV4 population. Dr. Massie states the following in his review:

"Placebo was dramatically worse in the APOE+ stratum post-PV4 for CDRSB as compared to pre-PV4, while the low dose was slightly better and the high dose was slightly worse from pre-PV4 to post-PV4. The low dose being numerically better than high is the opposite of what would be expected, since only the high dose got a dose increase for post-PV4. Since placebo worsened significantly compared to pre-PV4 and the high dose is numerically worse than low post-PV4, it suggests that placebo worsening after PV4 could be the driver of the overall result."

This argument was also presented by Dr. Massie at the Advisory Committee meeting as a reason for doubting the results of Study 302, and the committee members appeared to find this argument persuasive. In the clinical review, Dr. Krudys has identified some issues with these analyses:

"Comparing the placebo-corrected effect size for the high-dose treatment arm in the Pre-PV4 population to the placebo-corrected effect size for the high-dose treatment arm in the Post-PV4 population is a straightforward way to determine whether the Post-PV4 population is driving the overall results of Study 302. The effect sizes for CDR-SB are -0.35 for Pre-PV4 and -0.38 for Post-PV4. The similarity of the two estimates and their consistency with the overall treatment effect estimate clearly demonstrate that there is no basis for the conclusion that placebo change in the Post-PV4 population is driving the result in Study 302."

The Division Director memo in the OCP review also comments on the analysis and concurs with Dr. Krudys's conclusion, noting, "based on the correct numbers, there is no impact of placebo worsening on the placebo-corrected effect sizes in CDR-SB values for the high dose."

Dr. Krudys argues that because there is a greater proportion of patients who are missing data at Week 50 or Week 78 in the Post-PV4 population compared to the Pre-PV4 population due to early study termination, there are limitations to using PV4 as a parameter by which to analyze the datasets from Studies 301 and 302. He suggests that the OTC dataset, which is

limited to patients who had the opportunity to receive all doses, is the more relevant dataset for analyzing the impact of dosing in Studies 301 and 302, and this was the dataset that was used for the exploratory analyses that are described further below.

In general, differences in placebo response do not appear to explain why Study 302 was successful and Study 301 was not. As Dr. Krudys states in his review, "First, the placebo decline for CDR-SB in both studies was consistent with expectation (i.e., placebo decline was assumed to be 2 for power calculations) and not markedly different from other studies in similar populations. Second, placebo decline was actually lower for MMSE in Study 302 compared to Study 301 and placebo decline was similar for ADAS-Cog 13 between the two studies. Positive outcomes were observed across endpoints in Study 302, not just ones with a greater placebo decline. Third, similar treatment effect estimates relative to placebo for CDR-SB were obtained for the two low dose arms. Finally, placebo decline cannot account for the apparent dose-response relationship observed in 302."

Demographic/disease differences in the analysis populations. Dr. Massie notes in the statistical review that there were some differences in demographics and disease characteristics between the total population and those who completed the Week 78 assessment. However, the differences are generally small and are unlikely to have a meaningful impact on the overall treatment effect in this study. Furthermore, the choice of dataset, ITT or OTC, did not influence the conclusions.

Secondary Endpoints

Significant differences from placebo were observed for the high-dose treatment arm at Week 78 for all secondary endpoints. A summary of the analysis results for the secondary endpoints has been adapted from Dr. Krudys's review (Table 3). The low-dose treatment arm demonstrated favorable numerical trends for ADAS-Cog 13 and ADCS-ADL-MCI, but not for MMSE. Subgroup analyses for the secondary endpoints showed that all prespecified subgroups favored high-dose aducanumab, except for one (MMSE in ApoE ε4 non-carriers).

Sensitivity analyses were also performed for secondary endpoints, and were consistent with the primary analysis, except for MMSE, after censoring for intercurrent events. Although the p-value for this sensitivity analysis increased from 0.0493 to 0.1008, the magnitude of the treatment effect only dropped from -18% to -16%. The choice of dataset (ITT or OTC) did not alter the conclusions.

Table 7: Study 302 Secondary Endpoint Analysis (ITT population)

	Placebo	Aducanumab Low Dose	Aducanumab High Dose
Baseline MMSE			
n	548	543	547
Mean	26.4	26.3	26.3
Change from Baseline in MMSE at Week 78			
n	288	293	299
Adjusted mean (standard error)	-3.3 (0.22)	-3.3 (0.22)	-2.7 (0.21)
Difference from placebo (%)		-0.1 (3%)	0.6 (-18%)
95% CI for difference		(-0.65, 0.48)	(0.00, 1.13)
p-value (compared with placebo)		0.7578	0.0493
Baseline ADAS-Cog 13			
n	545	542	546
Mean	21.87	22.49	22.25
Change from Baseline in ADAS-Cog 13 at Week 78			
n	287	289	293
Adjusted mean (standard error)	5.16 (0.40)	4.46 (0.41)	3.76 (0.40)
Difference from placebo (%)		-0.70 (-14%)	-1.40 (-27%)
95% CI for difference		(-1.76, 0.36)	(-2.46, -0.34)
p-value (compared with placebo)		0.1962	0.0097
Baseline ADCS-ADL-MCI			
n	545	540	545
Mean	42.6	42.8	42.5
Change from Baseline in ADCS-ADL-MCI at Week 78			
n	283	286	295
Adjusted mean (standard error)	-4.3 (0.38)	-3.5 (0.38)	-2.5 (0.38)
Difference from placebo		0.7	1.7
95% CI for difference		(-0.27, 1.73) (-16%)	(0.75, 2.74) (-40%)
p-value (compared with placebo)		0.1515	0.0006

Source: Tables 92, 104 and 116 in Study 302 CSR

Tertiary Clinical Endpoint

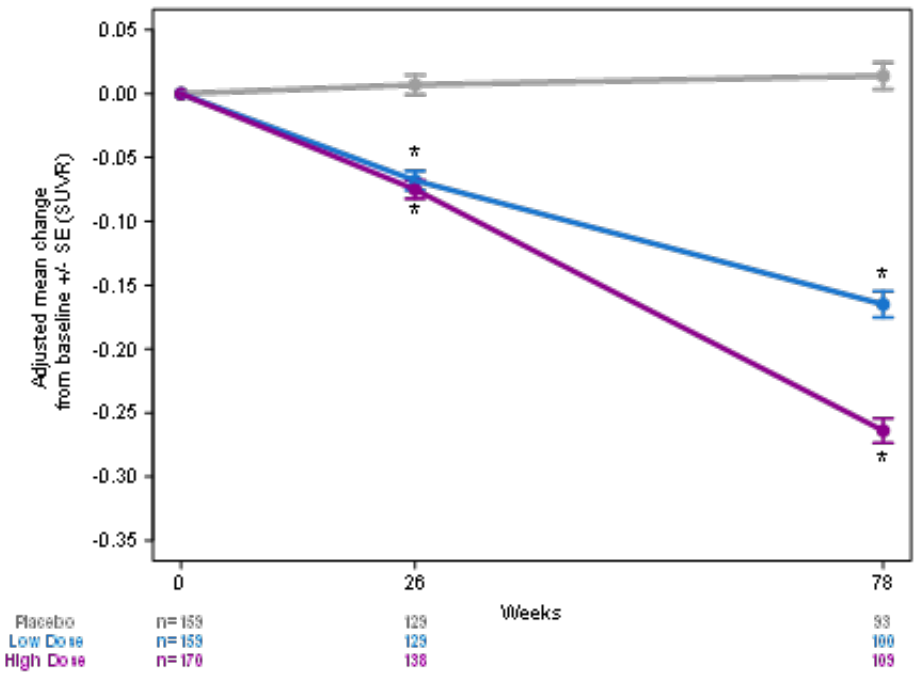
The adjusted mean change from baseline in NPI-10 at Week 78, compared to placebo, was -1.3 (-87%, nominal p = 0.0215) for aducanumab high dose, and -0.5 (-33%, p=0.3921) for aducanumab low dose.

Pharmacodynamic Endpoints

Amyloidβ Pathology

An Aβ PET sub-study enrolled approximately 30% of the ITT population in Study 302. In the 18F-florbetapir Aβ PET analysis population (n=488; 159 low dose, 170 high dose, and 159 placebo), aducanumab treatment produced significant, dose- and time-dependent reductions in brain amyloid beta plaque. Change from baseline in brain amyloid signal relative to placebo as measured by SUVR was similar in the low-dose and high-dose groups at Week 26, -0.075 ($p<0.0001$) and -0.082 ($p<0.0001$), respectively, due to similar dosing during titration. At Week 78, the adjusted mean change from placebo was -0.179 ($p<0.0001$) and -0.278 ($p<0.0001$) in the low-dose and high-dose groups, respectively, indicating time- and dose-dependent relationships (Figure 2). Consistent findings were observed for other brain regions and when using additional reference regions. Adjusted mean changes from baseline in brain amyloid for all subgroups of interest demonstrated significant reduction in SUVR relative to placebo, with larger reductions for the high-dose treatment arm compared to the low-dose treatment arm. In addition, a statistically significant, dose-dependent increase in CSF $A\beta_{1-42}$ levels was observed at Week 78 for both the low-dose and high-dose groups as compared to placebo ($p<0.0001$).

Figure 2: Study 302 Change from Baseline in Aβ PET Composite SUVR



Created by reviewer from Table 23 in Study 302 CSR
* $p<0.0001$

Continued reduction in brain amyloid, as measured by SUVR, was observed in patients who remained on aducanumab treatment throughout the placebo-controlled and LTE periods. The mean change from baseline in SUVR (95% CI) was -0.262 (-0.2811, -0.2432) at Week 78, and -0.330 (-0.3534, -0.3056) at Week 132 for the high dose, and -0.163 (-0.1831, -0.1433) at Week 78, and -0.218 (-0.2450, -0.1905) at Week 132 for the low dose.

Prespecified correlation analyses of individual CDR-SB and brain Aβ plaque levels were performed for the ^{18}F-florbetapir amyloid PET analysis population. A total of 329 patients were pooled from the low-dose and high-dose treatment groups and were included in the analyses. A positive, but relatively weak (Spearman correlation of 0.19 [95% CI: 0.048, 0.327]) relationship was observed between change from baseline in PET composite SUVR at Week 78 and change from baseline in CDR-SB Week 78. Nominally significant correlations in the expected direction for all three secondary endpoints were also observed. To investigate potential lag between reduction of brain Aβ plaque levels and clinical endpoints, correlations between Week 78 SUVR and Week 106 clinical endpoints were assessed. The correlations were all nominally significant and stronger than when Week 78 clinical endpoints were used.

Tau Pathology and Neurodegeneration

CSF biomarker longitudinal assessments were conducted in small subsets of participants (approximately 5% of the ITT population) in Study 302.

Aducanumab treatment reduced markers of tau pathophysiology (CSF p-Tau and Tau PET) and neurodegeneration (t-Tau). A substudy in 78 patients (33 low dose, 17 high dose, and 28 placebo) demonstrated a dose-dependent decrease in CSF p-Tau levels at Week 78, relative to placebo, for the aducanumab low dose (-15.64 pg/mL, p=0.0035) and high dose (-22.44 pg/mL, p=0.0005).

Another substudy was conducted with pooled data from Study 301 and Study 302 to evaluate the effect of aducanumab on tau using PET imaging with the ^{18}F-MK6240 tracer. The PET signal was quantified using the SUVR method to estimate brain levels of tau in areas expected to be affected by Alzheimer's disease pathology, compared to a brain region expected to be spared of such pathology. The population consisted of 37 patients (14 low dose, 11 high dose, and 12 placebo). The adjusted mean change from baseline in tau PET SUVR relative to placebo at follow-up was in favor of the aducanumab high dose in the medial temporal ($p<0.001$), temporal ($p<0.05$) and frontal ($p<0.05$) brain regions. No statistically significant differences were observed for the cingulate, parietal, or occipital cortices.

In a substudy of 78 patients (33 low dose, 17 high dose, and 28 placebo), aducanumab produced a dose-dependent decrease in CSF t-Tau levels relative to placebo at Week 78 (-86.74 pg/mL, p=0.0148 for low dose and -112.05 pg/mL, p=0.0088 for the high dose).

Conclusions of Study 302

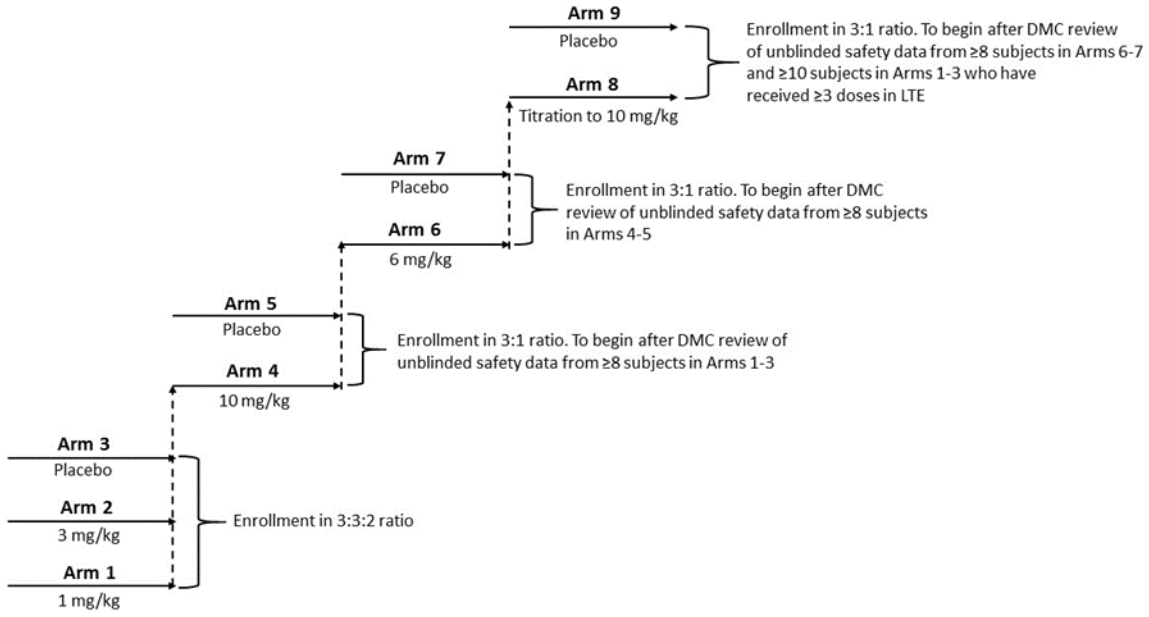
Study 302 is an adequate and well-controlled study that demonstrated a clinically meaningful and statistically significant treatment effect for the high dose of aducanumab on an accepted

primary endpoint, the CDR-SB, and across multiple secondary and tertiary endpoints. The study showed statistically significant time- and dose-dependent effects on reduction of Aβ plaques and tau proteins. The change on measures of Aβ plaques were highly persuasive, and correlated with changes on clinical outcomes.

Study 103

Study 103 was a multicenter, randomized, double-blind, placebo-controlled, staggered, parallel-group study of aducanumab in patients with prodromal or mild Alzheimer's disease (i.e., mild Alzheimer's disease dementia). The primary objective of the study was to assess the safety and tolerability of multiple doses of aducanumab; however, the study also included many of the same efficacy and pharmacodynamic assessments as Studies 301 and 302, and was conducted in a similar patient population. Figure 1 shows the study design. Patients were initially randomized into Arms 1-3 in parallel, with the initiation of subsequent Arms 4-5, Arms 6-7, and Arms 8-9, based on an unblinded review of safety data in a subset of patients. Each cohort included a placebo arm. Randomization was stratified by ApoE ε4 status (carrier or non-carrier), except for Arms 8-9, which only included ApoE ε4 carriers to test the hypothesis that titration would lower the incidence of ARIA in this population. The study included an 8-week screening period, a 52-week placebo-controlled treatment period, and a safety follow-up period of 18 weeks after the final dose. Patients who completed the placebo-controlled period had the option to enter a dose-blind long-term extension period.

Figure 3: Study 103 Schematic



Source: Clinical review by Dr. Krudys

The study enrolled patients age 50 to 90 years who fulfilled clinical criteria for either prodromal AD (consistent with criteria for MCI due to AD) or mild Alzheimer's disease dementia, as defined by the 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) framework (Albert et al., 2011), with evidence of brain Aβ pathology by visual read of a positron emission tomography (PET) scan. For prodromal AD, patients were also required to have a spontaneous memory complaint, Clinical Dementia Rating Scale global score of 0.5, Mini-Mental State Examination (MMSE) score ≥24, and a free recall score on the Free and Cued Selective Reminding Test (FCSRT) of ≤27. For mild dementia due to AD, patients were also required to have a MMSE scores between 20 and 26 (inclusive) and Clinical Dementia Rating Scale global score of 0.5 or 1.0. Patients were excluded for clinically significant, uncontrolled medical, neurologic, or psychiatric conditions other than AD, history or bleeding disorders, or use of antiplatelet or anticoagulant therapies other than aspirin at ≤325 mg daily. Patients were also excluded if a brain MRI performed at screening showed evidence of acute or sub-acute hemorrhage, prior macrohemorrhage or prior subarachnoid hemorrhage (unless finding is not due to an underlying structural or vascular hemorrhage), greater than 4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis, or history of diffuse white matter disease.

The primary endpoint was safety and tolerability, as measured by incidence of adverse events and monitored by clinical assessments. The secondary endpoint, for which the study was powered, was the change from baseline in amyloid signal, as measured by ^{18}F-florbetapir PET at Week 26. The change from baseline in amyloid signal at Week 54 was considered an exploratory endpoint. Change from baseline in CDR-SB and MMSE were also included as exploratory endpoints.

The originally intended doses were 1 mg/kg, 3 mg/kg, up to 10 mg/kg, and up to 30 mg/kg, based on findings in nonclinical studies; however, these doses were later revised, based on review of ongoing safety data and IDMC recommendations. The final doses studied were fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg, and 10 mg/kg. An additional arm investigating titration to 10 mg/kg was added to test the hypothesis that titration could mitigate the incidence and severity of ARIA in ApoE ε4 patients. Dr. Krudys notes in his review that the 10 mg/kg titration regimen in Study 103 is much slower (44 weeks) than the titration regimen in Studies 301 and 302 (24 weeks). The 10 mg/kg fixed-dose arm (14 doses of 10 mg/kg over 54 weeks) is the relevant arm for comparisons to the high dose regimen in Studies 301 and 302 (14 doses of 10 mg/kg over 78 weeks).

Dose modification criteria were established to account for the expected occurrence of ARIA, which had been seen in other trials of anti-amyloid monoclonal antibodies. Dose reduction, suspension, or termination were dependent on the radiographic severity of ARIA, as detected by MRI, the presence or absence of clinical symptoms, and the severity of symptoms, if present. Please refer to Dr. Krudys's review for a detailed description of the dose modification/discontinuation rules for ARIA.

Statistical Analysis Plan

The initial SAP was finalized on February 7, 2014. The SAP was modified on August 5, 2016, to specify the analysis plan for Arms 8-9 and the integrated plan for Arms 1-9.

The study was planned to have approximately 90% power to detect a treatment difference of 1 SD for change from baseline to Week 26 in PET SUVR at a 2-sided significance level of 0.05 and assuming a dropout rate of 20%.

Change from baseline in brain amyloid signal, as measured by SUVR, was analyzed with an analysis of covariance (ANCOVA) model adjusting for baseline SUVR and ApoE ε4 status.

CDR-SB and MMSE were analyzed by ANCOVA, adjusting for their baseline values and ApoE ε4 carrier status, at Week 24 and Week 52, separately. An MMRM model was used as a sensitivity analysis. Placebo data were pooled across Arms 3, 5, 7, and 9. Values for missing data were not imputed for the ANCOVA analysis.

As this study was designed as a safety and tolerability study, no adjustments for multiplicity were specified.

Results of Study 103

A total of 197 patients were randomized into the study, and 196 received at least one dose. Table 8 shows the key baseline demographics for Study 103. Demographic characteristics are representative of the patient population, except for an under-representation of African American and Hispanic patients, and are reasonably balanced across the treatment arms, considering the number of patients in each arm. Patients in Study 103 were enrolled in 27 sites in the United States. The mean age at baseline was 73 years, with a range of 51 to 91. The study included 43% patients with prodromal AD, and 57% with mild Alzheimer's dementia. About 66% of the overall population was receiving a concomitant AD medication at baseline. Treatment and study discontinuation was highest in the fixed-dose 10 mg/kg treatment arm, due to discontinuation rules for ARIA. The study population was similar to that of Studies 301 and 302, but with a greater proportion of mild dementia patients. Baseline CDR-SB was lower in the placebo arm (2.69) than any of the aducanumab treatment arms (3.14 to 3.50). The rate of concomitant Alzheimer's disease medication was lowest in the fixed 10 mg/kg and titration arms. By design, the aducanumab titration arm included only ApoE ε4 carriers. Otherwise, the distribution of ApoE ε4 carrier status was similar to that observed in Studies 301 and 302.

Table 8: Study 103 Baseline Demographics (ITT)

Demographic Parameters	Placebo (N=48) n (%)	Treatment Group					
		1 mg/kg (N=31) n (%)	3 mg/kg (N=32) n (%)	6 mg/kg (N=30) n (%)	10 mg/kg (N=32) n (%)	Titration (N=23) n (%)	**Total** (N=196) n (%)
Sex							
Male	20 (42%)	18 (58%)	15 (47%)	15 (50%)	17 (53%)	13 (57%)	98 (50%)
Female	28 (58%)	13 (42%)	17 (53%)	15 (50%)	15 (47%)	10 (43%)	98 (50%)
Age							
Mean years (SD)	73.3 (6.8)	72.6 (7.8)	70.5 (8.2)	73.3 (9.3)	73.7 (8.3)	73.1 (7.8)	72.8 (7.9)
Median (years)	73.5	74.0	71.0	72.0	74.5	73.0	73.0
Min, max (years)	54, 85	55, 88	54, 86	57, 91	51, 87	52, 88	51, 91
Baseline Clinical Stage							
Prodromal AD	22 (46%)	10 (32%)	14 (44%)	12 (40%)	13 (41%)	13 (57%)	84 (43%)
Mild AD	26 (54%)	21 (68%)	18 (56%)	18 (60%)	19 (59%)	10 (43%)	112 (57%)
Laboratory ApoE ε4 Status							
Carrier	34 (71%)	19 (61%)	21 (66%)	21 (70%)	20 (63%)	23 (100%)	138 (70%)
Homozygote	7 (15%)	1 (3%)	5 (16%)	4 (13%)	6 (19%)	3 (13%)	26 (13%)
Heterozygote	27 (56%)	18 (58%)	16 (50%)	17 (57%)	14 (44%)	20 (87%)	112 (57%)
Non-carrier	14 (29%)	12 (39%)	11 (34%)	9 (30%)	12 (38%)	0	58 (30%)
Concomitant AD medication							
Any AD medication at baseline	32 (67%)	21 (68%)	28 (88%)	20 (67%)	17 (53%)	12 (52%)	130 (66%)
Cholinesterase inhibitors	30 (63%)	20 (65%)	27 (84%)	19 (63%)	17 (53%)	11 (48%)	124 (63%)
Baseline CDR-SB							
Mean (SD)	2.69 (1.54)	3.40 (1.76)	3.50 (2.06)	3.32 (1.54)	3.14 (1.71)	3.24 (1.84)	3.17 (1.74)
Median	2.50	3.00	3.00	3.25	2.75	3.00	3.00
Min, Max	0.5, 7.0	0.5, 7.0	0.5, 8.0	1.0, 8.0	0.5, 7.0	0.5, 10.0	0.5, 10.0
Baseline MMSE							
≤20	4 (8%)	3 (10%)	7 (22%)	0	0	0	14 (7%)
≥21 - <24	15 (31%)	11 (35%)	6 (19%)	11 (37%)	10 (31%)	9 (39%)	62 (32%)
≥24	29 (61%)	17 (55%)	19 (59%)	19 (63%)	22 (69%)	14 (61%)	120 (61%)

Source: adsl.xpt and Tables 14, 15, and Table 16 in Study 103 CSR

Clinical Endpoints

The results for CDR-SB and MMSE are presented in Table 9. The reduction in clinical decline of CDR-SB and MMSE reached nominal significance for the aducanumab fixed-dose 10 mg/kg treatment arm. Based on analyses (linear contrast in ANCOVA) of the aducanumab fixed-dose treatment arms only, a dose-dependent relationship was found for both clinical endpoints. An MMRM model with the same covariates as the ANCOVA model specified in the SAP was

used as a sensitivity analysis and provided similar results for the 10 mg/kg treatment arm for both endpoints. Subgroup analysis was not performed due to the small sample size in the treatment arms.

Table 9: Study 103 Clinical Endpoints (CDR-SB and MMSE) Analyses by ANCOVA

	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	Titration
Baseline CDR-SB						
n	44	28	32	29	30	22
Mean	2.65	3.27	3.47	3.22	3.14	3.23
Change from Baseline in CDR-SB at Week 54						
n	39	23	27	26	23	21
Difference from placebo (%)		-0.20 (-11%)	-0.56 (-30%)	-0.80 (-42%)	-1.26 (-67%)	-1.19 (-63%)
95% CI for difference		(-1.308, 0.912)	(-1.612, 0.499)	(-1.855, 0.264)	(-2.356, -0.163)	(-2.343, -0.037)
p-value (compared with placebo)		0.7249	0.2995	0.1398	0.0246	0.0432
Baseline MMSE						
n	45	26	29	28	30	21
Mean	24.82	23.65	22.97	24.32	24.90	24.67
Change from Baseline in MMSE at Week 52						
n	40	25	26	26	25	21
Difference from placebo (%)		0.25 (-8%)	1.70 (-68%)	0.47 (-20%)	1.91 (-76%)	1.46 (-60%)
95% CI for difference		(-1.612, 2.106)	(-0.141, 3.543)	(-1.356, 2.291)	(0.061, 3.754)	(-0.531, 3.445)
p-value (compared with placebo)		0.7932	0.0700	0.6133	0.0430	0.1496

Source: Table 23 and Table 24 in Study 103 CSR
p-values are nominal

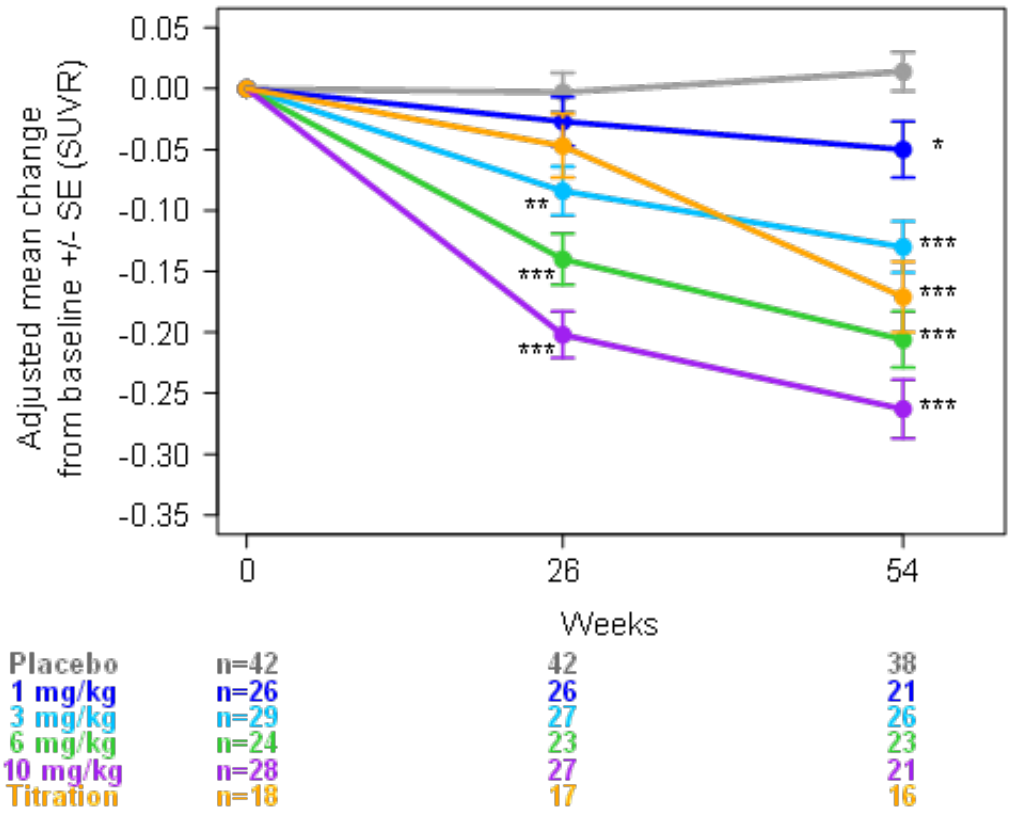
Pharmacodynamic Endpoints

Amyloidβ Pathology

Significant reductions in brain amyloid were achieved in the 3 mg/kg, 6 mg/kg, and 10 mg/kg fixed-dose treatment groups at Week 26, and all aducanumab treatment groups at Week 54 (Figure 4). The adjusted mean change from baseline at Week 26 and Week 54 for the fixed-dose 10 mg/kg treatment arm were -0.202 ($p<0.0001$) and -0.263 ($p<0.0001$), respectively. The effect of the titration group was consistent with the effect anticipated for the average expected dose in that group (2.9 mg/kg at Week 26 and 5.3 mg/kg at Week 54). Based on

analyses (linear contrast in ANCOVA) of the aducanumab fixed-dose treatment arms only, a dose-dependent relationship was found (p<0.0001). The reduction in Aβ PET composite SUVR, compared to placebo, for the fixed-dose 10 mg/kg arm at Week 54 (-0.277), was similar to the reduction at Week 78 in Study 302 (-0.278).

Figure 4: Study 103 Change from Baseline Aβ PET Composite SUVR



Created by reviewer from Table 22 in Study 103 CSR
*p<0.05, **p<0.01, ***p<0.001

Continued reduction in brain amyloid as measured by SUVR was observed in patients who remained on aducanumab treatment throughout the placebo-controlled and LTE periods. For patients who switched from placebo in the placebo-controlled period to aducanumab treatment in the LTE, SUVR declined as expected.

Conclusions of Study 103

Although Study 103 was intended to be a safety and tolerability study, the study design was randomized, double-blind, and placebo-controlled, typical characteristics of an adequate and well-controlled study. It was also conducted in a similar population and used many of the same endpoints that were used in Studies 301 and 302. The study showed a statistically significant time- and dose-dependent effect on reduction of Aβ plaques. The change on measures of Aβ plaques were highly persuasive. The dose-response relationship for Aβ

reduction in Study 103 provides support for the reduction in amyloid observed in Study 302, and the effects on CDR-SB and MMSE are consistent with the dose-response relationship observed in Study 302 for CDR-SB and MMSE.

Exploratory Analysis of Discordant Results in Study 301 and Study 302

Study 301 and Study 302 had partially discordant results, with one study (301) being negative for the high dose, but the second (302) being positive for the high dose, with persuasive results on secondary endpoints; the two studies had similar but non-significant findings for the low dose. As discussed above, an effort was undertaken to explore the discordance between the studies, with no a priori hypothesis that aducanumab was or was not effective for the treatment of AD, or that one study had the "right" results and the other study had the "wrong" results. Although the analyses were exploratory, they were hypothesis-driven regarding potential sources of discordance, and were designed to address specific questions. The hypotheses were predetermined to the furthest extent possible, although some questions were informed by the review of the data. Importantly, the analyses were not intended to obtain independent support from Study 301; Study 301 is clearly a negative study.

Demographics and Baseline Disease Characteristics

The individual studies were reviewed, and differences in demographics or baseline disease characteristics between the studies were minor, and did not have a meaningful impact on the outcome of the studies.

Influence of ARIA and ARIA Management

The potential impact of ARIA and ARIA management on clinical outcomes was investigated because the occurrence of ARIA prompts differential management of patients and thus has the potential to cause functional unblinding of investigators, patients, and caregivers. Analyses, therefore, were aimed to investigate whether the positive results of Study 302 were simply the result of unblinding.

The incidence and radiographic severity of ARIA were generally similar between Study 301 and Study 302. Therefore, differences in the occurrence or severity of ARIA are not likely to explain the discordant results at the high dose in the two studies. Nevertheless, the results of the primary analysis of Study 302 for the primary and secondary endpoints using the ITT dataset were compared to results using a reduced ITT dataset in which all assessments after occurrence of ARIA were excluded. For the low-dose and high-dose arms, approximately 30% and 40% of the observations were excluded, respectively. Overall, the results did not suggest a systematic bias due to functional unblinding. The treatment difference for the high-dose arm in Study 302 was actually higher (33% vs. 22% for CDR-SB) after excluding observations post-ARIA.

Differences in Placebo Progression

Although the placebo decline for CDR-SB was numerically greater in Study 302 (1.74) than Study 301 (1.56), differences in placebo response do not explain why Study 302 was

successful and Study 301 was not. First, the placebo decline for CDR-SB in both studies was consistent with expectation (i.e., placebo decline over the duration of the studies was assumed to be 2 for power calculations) and not markedly different from other studies in similar populations. Second, placebo decline was lower for MMSE in Study 302 compared to Study 301, and placebo decline was similar for ADAS-Cog 13 between the two studies. Positive outcomes were observed across endpoints in Study 302, not just ones with a greater placebo decline. Third, similar treatment effect estimates relative to placebo for CDR-SB were obtained for the low dose arms in each study.

Influence of Study Participants with Rapid Progression

Investigation of individual treatment responses, particularly identification of participants with a rapid rate of disease progression, was an area of focus because diagnostic plots of the primary endpoint analysis demonstrated that the distribution of the change from baseline in CDR-SB was highly skewed.

The existence of a small proportion of patients with a rapid rate of disease progression has been noted in the literature. The question was not whether these rapid progressors existed in the data, but rather what potential impact they had on the primary analysis, and whether that impact was similar across treatment groups.

A cutoff of an 8-unit increase in CDR-SB over 78 weeks was initially chosen to define patients with rapid progression. This increase is 4 times the expected estimate of mean progression used to power Studies 301 and 302. The numbers of patients in each study who met the cutoff were evenly distributed across the treatment groups (4 or 5 patients), except for the high-dose group in Study 301 (9 patients).

Analyses for the primary and secondary endpoints were conducted using a dataset with all rapid progressors removed, and compared to the results from the ITT population. Results for the primary and secondary endpoints were most sensitive to rapid progressors in the high-dose treatment arm in Study 301. For example, the results for CDR-SB went from a 2% increase relative to placebo to a -6% decrease when the rapid progressors were removed. Notably, the results for ADAS-Cog13 and ADCS-ADL-MCI aligned more closely with the results from Study 302 after removal of rapid progressors. Minor differences were observed at the lower dose in Study 301. Likewise, results of Study 302 were not sensitive to exclusion of rapid progressors. The analysis was repeated for other cutoff values to define rapid progressors, and the results were similar.

Further investigation did not reveal individual-level factors that may have contributed to the rapid decline in patients defined as rapid progressors. There was also no evidence that aducanumab treatment itself was the cause of the progression.

Taken together, these analyses suggest that (1) small imbalances in the number of rapid progressors can have a relatively large impact on the magnitude of the primary and

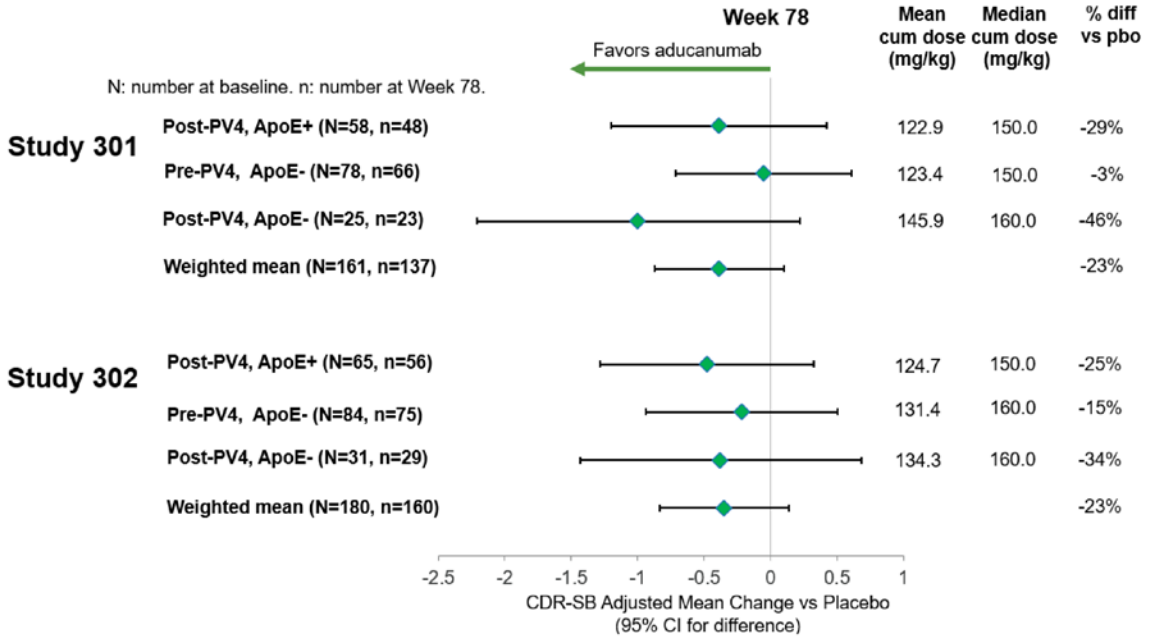
secondary endpoints and (2) the high-dose arm in Study 301 was disproportionately affected by such an imbalance in rapid progressors.

Influence of Dosing

The motivation to investigate the potential importance of dosing in the interpretation of Studies 301 and 302 is supported by the conduct of these clinical studies, including two protocol amendments which increased the dose or allowed patients to continue dosing in response to ARIA. The timing of the studies and pace of enrollment was such that Study 302 was more likely to benefit from changes to the protocol than Study 301.

To assess the impact of differences in dosing on clinical outcomes in the high-dose arms, subsets of the arms were defined by randomization (ApoE ε4 carriers and non-carriers) and protocol version (pre-protocol version 4 and post-protocol version 4). Results from the three subgroups in each study that had the opportunity to titrate to the maximum number (14) of 10 mg/kg doses are illustrated in Figure 5. The percent weighted mean treatment effects for CDR-SB for patients who had the opportunity to receive the maximum number of 10 mg/kg doses was similar in Studies 301 and 302. This result suggests that regardless of study, patients randomized to groups with the opportunity for full 10 mg/kg dosing had similar and favorable results on clinical outcomes.

Figure 5: Comparison of CDR-SB in Subsets with Opportunity to Receive All 14 Doses of 10 mg/kg



Source: Figure 20 in AC Background Document

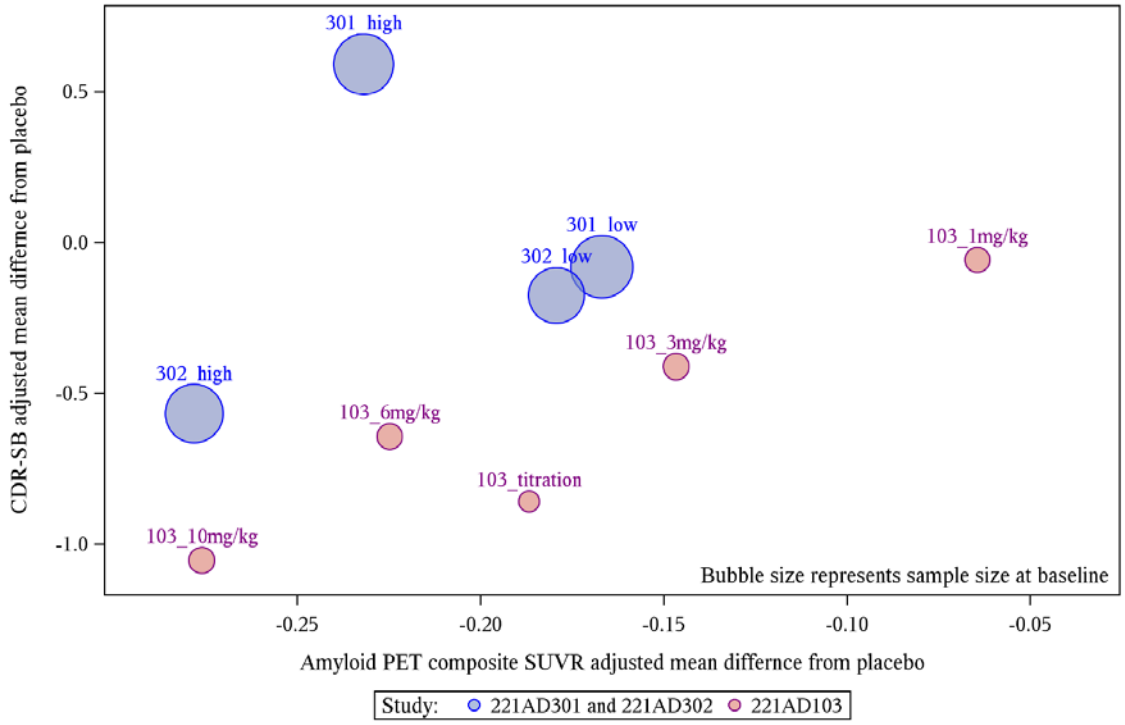
Several different analyses, including exposure-response modeling and propensity score matching, were performed and suggest that consistent exposure to high doses of aducanumab leads to similar treatment effects in the two studies.

Overall, the analyses on dose indicate that dosing is an important consideration for interpretation of the efficacy results in Studies 301 and 302, and patients in Study 301 with higher exposure to the 10 mg/kg dose had treatment effects similar to patients in Study 302. Lower exposure to the target dose of 10 mg/kg in Study 301 appears to be a small but contributing factor to the differences in results of Study 301 and Study 302.

Association between Reduction in Brain Amyloid and Clinical Endpoints

In order to correctly assess the relationship between two endpoints, all potential confounders should be balanced across the data points. Therefore, an analysis at the randomized group level was performed to investigate the relationship between change from baseline in reduction in brain Aβ and the estimate of the treatment effect for CDR-SB. The group-level correlation across the three studies is presented in Figure 6. Due to differences in study design, Week 78 was used for Studies 301 and 302, and Week 54 was used for Study 103. The analysis is consistent with a relationship between brain amyloid reduction and treatment effect for CDR-SB. Figure 6 also highlights the apparently aberrant performance of the high dose in Study 301, which is inconsistent with remainder of the study/dose groups. The Office of Clinical Pharmacology (OCP) also concludes that there is a clear association between Aβ plaque reduction and treatment effect for CDR-SB. In addition, OCP has reviewed data from publicly accessible resources for multiple similar compounds targeting amyloid beta under development and concludes that the relationship observed for aducanumab is consistent with the relationship observed in other recent clinical development programs.

Figure 6: Group-Level Correlation Between Adjusted Mean Difference from Placebo in Aβ PET Composite SUVR and CDR-SB



Source: Figure 61 in ISE

The relationship between brain amyloid reduction and maintenance of treatment effect on clinical endpoints was also investigated with data from Study 304. Study 304 is an ongoing, single-arm, open-label study to assess long-term safety and efficacy of aducanumab in participants who were participating in active clinical trials of aducanumab at the time of study termination. Patients who received high-dose aducanumab treatment in the placebo-controlled period of Study 302 were dichotomized by the value of their last SUVR assessment. An SUVR value of 1.1 was chosen because this value has been reported to discriminate between a positive and negative amyloid PET scan. Preliminary results suggest that patients who achieved SUVR ≤1.1 tended to have less progression on the CDR-SB. Similar results were observed for the other clinical endpoints. These exploratory findings provide further support to the relationship between amyloid reduction and clinical benefit.

Advisory Committee Meeting November 6, 2020

Results of the Advisory Committee meeting vote are provided in Section 9. The following excerpt from Dr. Krudys's review summarized the findings of the Advisory Committee:

"Briefly, the committee members concluded that they were unable to evaluate the evidence of effectiveness provided by Study 302 independently of the results of Study 301. In addition, panel members expressed concern about the clinical meaningfulness of the results of Study 302. A majority of the committee members did not view Study 103 as providing supportive evidence of effectiveness because the study was either not designed to measure

effectiveness, too small, or not robust to sensitivity analyses. The committee mostly agreed that there was evidence showing an effect of aducanumab on amyloid plaques but were skeptical that this effect was related with changes on clinical endpoints. Exploratory analyses to investigate the results in Studies 301 and 302 were generally dismissed. Overall, the committee members largely endorsed the analyses and conclusions in the draft statistical review. Approximately 6 months after the committee meeting, three members of the committee published a commentary reinforcing many of the arguments they made during the meeting (Alexander et al. 2021)."

Dr. Krudys's (clinical reviewer) Efficacy Conclusions

Despite the early termination of Study 302, Dr. Krudys considers the data submitted to be interpretable and capable of providing evidence for the effectiveness of aducanumab for AD. He considers Study 302 to be a robust and exceptionally persuasive study that can serve as a single study to support approval. He bases this conclusion on a treatment effect demonstrated on a clinically meaningful endpoint, and reinforced by effects on secondary endpoints, biomarkers, and in relevant subgroups. Dr. Krudys also considers that Study 103, as an adequate and well-controlled study design with components consistent with Study 302, provides support for the findings of Study 302. In Study 103, aducanumab demonstrated a treatment effect on both clinical endpoints, and the dose-response relationship for Aβ reduction provides support for the positive findings in the 10 mg/kg treatment arm and for dose-related effects observed on clinical outcomes in Studies 103 and 302. Dr. Krudys notes that Study 301 is a negative study and does not contribute to the evidence of effectiveness on clinical outcomes; however, he feels that the results of the exploratory analyses contribute to an overall understanding of Study 301 and do not detract from the persuasiveness of Study 302. Dr. Krudys has concluded that the applicant has provided substantial evidence of effectiveness with respect to clinical endpoints to support approval of aducanumab for AD.

Dr. Krudys has also reviewed the evidence to support accelerated approval and concludes that there is substantial evidence that aducanumab reduces brain amyloid, and that this reduction in brain amyloid as measured by PET is reasonably likely to predict clinical benefit. He also notes that the time- and dose-dependent effect of aducanumab on brain amyloid observed across Studies 103, 301, and 302 meets the standard for substantial evidence of effectiveness in this context. In this setting where the evidence supporting clinical benefit is strong but associated with the residual uncertainty conveyed by the results of Study 301 (and the associated contribution of those results to the premature termination of both studies), Dr. Krudys concludes that the accelerated approval pathway is also a viable option.

Dr. Massie's (biostatistics reviewer) Efficacy Conclusions

Dr. Massie does not agree that the totality of the data provides sufficient evidence to support the efficacy of aducanumab in AD and does not recommend approval. He cites the following primary issues in his review:

- Inconsistency in the data with one positive study (302) and a second negative study (301)

- Neither Phase 3 study was completed due to early termination, resulting in a substantial proportion of patients that were unable to have the Week 78 time point assessment of CDR-SB.
- Dr. Massie does not agree with the sponsor's argument that the high dose in Study 301 was hampered by intermediate dosing rather than full dosing, noting that the low dose was numerically better than the high dose and that the ApoE ε4 non-carriers have less treatment effect on all efficacy endpoints despite having 10 mg/kg dosing from study start and less ARIA adverse events than ApoE ε4 carriers.
- Dr. Massie has conducted exploratory analyses that suggest that increased placebo progression post-PV4 may account for the treatment effect observed in Study 302.
- He does not agree that Study 103 can serve as a supportive study, as it was designed as a safety and tolerability study and efficacy endpoints were exploratory.
- The amyloid PET substudy data suggested a larger effect in ApoE ε4 non-carriers, which is the opposite of what was observed for the clinical outcome data in the Phase 3 studies.

OCP's Efficacy Conclusions

The OCP review team supports approval of aducanumab based on the following observations from Studies 302, 301, and 103:

- Positive findings for the high dose group from Study 302
- The dose-response relationship observed in Study 103
- Positive exposure-response relationships for CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI from Studies 301 and 302
- Exposure-SUVR and SUVR-clinical endpoint relationships observed in Studies 301, 302, and 103
- The review team concluded that the relationship between brain amyloid reduction and CDR-SB for aducanumab was consistent with the relationship observed for other compounds targeting amyloid beta based on a review of publicly available information, including compounds for which the reduction in amyloid beta plaque ranged from minimal to a similar extent as that seen with aducanumab
- Based on extensive clinical trial simulations, the review team concluded that the probability of the high dose group in Study 302 being a false positive is very low, and the high dose group in Study 301 is likely a chance finding driven by the pre-PV4 subgroup. Also, the probability of observing the overall positive findings from Studies 103, 301, and 302 under the null assumption that aducanumab is the same as placebo was extremely low.

Efficacy Discussion

This application presents an unusual and challenging situation for review, in which two large, international Phase 3 trials (Studies 301 and 302) were near completion, but were terminated prior to their planned conclusion, with a public declaration of futility based on an interim futility analysis of the pooled data from the two studies. Further review of the data collected per protocol prior to the futility declaration showed that there were partially discordant

results for the two studies, with one study (301) being clearly negative for its primary outcome, but the second study (302) being positive for the high dose, with very persuasive results across primary, secondary, tertiary, and biomarker endpoints, on face. In view of these results, the applicant initially sought advice from the Agency about the appropriate interpretation of the data and next steps. Recognizing the unique and complex circumstances, the Division recognized that it was premature to provide specific guidance to the applicant on interpretation without a maximized understanding of the data that exceeds that which could be achieved in a single meeting with only a high-level summary presentation of results and issues. Given the tremendous unmet need in AD and the potential importance of these findings, plans for an ongoing analytical dialogue were initiated between the Applicant and the Agency to maximally understand the findings from Study 301 and Study 302, in order to fully inform advice on appropriate next steps. Modeling and simulation methodologies were used to "virtually complete" the studies. Based on the results of these analyses, it was determined that the results of Studies 301 and 302 were interpretable.

The Applicant presents the results of Study 302 as the primary evidence of effectiveness for aducanumab in AD, supported by data from Study 103. The clinical review team and biostatistics review team have reached different conclusions on the approvability of this application. Dr. Krudys has concluded that the data from Study 302, with support from Study 103, are capable of providing evidence of substantial evidence of effectiveness to support approval of aducanumab for AD. However, Dr. Massie has concluded that, due to inconsistencies in the data, the totality of the data do not provide sufficient evidence to support the efficacy of aducanumab in AD. The rationale for these conclusions is described above.

An Advisory Committee meeting on November 6, 2020, provided an opportunity to present the data from the application publicly and to discuss with the committee the evidence provided in support of the effectiveness for aducanumab. Overall, the committee members largely endorsed the analyses and conclusions from the presentation of the statistical review by Dr. Massie.

Additional internal Agency meetings were held following the Advisory Committee to discuss the application and differences of opinion on approvability.

The application was presented at the Medical Policy and Program Review Council (MPPRC) meeting in the Center for Drug Evaluation and Research (CDER) on March 31 and April 7, 2021. This meeting provided an opportunity to discuss the reviews conducted by the review team and receive input and feedback from the members of the committee. At the MPPRC meetings, many different perspectives were discussed extensively as to whether there is substantial evidence of effectiveness for aducanumab's intended use to treat Alzheimer's disease (AD).

Overall, although the isolated data from Study 302 are, on face, highly persuasive, and are supported by multiple lines of exploratory and sensitivity analysis, the clinical evidence has

several remaining areas of uncertainty, most notably, and primarily, the negative result for the high dose of aducanumab in Study 301. Considering these uncertainties, it is not clear that a conclusion that substantial evidence of effectiveness on the clinical endpoints has been provided by the Applicant can be reached with the existing data. There is, however, convincing evidence for a robust treatment-related reduction in brain amyloid beta plaque, as measured by PET imaging in the three clinical trials (Studies 103, 301, and 302). In addition, a generally linear relationship between this reduction in amyloid beta plaque and reduction (versus placebo) in the clinical endpoint of CDR-SB score in the clinical trials is present. There is also extensive scientific evidence of amyloid's role in AD. Based on the available clinical data, and the current understanding of the pathophysiology of Alzheimer's disease, the reduction in amyloid identified in aducanumab clinical studies is reasonably likely to predict clinical benefit in AD, and supports the accelerated approval of aducanumab. The accelerated approval provisions in section 506(c) of the FD&C Act (as amended by FDASIA) provide that FDA may grant accelerated approval to: . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

The regulatory decision regarding this application was also discussed with Dr. Patrizia Cavazzoni, CDER director, at a Center Director Briefing on April 26, 2021. The meeting included CDER senior leaders, as well as Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research (CBER), and Dr. Rick Pazdur, Director of the Oncology Center of Excellence (OCE). The meeting reviewed the approach to approval the Office of Neuroscience and the Office of New Drugs supported, specifically, using the accelerated approval pathway based on substantial evidence of the effect of aducanumab on reduction in brain amyloid plaques, an effect that is reasonably likely to predict clinical benefit. This approach was supported by Dr. Cavazzoni, Dr. Marks, Dr. Pazdur, and the Office Directors for Clinical Pharmacology (OCP) (Dr. Issam Zineh) and Medical Policy (Dr. Jacqueline Corrigan-Curay). The Director of the Office of Translational Sciences (that includes both the Office of Biostatistics and the Office of Clinical Pharmacology), Dr. Shahvree Buckman-Garner, commented that she understood the arguments for and against approval. Dr. Sylva Collins, Director of the Office of Biostatistics (OB), dissented on the approach, stating her belief that there is insufficient evidence to support accelerated approval or any other type of approval.

7. Safety

Dr. Natalie Branagan performed the safety review for the submission with team leader Dr. Sally Yasuda. Dr. Brian Trummer performed a focused safety review of amyloid-related imaging abnormalities (ARIA) with team leader Dr. Ranjit Mani.

The safety analyses were performed by Dr. Natalie Branagan (team leader Dr. Sally Jo Yasuda) for all safety except for the details of the ARIA evaluation, Dr. Brian Trummer (team leader Dr. Ranjit Mani) for ARIA analysis, and Dr. Rui Li, clinical analyst.
The safety of aducanumab was evaluated based primarily on Studies 103, 301 and 302.

Exposures and Adequacy of the Safety Database

Dr. Branagan's review indicates that the exposure to aducanumab included 2,942 patients in Studies 103, 301, and 302, and 3,078 patients who received at least one dose across the development program. The database includes 1,505 patients who received at least one dose of 10 mg/kg. At the proposed dose of 10 mg/kg, 834 patients were treated for at least 6 months, and 551 treated for at least 1 year, exceeding ICH criteria (1500 total, 300-600 for 6 months, 100 for 1 year) for drugs intended for long-term use.

Dr. Branagan notes that in the applicant's analyses of safety, 72 patients who were ApoE ε4 carriers in Studies 301 or 302 were analyzed in the 6 mg/kg assigned treatment arm despite a protocol change that resulted in increasing dosage to 10 mg/kg. In the applicant's analyses of efficacy, these patients were included in the 10 mg/kg treatment arm. In order to better reflect the safety outcomes of the population analyzed for efficacy, Dr. Branagan in her review reassigned these 72 patients to the 10 mg/kg treatment arm for analyses, as reflected in the remainder of this safety discussion.

In pooled Studies 301 and 302 , 43% of the population treated with aducanumab (all doses) was from the United States. Sixty-eight percent were ApoE ε4 carriers. The mean age in pooled Studies 301 and 302 was approximately 70 years. Approximately 47% percent of patients were 65 -74 years old, and 32% were 75 years and older. Approximately 51% were women. White patients accounted for 77%, and Black or African American accounted for 1% of the population. The population demographics were similar in all treatment groups. Dr. Branagan notes that the clinical trial population under-represents women and African Americans compared with those demographics in the United States, and that patients in aducanumab clinical studies were, on average, younger than in the Alzheimer's disease overall population. Given the younger age of the population and that patients with moderate or severe dementia were not included in the clinical trials, as Dr. Branagan notes, the safety outcomes may underestimate the impact of adverse events in a broader population, given the increased likelihood of occurrence of other comorbid conditions.
Dr. Branagan considered the applicant's translation of adverse events from verbatim terms to preferred terms to be adequate.

Deaths

Dr. Branagan does not identify any deaths attributable to treatment with aducanumab. Dr. Branagan notes that in the placebo-controlled periods of Studies 301 and 302, there was not an excess of deaths in the aducanumab-treated group (0.5%, 11/2198) compared to placebo (0.5%, 5/1087). In the placebo-controlled period of Study 103, there was one death each in

the aducanumab group (0.7%, 1/148) and in the placebo group (2.1%, 1/48). There were too few deaths during the controlled periods to support any conclusion about relative mortality risk by treatment dose. In the combined placebo-controlled and long-term extension periods of Studies 301 and 302, there were 19 deaths (0.7%, 19/2757). Dr. Branagan identified one death due to malignant lung neoplasm for which she could not rule out or attribute a role for aducanumab, in a patient with a history of basal cell carcinoma whose most recent dose occurred 302 days prior to the event. Dr. Branagan noted one completed suicide in a subject who had received 16 doses of aducanumab prior to the event, the most recent dose 8 days prior to the event, in a subject with no previous history of psychiatric illness.

Aducanumab is associated with amyloid related imaging abnormalities-edema (ARIA-E), and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H). ARIA H may include brain microhemorrhages, superficial siderosis, and brain hemorrhages greater than 1 cm. Dr. Branagan identified four cases of death in which ARIA preceded the deaths by less than 4 weeks, (patients (b) (6), and (b) (6) Drs. Mani and Trummer have reviewed these four cases, described in detail in Dr. Trummer's review, and do not consider these to be related to ARIA or to aducanumab. Dr. Branagan also identified a case of death involving cerebral hemorrhage (b) (6) that Drs. Mani and Trummer attribute to an arterio-venous malformation vs. arterio-venous fistula, and not related to aducanumab.

Dr. Branagan notes that the incidence of death by person-years of exposure in aducanumab-assigned patients in Studies 103, 301, and 302 was 4.7/1,000 person-years, compared to the reported incidence from Alzheimer's disease in the US of 133.8/1,000 person years.

Serious and Significant Adverse Events

In the placebo-controlled periods of Studies 301 and 302, serious adverse events (SAEs) occurred in 13.8% (152/1105) of 10 mg/kg aducanumab-treated patients, and in 13.9% (151/1087) of placebo-treated patients. The most frequently reported SAEs included ARIA-E (1.4% for aducanumab 10 mg/kg vs. 0.1% for placebo), hemorrhage (1% for aducanumab 10 mg/kg vs. 0.6% for placebo), and presyncope or syncope (0.9% for aducanumab 10 mg/kg vs. 0.6% for placebo). In the combined placebo-controlled and long-term extension period of pooled Studies 301 and 302, SAEs occurred in 16% of patients in the 10 mg/kg arm. The only SAE with an incidence of at least 2% in the 10 mg/kg arm was infection (2%).

Dr. Branagan notes that most TEAEs were mild or moderate, with approximately 15% considered severe across studies. The most frequent severe TEAEs in the 10 mg/kg aducanumab-treated group in the controlled periods of Studies 301 and 302 (pooled) were ARIA-E (4% vs. 0% on placebo), ARIA-H (3% vs. 0% on placebo), and superficial siderosis (3% vs 0.2% on placebo). These were also the most frequent severe TEAEs in the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302, occurring in 5%, 3%, and 4% of patients, respectively.

Discontinuations Due to Adverse Events

In pooled Studies 301 and 302, 55% of patients completed the placebo-controlled period. Adverse events leading to treatment discontinuation occurred in 9% of aducanumab-treated patients; Dr. Branagan notes that these were driven by protocol for ARIA events. The most frequently reported TEAEs leading to study discontinuation were superficial siderosis of the central nervous system (3%) , ARIA-microhemorrhages and hemosiderin deposits (2%), and ARIA-E (2%) in the 10 mg/kg aducanumab-treated patients compared to 0.2% or less in patients on placebo.

Treatment-Emergent Adverse Events (TEAEs) of All Severities

The most frequently reported TEAEs in the placebo-controlled periods of Studies 301 and 302 (pooled) were ARIA-E, headache, ARIA-H, superficial siderosis of the central nervous system, and fall (see Table 10). Dr. Branagan notes the significance of falls as a risk factor for hip fracture, and cites a publication suggesting an association between hip fracture in Alzheimer's disease and increased mortality.

Table 10: TEAEs with Incidence in the Aducanumab 10 mg/kg Group of at Least 2% and at Least 2% Higher Than Placebo in Studies 301 and 302

Adverse Event	ADU 3 mg/kg N=760 n (%)	ADU 6 mg/kg N=333 n (%)	ADU 10 mg/kg N=1105 n (%)	ALL ADU N=2198 n (%)	Placebo N=1087 n (%)
Total with at least one TEAE	92	84	92	91	87
Amyloid related imaging abnormality-edema/effusion	29	17	35	30	3
Superficial siderosis of central nervous system	12	4	15	12	2
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	19	11	19	18	7
*Headache Fda B MQG	24	15	22	22	17
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	7	6	8	7	5
Fall	14	13	15	14	12
Diarrhea Fda N MQG	8	8	9	8	7

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; Group by USUBJID, AEDECOD; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.
*Modified by Dr. Branagan

Dr. Branagan presents in her review the FDA grouped term of Hemorrhage (FDA N MQG), with a greater reported rate of events in aducanumab 10 mg/kg-treated patients (14%) than in placebo-treated patients (11%). Grouping of terms may be performed to detect a signal that would not otherwise be seen if similar terms were evaluated individually. In this case, as Dr. Branagan notes, the Hemorrhage grouping finding was driven by terms related to contusion. Terms related to contusion, when evaluated as a separate grouping, did not meet the definition for inclusion in the table. When contusion terms were excluded from the Hemorrhage grouping, the Hemorrhage grouping did not meet the criteria for inclusion in the table above. Similarly, Dr. Branagan did not find an imbalance in the MeddRA Query Group (MQG) of Intracranial Hemorrhage. Dr. Branagan excluded terms of subdural hematoma and subdural hemorrhage from her analysis, based on a discussion with Dr. Mani, because they are frequently caused by an underlying traumatic event.
In the combined placebo-controlled and long-term extension periods of Studies 301 and 302, the incidence of TEAEs was 89% in patients treated with aducanumab 10 mg/kg, and 88% in patients treated with an aducanumab dosage less than 10 mg/kg. Infection was the most frequently reported, with an incidence of 42% in the aducanumab 10 mg/kg treatment group, and 41% in patients treated with an aducanumab dosage less than 10 mg/kg. Infection was not among the most frequently reported TEAEs in the placebo-controlled portion of the clinical trials.

Laboratory Findings

Review of laboratory findings or of TEAEs belonging to the SOC Investigations did not identify any clinically meaningful change in patients treated with aducanumab.

Vital Signs

There were no clinically meaningful changes in vital sign parameters in patients treated with aducanumab.

ECG/QT

There were no clinically meaningful changes in ECG parameters in patients treated with aducanumab. In accordance with ICH E14 guidelines for monoclonal antibodies, a thorough QT study was not conducted.

Subgroup analyses

In pooled Studies 301 and 302, the incidence of ARIA-E in the 10 mg/kg aducanumab-treated patients was greater in patients less than 75 years old (37%) than in patients 75 years of age and older (31%). Women had a lower incidence of superficial siderosis of the CNS (11% for aducanumab 10 mg/kg vs. 2% for placebo) than men (19% for aducanumab 10 mg/kg vs. 3% for placebo). Dr. Branagan finds that the incidence of ARIA-E in the 10 mg/kg aducanumab-treated patients was lower in Asians than in Whites (24% vs. 36%). Similarly, the incidence of

superficial siderosis of the CNS was lower in Asians than in Whites (8% vs. 15%). Dr. Branagan notes the potential confounding factor of regional differences in those events, as Ninety-four percent of Asians in aducanumab studies were from Asia. Other common TEAEs were generally balanced across the specific demographic subgroup.

There were too few SAEs to meaningfully evaluate by subgroup.

Other Events of Interest

Amyloid-Related Imaging Abnormalities (ARIA)

The following discussion refers to data from pooled Studies 301 and 302 unless otherwise indicated and reflects the review of Drs. Trummer and Mani.

In the placebo-controlled portion of pooled Studies 301 and 302, ARIA (-E and/or -H) was observed in 41% of patients treated with aducanumab 10 mg/kg, compared to 10% of patients on placebo.

ARIA-E was observed in 35% of patients treated with a planned dose of aducanumab 10 mg/kg, compared to 3% of patients on placebo. Isolated ARIA-E was observed in 13% of patients treated with aducanumab 10 mg/kg, compared to 2% of patients on placebo. Among patients treated with aducanumab 10 mg/kg who had ARIA-E, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients. Routine MRI monitoring for ARIA in clinical studies started prior to the 5th dose of aducanumab. The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses). In pooled Studies 301 and 302, approximately 8.4% of patients (out of 1105 exposed to 10 mg/kg aducanumab) had a first episode of ARIA-E prior to the 5th dose (doses 1-4), approximately 51% prior to the 7th dose, approximately 90% prior to the 12th dose, and approximately 4% had a first episode after the 11th dose. Approximately 14% of patients on aducanumab 10 mg/kg had either the first or a recurrent episode of any type of ARIA beyond the 11th dose. Dr. Trummer identified 2 patients with serious ARIA that occurred as early as following the 2nd dose. After detection, resolution of ARIA-E was reported in 68% of patients by 12 weeks, 91% by 20 weeks, and 98% overall. Ten percent of all patients who received aducanumab 10 mg/kg (n= 1105) had more than one episode of ARIA E. The incidence of ARIA-E was higher in ApoE ε4 carriers than in ApoE ε4 non-carriers (42 and 20%, respectively).

ARIA-H in the setting of ARIA-E associated with the use of aducanumab 10 mg/kg was observed in 21% of patients treated with aducanumab 10 mg/kg, compared to 1% of patients on placebo. There was no imbalance in isolated ARIA-H. There was no imbalance in hemorrhage greater than 1 cm between aducanumab and placebo.

The majority of ARIA cases were asymptomatic. Clinical symptoms were present in 24% of patients treated with aducanumab 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 5% of patients on placebo. The most common symptom in patients with ARIA was headache, which, among patients with ARIA, was reported in 13% of patients treated

with aducanumab 10 mg/kg, compared to 3% of patients on placebo. Confusion, delirium, altered mental status, or disorientation (considered as a grouping of terms) were reported in 5% of patients treated with aducanumab 10 mg/kg with ARIA, compared to fewer than 1% of patients on placebo. Other adverse reactions that were reported in at least 2% of patients treated with aducanumab 10 mg/kg in the setting of ARIA include dizziness or vertigo (4%), visual disturbance (2%), and nausea (2%); these adverse reactions were not observed in patients on placebo who experienced ARIA. Although there were events of seizure reported, there was no imbalance between aducanumab 10 mg/kg and placebo. Serious ARIA reactions were reported in 0.3% of patients with ARIA treated with aducanumab 10 mg/kg. There were no deaths attributable to ARIA events.

Dr. Trummer notes that the protocols for studies 301 and 302 excluded patients on an antiplatelet or anticoagulation medication other than aspirin ≤ 325 mg, although 7% of aducanumab 10 mg/kg treated patients had concomitant use of a non-aspirin antiplatelet or anticoagulant medication for treatment or prophylaxis, with median duration of use of 19 days. The protocols also excluded patients with history of bleeding disorder, blood clotting disorder, abnormal coagulation profile, hypertension, prior cortical or lacunar infarct, or seizure within 10 years of screening; fewer than 2% of patients on aducanumab 10 mg/kg had such a history.

Although frequent MRI monitoring was performed in the aducanumab clinical trials, the optimal MRI monitoring frequency is difficult to characterize. A June 2, 2021, response to an information request showed that the majority of cases (84%) of ARIA in the 10 mg/kg group were asymptomatic. It is notable that even with severe ARIA on MRI, only 27% of patients developed symptoms, with most symptoms (79%) being of mild or moderate severity. Among patients with moderate/severe ARIA who had dosing held because of MRI findings, 11% developed symptoms even after dosing was stopped, making the clinical utility of frequent MRI monitoring uncertain. As shown in Dr. Trummer's review, approximately 50% of radiographic ARIA was detected prior to the 7th infusion of aducanumab, which corresponds to the end of the titration period. Approximately 90% of radiographic ARIA was detected prior to the 12th infusion, which corresponds to prior to the 6th infusion of 10 mg/kg aducanumab. Given that radiographic ARIA can take several months to resolve, MRIs performed at these time points should capture the majority of asymptomatic ARIA events in the first year of treatment. The recommendations for monitoring and dosing take into consideration the uncertainty in the benefit of frequent monitoring by MRI, acknowledging the burden to patients from frequent MRI monitoring in the absence of ARIA-related symptoms, and that simulations indicate that interruptions in dosing can have a prolonged impact on brain amyloid plaque removal, as noted in Dr. Krudys' review and the OCP review. Therefore, the recommended monitoring and dosing will be as follows:

- Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment.
- Obtain MRIs prior to the 7th and 12th infusions to evaluate for the presence of asymptomatic ARIA.

- For patients with radiographic findings of ARIA, enhanced clinical vigilance is recommended. Additional MRIs may be considered if clinically indicated.
- If radiographic severe ARIA-H (10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis) is observed, follow-up MRI is recommended before treatment is continued.
- If radiographically severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).
- For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution.

Requested postmarketing vigilance will address the uncertainty in the optimal monitoring plan (see Section 13. Comments to Sponsor).

Hypersensitivity reactions

Serious adverse events (SAEs) of angioedema and urticaria occurred in one patient. These events occurred during an aducanumab infusion in Study 302. There was no imbalance in hypersensitivity events between aducanumab 10mg/kg and placebo in the placebo-controlled portion of pooled studies 301 and 302.

Suicidal behavior/ideation

A role for aducanumab in one completed suicide could not be ruled out. However, there is not a signal for suicide-related events.

Abuse Potential

Dr. Branagan did not identify a safety signal for abuse potential or for withdrawal or rebound in her evaluation of TEAEs.

Immunogenicity

Treatment emergent anti-aducanumab antibodies (ADA) occurred in 0.6% of patients in the placebo-controlled and long-term extension periods of Studies 301 and 302. The available data are too limited to evaluate an effect on pharmacokinetics, safety, or efficacy of aducanumab.

Carcinogenicity

An imbalance in the incidence of neoplasms was not identified. However, the mean duration of exposure to 10 mg/kg aducanumab (less than 73 weeks) does not allow for conclusions regarding the carcinogenic potential in humans.

Human Reproduction and Pregnancy

There are no data on the use of aducanumab in pregnant women.

Safety Conclusions

There are no safety issues that would preclude approval of aducanumab for the proposed indication.

ARIA was characterized in the development program by radiographic findings on MRI and by symptoms associated with ARIA. Recommendations for clinical evaluation, including MRI monitoring and symptom recognition, are provided for in the prescribing information (sections 2.3, 2.4, and 5.1) and in the medication guide.

Although the applicant proposed a communication plan REMS, we agree with the Division of Risk Management that a REMS is not necessary.

The sponsor provided a summary of their training program for detection and management of ARIA directed at Alzheimer's disease specialists and their multidisciplinary teams including neuroradiologists on May 7, 2021, and discussed it in a teleconference on May 6, 2021. The sponsor also provided a brief description of their proposed post-market structured data collection registry program regarding ARIA that will be a global program with sites in the United States. The proposal has as a primary objective to characterize and evaluate long-term disease progression in patients who are treated with aducanumab. Its safety objectives are to evaluate the incidence of SAEs in aducanumab-treated patients, to assess the incidence and clinical and radiographic outcomes of ARIA-E associated with aducanumab treatment in real-world routine clinical practice, and to evaluate aducanumab utilization in routine clinical practice, including patient and disease severity characteristics, duration of use, and reasons for continuation. The program generally captures information that would be useful to the Agency in postmarketing assessment of the risk:benefit balance. We will request detailed pharmacovigilance that will be supported by the sponsor's registry program.

In addition to ARIA, safety issues of interest include serious hypersensitivity reactions, further characterization of the optimal timing and frequency of MRI monitoring, the risk of continuing to treat through an episode of ARIA, and whether the concomitant use of medications that cause bleeding or patients with a baseline increased risk of bleeding impart any additional risk of hemorrhage in patients with ARIA-H.

8. Advisory Committee Meeting

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held via an online teleconference on November 6, 2020. Prior to the meeting, the members were provided with the briefing materials and pre-recorded presentations from the FDA and the applicant. The questions to the committee and voting results, where appropriate, are

reproduced below:

1. (Discussion) The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Discuss the evidence of effectiveness provided by Study 302, viewed independently and without regard for Study 301, with particular consideration of the size of the study, design of the study, analysis of the results to assess the effects of the drug, and consistency of results among various subgroups in the study.

2. (Vote) Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease?
   Vote Results: Yes: 1 No: 8 Uncertain: 2

3. (Discussion) The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Study 103 is presented as supportive evidence of aducanumab's effectiveness. Discuss the evidence of effectiveness provided by Study 103.

4. (Vote) Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's disease?
   Vote Results: Yes: 0 No: 7 Uncertain: 4

5. (Discussion) The application presented evidence in support of the pathological hallmarks of Alzheimer's disease, including effects on amyloid beta, tau, and downstream markers of neurodegeneration, using multiple assessment modalities. Discuss the impact of these results.

6. (Vote) Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology?
   Vote Results: Yes: 5 No: 0 Uncertain: 6

7. (Discussion) Study 301 was a negative study. Post hoc exploratory analyses were conducted in order to achieve maximum understanding of the partially discordant results of Study 301 and Study 302, and to determine if this understanding precludes independent consideration of Study 302. Additional contribution to the understanding of aducanumab's pharmacological activity and clinical effects is provided by the results of Study 103. In light of the exploratory analyses that were conducted and the results of Study 103, discuss the impact of the results of Study 301 on the consideration of the results of Study 302.

8. (Vote) In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, it is reasonable to

consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?

Vote Results: Yes: 0 No: 10 Uncertain: 1

9. Pediatrics

Pediatric patients were not enrolled in trials because AD typically affects older adults. The applicant was granted a waiver for Pediatric Research Equity Act (PREA) requirements for this reason.

10. Other Relevant Regulatory Issues

- Dr. Krudys did not identify any Good Clinical Practice (GCP) issues.
- Dr. Krudys concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Office of Scientific Investigations (OSI) conducted inspections of two clinical sites and an inspection of the Applicant, Biogen. Site selection was based primarily on location (within the United States) and participation in Studies 103 and 302. Special attention was given to identifying any changes made to the data after unblinding of the studies. The review concludes that the studies appear to have been conducted adequately and the data generated by the sites were acceptable.

11. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Sponsor proposed a communication plan Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of ARIA. The Agency has determined that at this time there is not a need for a REMS. Please refer to the review by Dr. Crist from the Division of Risk Management for further details of this assessment.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following PMRs will be issued:

- In order to verify the clinical benefit of aducanumab, conduct a randomized, controlled trial to evaluate the efficacy of aducanumab compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

The following PMC's will be issued:

- Perform shipping qualification studies for drug product and finished goods
- Implement a validated product-specific host cell protein (HCP) assay in the aducanumab drug substance manufacturing process. Submit the HCP method and method validation report in a supplement within 9 months of licensure.
- Evaluate matrix interference from hemolysis and lipidemia in the aducanumab anti-drug antibody assay.
- Provide the KTA bacterial endotoxin test method qualification data from Biogen US Corporation and submit the report as a CBE-0.
- Implement the bacterial endotoxins test for the (b) (4) and submit as the final report as a CBE-0.

13. Comments to the Applicant

The following request for enhanced pharmacovigilance will be conveyed in the approval letter:

We request that you perform postmarketing pharmacovigilance to characterize the risk of ARIA and monitoring for ARIA associated with the use of Aduhelm. Please provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 cm. Provide a synthesized summary and analysis, including incidence of clinical trial cases, postmarketing cases, and total cases. Include an evaluation of CNS hemorrhage in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. Include an analysis that addresses the monitoring recommendations provided for in the prescribing information. The summary should provide analysis for all subjects and separately for those in the United States and those in the rest of the world. For each case, provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from the registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including APOε4 genotype if available
- Country where patient is treated
- Concomitant medications
- Time from first Aduhelm dose to ARIA
- Listing of dates of Aduhelm dosing
- Dates of MRI
- Description of MRI findings
- Whether patient was symptomatic and if so, list symptoms

- Whether initial finding was symptom or MRI
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Aduhelm was held, and date that aducanumab Aduhelm dosing resumed
- Whether Aduhelm was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

We request that you perform postmarketing pharmacovigilance to characterize the risk of hypersensitivity associated with the use of Aduhelm. Please provide biannual reports of serious hypersensitivity reactions, including line listings of the cases, FAERS reports, and a synthesized summary and analysis including incidence of clinical trial cases, postmarketing cases, and total cases.

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/

TERESA J BURACCHIO
06/07/2021 10:23:45 AM

SALLY U YASUDA
06/07/2021 10:27:54 AM

ERIC P BASTINGS
06/07/2021 10:31:04 AM

WILLIAM H Dunn
06/07/2021 10:32:49 AM