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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Kevin Krudys, PhD
BLA 761178
Aduhelm (aducanumab)

FDA CLINICAL REVIEW

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Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of Alzheimer's disease

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Glossary

Aβ	amyloid beta
AC	advisory committee
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale – Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
BLA	biologics license application
BRF	Benefit Risk Framework
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
DIAD	dominantly inherited Alzheimer's disease
FDA	Food and Drug Administration
GCP	good clinical practice
HCP	health care professional
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IgG1	immunoglobulin gamma 1
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ITT	intent to treat
IWG	International Working Group
IxRS	interactive voice/web response system
LTE	long-term extension
MCI	mild cognitive impairment

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MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging at the National Institutes of Health and the Alzheimer's Association
NDA	new drug application
NME	new molecular entity
NPI-10	Neuropsychiatric Inventory-10
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
OTC	opportunity to complete
PD	pharmacodynamics
PET	positron emission tomography
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PRO	patient reported outcome
PV4	protocol version 4
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
REMS	risk evaluation and mitigation strategy
ROI	region of interest
SAP	statistical analysis plan
SPA	special protocol assessment
SUVR	standard uptake value ratio

1. Executive Summary

1.1. Product Introduction

Aducanumab (previously BIIB037) is a human immunoglobulin gamma 1 (IgG1) anti-amyloid beta (A β) monoclonal antibody targeting aggregated forms of A β . Extracellular deposits of A β are one of the two pathological hallmarks of Alzheimer's disease, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of A β in the brain has been proposed to be the primary driver of the disease process. Aducanumab reduces levels of brain A β plaque by targeting aggregated forms of A β including soluble oligomers and insoluble fibrils.

The applicant's proposed indication is to delay clinical decline in patients with Alzheimer's disease. The dosing regimen consists of an intravenous infusion over approximately one hour every four weeks. To initiate treatment, patients should receive two doses of 1 mg/kg, two doses of 3 mg/kg, then two doses of 6 mg/kg over a total of 24 weeks. Thereafter, the target maintenance dose is 10 mg/kg. Aducanumab is available as a 100 mg/mL solution in a single-dose vial for intravenous infusion.

Aducanumab is a new molecular entity (NME) and is not marketed in any country. The proposed proprietary name is Aduhelm.

1.1. Conclusions on Substantial Evidence of Effectiveness

Evaluation of the evidence intended to establish the effectiveness of aducanumab was originally complicated by the fact that the two large, international pivotal trials (Studies 301 and 302) were near completion but were terminated prior to their planned conclusion with a public declaration of futility. Therefore, a critical and necessary first step in the consideration of these data was to assess the interpretability of the observed efficacy data considering the termination of the studies. Modeling and simulation methodologies were used to "virtually complete" the studies. The results of these analyses established that the results of Studies 301 and 302 were interpretable and suitable for additional consideration. Agreement on the interpretability of the data and the final dataset for further consideration was documented in the October 2019, Type C Meeting Minutes.

The applicant presents the results of Study 302 as the primary evidence of effectiveness. Study 302 is a large, multicenter trial that demonstrated aducanumab, as compared to placebo, reduced the change from baseline on the primary outcome measure, CDR-SB (-0.39, p=0.012). The CDR-SB is an acceptable primary outcome measure and its use was accepted by FDA in a Special Protocol Assessment of Study 302 in September 2015. The effect of aducanumab in

Study 302 was robust, including convincing effects on the primary endpoint, all three multiplicity-controlled secondary endpoints, and the tertiary clinical endpoint, and was exceptionally persuasive on several of the instruments used to evaluate efficacy. To some degree, each of these endpoints captures distinct information regarding cognitive decline. Statistically significant effects on ADAS-Cog 13 (-1.400, $p=0.0097$) and ADCS-ADL-MCI (1.7, 0.0006), endpoints which independently assess cognition and daily function, represent another acceptable co-primary endpoint approach in studies of Alzheimer's disease. Statistically significant treatment effects were maintained in sensitivity analyses, including one which included only patients who completed the study before its early termination. Further support for the results of the high dose is provided by the numerically favorable results for the low dose on the primary endpoint (-0.26, $p=0.0901$). Numerically favorable trends in the low dose were also observed for two of the secondary endpoints. These results are also suggestive of a dose-response relationship for aducanumab. Simulations suggest the probability of observing this pattern of results if aducanumab is no different than placebo is extremely small.

The treatment effect in Study 302 is supported by consistently favorable results for the primary and secondary endpoints across 79 of 80 prespecified subgroups of interest defined by demographic and baseline disease characteristics. Brain A β measured by PET was significantly reduced in a dose-dependent manner in all prespecified subgroups and a relationship between brain amyloid reduction and treatment effect for CDR-SB was identified. Biomarkers reflecting target engagement (brain A β reduction and CSF A β_{1-42} levels), effects on downstream Alzheimer's tau pathophysiology (p-Tau and Tau PET), and neurodegeneration (t-Tau) supported the observations on the clinical outcomes. Dose- and concentration-dependent relationships for biomarkers offer further support to the apparent dose-response relationship for clinical endpoints.

Although designed primarily as a safety and tolerability study, Study 103 was an adequate and well-controlled study that explicitly included assessment of prespecified clinical (CDR-SB and MMSE) and biomarker endpoints and a prospectively specified statistical analysis plan. The results of Study 103 are appropriately viewed as supportive evidence of effectiveness. Despite the limitations of a trial designed primarily to assess safety and tolerability, the 10 mg/kg dose arm was able to show a reduction, as compared to placebo, in the change from baseline in the clinical endpoints, CDR-SB (-1.08, $p=0.0464$) and MMSE (1.9, $p=0.0356$). The dose-response relationship for A β reduction provides support for the positive finding and is consistent with the dose-response relationship observed in the study for CDR-SB and MMSE.

Study 301 is a negative study and does not contribute to the evidence of effectiveness for clinical outcomes. One key observation, however, is that primary and secondary endpoints for the low dose had responses that were numerically favorable and similar in magnitude to those in Study 302. The response of the high dose, specifically the primary endpoint, was the notable difference between the studies. At the June 14, 2019, Type C Meeting, the Division clearly

stated that, “available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness supporting the approval of aducanumab.” Rather, the Division noted the possibility that analyses “may be understood well enough... to not represent evidence that the drug is ineffective.”

Given the enormous unmet medical need, extensive resources were brought to bear on achieving a maximum understanding of the existing data. The analyses were exploratory by design but limited in scope and focused on pre-defined areas of interest. These explorations were not intended to provide supportive evidence of effectiveness nor were they intended to fully account for the partially discordant results in Studies 301 and 302. The detailed considerations given to those analyses in this review, however, attest to their relevance. The rapid progressor analysis indicated that a small imbalance in the number of rapid progressing patients in the high-dose arm in Study 301 had a disproportionate impact on the estimate of the treatment effect using the primary analysis method. An examination of dosing in Study 301 indicates that patients with higher sustained exposure to the 10 mg/kg dose in Study 301 had similar responses to patients in Study 302. These two factors contribute to the overall understanding of Studies 301 and 302.

Based on the considerations above, the applicant has provided substantial evidence of effectiveness to support approval. Study 302 provides the primary evidence of effectiveness as a robust and exceptionally persuasive study demonstrating a treatment effect on a clinically meaningful endpoint and reinforced by effects on secondary endpoints, biomarkers, and in relevant subgroups. Study 103 was an adequate and well-controlled study which included design components consistent with Study 302 and demonstrated a persuasive treatment effect on both clinical endpoints. The dose-response relationship for A β reduction provides support for the positive finding in the 10 mg/kg treatment arm and to the apparently dose-related effects observed on clinical outcomes in Studies 103 and 302. Study 301 does not contribute to the evidence of effectiveness. The results of exploratory analyses, however, contribute to the overall understanding of Study 301 and together do not meaningfully detract from the persuasiveness of Study 302.

Although this review concludes that the standard for substantial evidence of effectiveness to support approval has been met, the reviewer also acknowledges the residual uncertainty introduced by the early termination of the studies and the failure of Study 301 to replicate the positive findings in Study 302. In the presence of residual uncertainty, it is reasonable to consider accelerated approval as a potential pathway. Alzheimer’s disease clearly meets the definition of a serious disease, and given the unmet need in patients at the early stages of the disease, aducanumab provides a meaningful therapeutic benefit over available therapies which offer modest and short-lived effects and do not target the underlying pathophysiology.

The critical question is whether reduction in brain amyloid plaque as measured by PET is an endpoint that is reasonably likely to predict clinical benefit. Although the precise relationship between brain amyloid and the emergence and progression of clinical symptoms is not fully understood, the presence of brain amyloid is a necessary condition for a diagnosis of Alzheimer's disease. Aducanumab distinguishes itself from previous amyloid-targeting therapies because it is the first anti-amyloid antibody to reach this stage of development and demonstrate a robust reduction of brain amyloid quantified using SUVR on PET imaging. The evidence to show that an effect on the surrogate endpoint affects the clinical outcome is provided by the treatment effects on clinical endpoints as described earlier. Further support is provided by the clear group-level correlation between change from baseline in PET SUVR and treatment effect for CDR-SB across the aducanumab development program. Long-term data also suggests that patients who achieved an SUVR <1.1 (the value reported to discriminate between a positive and negative amyloid PET scan) had more stable results on clinical measures than patients who did not. Important evidence of the relationship between aducanumab's effect and the disease process is also provided by the effects observed on downstream markers of tau pathophysiology and neurodegeneration. The accelerated approval pathway also allows for consideration of whether the effect on the endpoint has been shown to predict a clinical benefit with another drug or drugs. The two other anti-amyloid antibodies which have demonstrated a similar degree of reduction of brain amyloid in controlled studies in this population (BAN2401 and donanemab) have also been associated with treatment effects on clinical endpoints of similar magnitude and character to those observed in Studies 302 and 103. Together, these observations make a convincing case that reduction in brain amyloid plaque as measured by PET is reasonably likely to predict clinical benefit. Acceptance of reduction in brain amyloid plaque as a surrogate endpoint should not imply an endorsement of one hypothesis over another, nor does it exclude other therapeutic targets as viable for the treatment of Alzheimer's disease.

Unlike the effect on clinical endpoints, there is no uncertainty that the effect of aducanumab on brain amyloid plaque meets the statutory standard for substantial evidence of effectiveness. All 3 studies demonstrated statistically significant, dose- and time-dependent reductions in amyloid beta plaque. For these reasons, 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), this review concludes that the accelerated approval pathway is also a viable option.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Aducanumab is an anti-amyloid beta (A β) monoclonal antibody targeting aggregated forms of A β and developed to treat patients with Alzheimer's disease. This reviewer recommends approval based on the efficacy and safety information currently available.

Alzheimer's disease is an irreversible and progressive disease that affects memory, thinking, and behavior and is ultimately fatal. After a diagnosis of Alzheimer's dementia, the average survival is 4 to 8 years. Alzheimer's disease is the sixth leading cause of death in the United States. Currently approved treatments for Alzheimer's disease do not target the underlying pathology of the disease and their effects are modest and short-lived. No treatments are explicitly approved for earlier stages of the disease. There is an urgent and unmet medical need for effective treatments for Alzheimer's disease, and 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.

The efficacy of aducanumab is demonstrated in Study 302, a randomized study 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 high dose (10 mg/kg) showed a reduction of 18% to 40% in several clinical scales which incorporate patient and caregiver input and measure a broad array of symptoms related to cognition, function, and behavior. The effect of aducanumab on clinical endpoints was supported by dose- and time-dependent reductions of relevant markers of brain amyloid, downstream Alzheimer's tau pathophysiology, and neurodegeneration. The efficacy of aducanumab is also supported by Study 103, a smaller randomized study of a range of doses and placebo over 1 year in a similar population. The results for clinical endpoints at the highest dose studied (10 mg/kg) were consistent with the positive results observed in Study 302. Uncertainty regarding the efficacy of aducanumab was introduced by Study 301, a randomized study with identical design as Study 302, that failed to demonstrate an effect of the high dose.

The primary safety event identified in clinical trials is amyloid imaging abnormalities (ARIA) which represent a spectrum of imaging findings on brain MRI. These findings include brain edema and brain microhemorrhage. Most patients who experience ARIA do not have symptoms, and when symptoms occur, they are usually mild or moderate. ARIA is a known consequence of anti-amyloid treatment and is mitigated by dose suspensions and discontinuations and MRI monitoring.

The aducanumab program is unique in having two identically designed studies with apparently divergent outcomes regarding efficacy. An initial examination of the results for the primary endpoint in the two studies does not resolve the uncertainty and suggests that more data would be

needed to adequately assess the efficacy of aducanumab. A thorough consideration of the entire set of data, however, suggests the pattern of results observed across the program is extremely unlikely if in fact aducanumab is no different than placebo. Context is also provided by emerging data from other anti-amyloid therapies targeting aggregated forms of A β , which, together with aducanumab, indicate a relationship between reduction in brain amyloid beta plaques and reduction in decline of clinical endpoints. The conclusion of this review to support approval is also informed by the relentless progression of Alzheimer's disease and lack of available treatments, and consequently, the risk to current patients in the early stages of Alzheimer's disease of waiting years for additional data before approval of an effective treatment.

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.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
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 and transitory. - 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 are no treatments explicitly approved for earlier stages of the disease.	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.
Benefit	- The efficacy of aducanumab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in two main clinical trials (Study 301 and Study 302) - Participants were randomized to receive placebo, low-dose aducanumab, or high-dose aducanumab - Together, the trials enrolled 3285 patients: 2192 in aducanumab treatment arms and 1093 in the placebo arms. - The trials were terminated early, but the data are interpretable and there were no significant issues with trial design, conduct, or analysis. - Clinical efficacy endpoints were chosen to measure a broad array of symptoms experienced by patients with Alzheimer's disease. The scales use structured interviews, performance tests, and caregiver	The efficacy of aducanumab for the treatment of Alzheimer's disease has been established. Study 302 provides the primary evidence of effectiveness. The effect of the high dose of aducanumab in this study is robust and exceptionally persuasive on several of the instruments used to evaluate efficacy. Its findings are robust to numerous sensitivity analyses and are supported by highly consistent findings in prespecified subgroups and well-characterized biomarker data. In the context of the results of Study 302, the results of Study 103 are appropriately viewed as an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and patient input to measure independent information related to cognition, function, and behavior. ○ The primary endpoint was the change from baseline in CDR-SB. CDR-SB is an integrated scale that adequately and meaningfully assesses both daily function and cognition in early Alzheimer's disease. ○ Key secondary endpoints include the MMSE (a widely used performance-based assessment of cognitive ability), ADAS-Cog 13 (a cognitive assessment consisting of clinical ratings and cognitive tasks), and ADCS-ADL-MCI (feedback from caregivers regarding activities of daily living). ○ Each of the clinical endpoints captures distinct information regarding the patient's disease status. ● Study 302 demonstrated that high-dose aducanumab, as compared to placebo, resulted in a statistically significant reduction in the change from baseline on CDR-SB by -0.39, or -22%, over 78 weeks. ○ Statistically significant treatment effects in favor of high-dose aducanumab were observed for all three secondary clinical endpoints: 0.6 (-18%) for MMSE, -1.4 (-27%) for ADAS-Cog 13, and 1.7 (-40%) for ADCS-ADL-MCI. ○ Favorable results were observed for the primary and secondary endpoints across 79 of 80 subgroups of interest. ○ Results were robust to sensitivity analyses. ○ Favorable trends were also observed for low-dose aducanumab for all endpoints, suggesting the presence of a dose-response relationship.	additional and supportive contribution to substantial evidence of effectiveness. The negative results on the primary endpoint of Study 301 raise uncertainty about the effects observed in Study 302, but upon further analyses and consideration, do not meaningfully detract from the persuasiveness of Study 302. The breadth of the treatment effect observed across several instruments assessing cognition, function, and behavior are meaningful in this early Alzheimer's disease population which does not currently have available treatment options to slow or delay disease progression. The effectiveness has not been studied in an earlier disease population, but there is a potential for a more meaningful benefit in this population, given the possible irreversibility of pathophysiological deterioration responsible for clinical findings.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Treatment effects on biomarkers reflecting brain amyloid, downstream Alzheimer’s tau pathophysiology, and neurodegeneration supported the observations on the clinical outcomes. ● Study 301 did not demonstrate an effect of high-dose aducanumab on the primary endpoint, raising doubts about the results observed in Study 302. Overall, though, there is also some consistency between the studies and the results of Study 301 are not a direct contradiction of the positive results observed in Study 302. For example, numerically favorable results of a similar magnitude were observed for low-dose aducanumab in the two studies. Also, patients in the high-dose treatment arm in Study 301 who had greater levels of exposure had similar outcomes to patients in Study 302. Additional analyses were performed to understand the results of the two studies and determine if this understanding either supports or undermines the outcome of Study 302. The results of these analyses suggest that the results of the primary endpoint in Study 301 do not meaningfully detract from the persuasiveness of Study 302. ● Study 103 was a smaller study that supports the effectiveness of aducanumab. ○ The trial randomized 197 patients: 48 to placebo and 149 to a range of aducanumab doses. ○ Although designed primarily to assess safety and tolerability, the study included assessments of CDR-SB and MMSE. ○ The high dose of aducanumab was able to show a	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	statistically significant reduction, as compared to placebo, in the change from baseline in CDR-SB (-1.08 or -57%) and MMSE (1.9 or -76%). ○ Observations over 4 years suggest that the magnitude of the treatment effect of high-dose aducanumab does not diminish over time ● 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 the disease.	
Risk and Risk Management	• The safety database includes 3,078 subjects exposed to at least one dose of aducanumab, including 959 subjects treating mild dementia or mild cognitive impairment due to Alzheimer’s disease for at least 6 months, and 770 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%), 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.	The safety database fulfills minimum ICH guidance. Risk management can be achieved through clear product labeling and routine postmarketing surveillance A Warnings and Precautions Section 5.1 of the prescribing information will alert prescribers to 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. This will also be addressed in the Medication Guide.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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.	Prescribers will be made aware of the risk of serious hypersensitivity reactions in Section 5.2 of Warnings and Precautions. This will all 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.	

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	[Sec 6.1 Study endpoints]
	☐ Patient reported outcome (PRO)	
	X Observer reported outcome (ObsRO)	
	X Clinician reported outcome (ClinRO)	
	X Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
X	Patient experience data that were not submitted in the application, but were considered in this review:	
	X Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. 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. According to a recent report

(Alzheimer's Association 2021), an estimated 6.2 million Americans age 65 and older are currently living with Alzheimer's disease dementia. In the absence of interventions to prevent or slow the disease the number is projected to reach 12.7 million by 2050. The report notes that Alzheimer's disease is the sixth-leading cause of death in the United States and the fifth-leading cause of death for those age 65 and older. 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 Association 2021).

Alzheimer's disease exists on a continuum from pathophysiological changes in the brain which are undetectable to the person affected, to subtle problems with memory and thinking, and ultimately difficulties with memory, language, problem-solving, and other skills that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise (Vermunt et al. 2019). Life expectancy varies depending on many factors, but after a diagnosis of Alzheimer's dementia the average survival is 4 to 8 years (Alzheimer's Association 2021). The long duration of the disease contributes to the burden not only of the individuals with the disease, but also their families and caregivers who provide most of the patient care and are at an increased risk for emotional distress and negative mental and physical outcomes.

The two pathological hallmarks of Alzheimer's disease are extracellular deposits of A β , or plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of A β 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. Consequently, therapies to inhibit A β production or enhance A β clearance have been investigated in an attempt to slow or halt the disease process. Anti-amyloid therapies have thus far had a disappointing record with many high-profile, late-stage failures. Critical evaluation of these programs has revealed many factors that may, in part, contribute to their lack of success, including insufficient dosing, unknown target engagement, off-target effects, and inclusion of individuals in trials without evidence of brain A β pathology or at later stages of Alzheimer's disease (Cummings 2017; Karran and Hardy 2014; Toyn and Ahljianian 2014; Selkoe and Hardy 2016). Importantly, "anti-amyloid" therapies are not a distinct class of drugs, but rather reflect many different modes of action. Even among anti-A β monoclonal antibodies there are differences due to effector function, binding at different epitopes, and selectivity for A β variants (e.g. monomers, soluble oligomers, aggregated forms) (Linse et al. 2020). Therefore, previous late-stage failures of anti-A β therapies do not constitute a demonstrated "class failure" and are not particularly informative for the assessment of the effectiveness of aducanumab.

The aducanumab development program in many ways stands apart from these previous failures. The pivotal trials of aducanumab included patients with evidence of brain A β pathology who were early in the disease process. Moreover, an early trial (Study 103) demonstrated

target engagement and confirmed reduction of A β 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.

Some anti-A β 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 imaging findings detected on brain magnetic resonance imaging (MRI) which include ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H).

2.2. Analysis of Current Treatment Options

Current treatment goals for patients with Alzheimer's disease are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Currently approved Alzheimer's disease treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. The most recent approval of a novel medication was for memantine in 2003.

There clearly remains an enormous unmet clinical need for effective treatments for Alzheimer's disease. Current treatments do not target the underlying pathology of Alzheimer's disease and are only able to modestly affect the manifestations of the disease. Furthermore, there are no treatments explicitly approved for earlier stages of the disease.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Aducanumab is a new molecular entity (NME) and is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 106230 for aducanumab (previously BILB037) was opened in the United States on April 6, 2011, for the treatment of Alzheimer's disease following a pre-IND meeting between the applicant and FDA on October 13, 2009. Relevant regulatory interactions between FDA and the applicant include the following:

- December 16, 2014 – A Type B End of Phase 2 Meeting was held. The meeting included

preliminary discussion regarding study population, endpoints, and dosing for the applicant's two proposed Phase 3 studies, and the Division suggested a Special Protocol Assessment (SPA) be requested for an in-depth review of the protocols. The Division and applicant agreed to the safety monitoring plan and the safety database.

- March 23, 2015 – The applicant's request for breakthrough therapy designation based on interim results from a multiple-dose study (Study 103) was denied by the Division.
- September 28, 2015 –SPA agreements for Study 301 and Study 302 were reached with the Division.
- February 8, 2016 – A second request for breakthrough therapy designation based on additional analyses of Study 103 was denied by the Division for many of the same reasons outlined in the original denial.
- August 19, 2016 – Aducanumab was granted fast track designation.
- March 21, 2019 – Biogen announces the termination of the Phase 3 program (Studies 301 and 302) based on results of a pre-specified interim futility analysis. The first formal request from Biogen to the FDA regarding a discussion of the decision to terminate the studies came on May 15, 2019, in the form of a Type C Meeting Request.
- June 14, 2019 – A Type C Meeting was held to discuss the applicant's analysis of the intent to treat (ITT) populations of Study 301 and Study 302 including all data prior to the March 21, 2019, announcement of the termination of the studies. The Division advised the applicant that the development of aducanumab should not be abandoned as the available clinical data suggested the drug may be clinically active and did not provide convincing evidence that the drug is ineffective. The Division recommended that further analyses of the available data should 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 as compared with those for Study 302.
- October 21, 2019 – A Type C Meeting was held to discuss the additional analyses proposed at the June 14, 2019, meeting. Based on these analyses, the Division agreed that the results of Study 301 and Study 302 are interpretable and suitable for additional consideration. The Division further advised that planning for submission of a marketing application was a reasonable option.
- February 20, 2020 – The applicant opened BLA 761178 and submitted nonclinical information.

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- February 27, 2020 – Another Type C Meeting was held to discuss scientific questions raised at the October 21, 2019, meeting. The Division agreed to review a protocol for an open-label, uncontrolled re-dosing study in subjects who were enrolled in previous aducanumab studies when they were halted.
- June 17, 2020 – A Type C meeting was held via teleconference to discuss the efficacy and safety data that were available for aducanumab in the context of the planned BLA submission. The Division informed the applicant that the extent to which the results of Study 301, Study 103, and the additional data analyses support or undermine the results of Study 302 would be a matter of review. The Division and applicant also agreed on the safety data to support filing. On June 8, 2020, the applicant submitted a meeting request for a Type B pre-BLA meeting. The Division determined that the questions for that meeting request were limited in scope and therefore provided answers as part of the June 17, 2020, meeting.
- July 7, 2020 – BLA submission complete.
- January 28, 2021 – The Division notified the applicant that their January 27, 2021, submission constituted a major amendment to the application.

3.3. Foreign Regulatory Actions and Marketing History

Aducanumab is not approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of two clinical sites and an inspection of the sponsor, Biogen. Site selection was based primarily on location (within the United States) and participation in Studies 103 and 302. Given the unique circumstances of the early termination of the studies, special attention was devoted to identifying any changes made to the data after unblinding of the studies. Changes to Week 78 CDR-SB scores after study unblinding for visits occurring before study termination were identified for 10 subjects in Study 302. These were made after centralized reading and subsequent discussion and concurrence by the blinded rater. The changes occurred in both low-dose and high-dose treatment arms and included both increases and decreases in scores. The review concludes that the studies appear to have been conducted adequately and the data generated by the sites were acceptable.

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Please see Dr. Alfaro's review for a complete discussion of OSI's findings.

4.2. Product Quality

Please see the OPQ review for any issues related to product quality.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Hawver's review for any issues related to nonclinical pharmacology /toxicology.

4.5. Clinical Pharmacology

The clinical pharmacology review team has concluded that aducanumab has demonstrated consistent pharmacodynamic effects and that A β plaque burden has clinical significance in the pathophysiology of Alzheimer's disease based on the following:

- Clear exposure-efficacy and dose-response relationships for aducanumab across multiple clinical endpoints and for reduction in brain amyloid
- Consistent pharmacodynamic effect (A β plaque reduction) in clinical studies and a clear relationship between A β plaque reduction and reduction in decline of CDR-SB for aducanumab
- Similar relationship between A β plaque reduction and effect on clinical endpoint (CDR-SB) reported with other candidate drugs targeting A β pathways
- Clinical trial simulations showed very low probability of a false positive finding for the high dose group in Study 302, suggesting that the Study 301 result could be a chance finding driven by a subgroup in the high dose group

No dose adjustments are needed based on age, race, sex, renal or hepatic impairment, food-intake, or drug/transporter mediated interaction.

In consultation with OPQ, the review team concluded that the to be marketed product is adequately bridged to the clinical trial formulation.

Please see Dr. Gottipati's review for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

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4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A summary of clinical studies pertinent to the evaluation of efficacy is presented in Table 1.

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Table 1: Clinical Studies Contributing Efficacy Data and Relevant to the Review of this BLA

Trial Identity/NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population (per categorization at the time of enrollment)	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
221AD302 (Study 302)/ NCT02484547	Randomized, double-blind, placebo-controlled, parallel group	IV infusion once every 4 weeks <u>Placebo</u> saline infusion <u>Low Dose</u> Titration to 3 mg/kg for ApoE ε4 carriers or 6 mg/kg for ApoE ε4 non-carriers <u>High Dose</u> Titration to 10 mg/kg	<u>Primary</u> Change from baseline in CDR-SB at Week 78 <u>Secondary</u> Change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI at Week 78	76-week treatment period 18-week follow-up period (or enrollment in LTE up to 5 years)	1643	MCI due to Alzheimer's disease or mild Alzheimer's disease dementia CDR global score of 0.5, MMSE between 24 to 30 and positive amyloid PET scan 50 to 85 years of age	181 centers in 13 countries
221AD301 (Study 301)/ NCT02477800	Randomized, double-blind, placebo-controlled, parallel group	IV infusion once every 4 weeks <u>Placebo</u> saline infusion	<u>Primary</u> Change from baseline in CDR-SB at Week 78	76-week treatment period 18-week	1653	MCI due to Alzheimer's disease or mild Alzheimer's disease	169 centers in 14 countries

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		<u>Low Dose</u> Titration to 3 mg/kg for ApoE ε4 carriers or 6 mg/kg for ApoE ε4 non-carriers <u>High Dose</u> Titration to 10 mg/kg	<u>Secondary</u> Change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI at Week 78	follow-up period (or enrollment in LTE up to 5 years)		dementia (with CDR global score of 0.5, MMSE of 24 to 30 and positive amyloid PET scan) 50 to 85 years of age	
221AD103 (Study 103)/ NCT01677572	Randomized, double-blind, placebo-controlled, 4-cohort, multiple-dose	IV infusion once every 4 weeks <u>Fixed Dose Cohorts</u> Placebo 1 mg/kg 3 mg/kg 6 mg/kg 10 mg/kg <u>Titration Cohort</u> Placebo 10 mg/kg (44-week titration)	<u>Primary</u> Safety and tolerability <u>Secondary</u> Change from baseline in Aβ PET composite SUVR at Week 54 <u>Exploratory</u> Change from baseline in CDR-SB at Week 54 and MMSE at Week 52	52-week treatment period 18-week follow-up period (or enrollment in LTE)	197	Prodromal Alzheimer's disease (IWG criteria) or mild Alzheimer's dementia CDR global score of 0.5 or 1.0 and MMSE between 20 and 30 and positive amyloid PET scan 50 to 90 years of age	27 centers in the United States

5.2. Review Strategy

Before evaluating the evidence submitted in support of effectiveness, the efficacy review addresses the applicant's declaration of futility and subsequent termination of Study 301 and Study 302. During the June 2019 Type C Meeting, the applicant and the Division agreed that it would have been more appropriate if futility had not been declared. Therefore, a critical first step was to assess the interpretability of the observed efficacy data considering the termination of the studies. 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. This analysis established the results of Studies 301 and 302 as interpretable and suitable for additional consideration. The applicant and Division agreed that the appropriate dataset should include all data from all randomized and dosed participants with censoring of data collected after the futility announcement (March 20, 2019). A new subheading has been added to the review template (Section 7.1.6) to fully describe the futility analysis and its consequences. Although an unusual situation, the early termination of the studies does not render the findings uninterpretable.

After concluding the studies were interpretable, the applicant had one study which, on face, met its primary and secondary endpoints (Study 302) and appeared exceptionally persuasive and one which did not meet the primary endpoint (Study 301). Both studies are reviewed in Section 6. As the positive study, Study 302 is presented first and in greater detail, with sensitivity and subgroup analyses. Study 301 results are also presented with a high-level focus on potential similarities or differences with Study 302. A more detailed consideration of the partially discordant results between Studies 301 and 302 is presented in Section 7.1.7. The analyses presented in this section are exploratory but were hypothesis-driven, designed to address specific questions, and predetermined to the furthest extent possible. Importantly, the analyses were not intended to obtain independent support from Study 301, nor were they intended to completely explain the discordant results. Study 301 is clearly a negative study. The intention was to provide maximum understanding of the partially discordant outcomes and to determine the degree to which Study 301 supports or undermines the persuasive results from Study 302.

The partially discordant results in Studies 301 and 302 elevate the importance of considering the results of Study 103. Although designed primarily as a safety and tolerability study, Study 103 was a randomized, double-blind, multicenter study which incorporated many of the characteristics of Studies 301 and 302, including blinded efficacy and pharmacodynamic assessments in a similar patient population. This study is therefore reviewed in detail in Section 6.3.

Given the unique nature of the aducanumab data, an integrated assessment of effectiveness is

particularly relevant for this review. Section 1.1 provides an integrated summary of the evidence in support of the effectiveness of aducanumab for the treatment of Alzheimer's disease.

This review focuses solely on clinical efficacy. This application is being reviewed separately for safety by Drs. Branagan and Trummer.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 302 (221AD302): A Phase 3 Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease

6.1.1. Study Design

Overview and Objective

Study 302 was one of two identically designed studies to evaluate the efficacy and safety of aducanumab in patients with Alzheimer's disease. The primary efficacy objective was to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) score as compared with placebo in participants with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's disease dementia.

Trial Design

Study Design

Study 302 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. The study was conducted in 181 centers globally. Randomization was stratified by site and by ApoE ε4 carrier status (carrier or non-carrier) and enrollment was monitored such that 80% of the population included patients with a baseline clinical stage of MCI due to Alzheimer's disease. The study included an 8-week screening period, a 78-week placebo-controlled treatment period and a safety follow-up period of 18 weeks after the final dose. For the placebo-controlled period, patients were randomized to aducanumab low dose, aducanumab high dose, or placebo treatment arms in a 1:1:1 ratio. Patients who completed the placebo-controlled period had the option to enter the 5-year, dose-blind, long-term extension (LTE) period. Patients randomized to placebo during the placebo-controlled period were switched to receive aducanumab (high dose or low dose as randomized at study entry) in the LTE. Patients

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randomized to aducanumab in the placebo-controlled period continued in the same treatment group for the LTE period.

Diagnostic Criteria

At the time of enrollment, patients 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). Patients were also required to have evidence of brain A β pathology by visual read of a positron emission tomography (PET) scan.

Key Inclusion Criteria

1. Male or female patients age 50 to ≤ 85 years
2. At least 6 years of education or work experience
3. Positive amyloid PET scan
4. CDR global score of 0.5
5. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score ≤ 85
6. Mini-Mental State Examination (MMSE) score ≥ 24
7. Must consent to ApoE genotyping
8. Has one informant/care partner who is able to provide accurate information about the subject's cognitive and functional abilities and should be available for the duration of the study

Key Exclusion Criteria

1. Any uncontrolled medical or neurological condition (other than Alzheimer's disease) that may be a contributing cause of the subject's cognitive impairment
2. Clinically significant unstable psychiatric illness within 6 months prior to screening
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening
4. Brain MRI performed at screening that shows evidence of any of the following: 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
5. Contraindications to having a brain MRI or PET scan
6. History of bleeding disorder
7. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤ 325 mg daily)
8. Uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic

heart failure or clinically significant conduction abnormalities

9. Participation in any active immunotherapy study targeting A β , any passive immunotherapy study targeting A β within 12 months of screening or any study with purported disease-modifying effect in AD within 12 months of screening unless documentation of receipt of placebo

Reviewer Comment: The patient population is consistent with Stage 3 and Stage 4 patients as described in the FDA 2018 Guidance for Industry Early Alzheimer's Disease: Developing Drugs for Treatment.

Dose Selection

Two dose levels (hereafter referred to as low dose and high dose) were chosen to balance dose-dependent A β reduction and occurrence of ARIA. The high dose was chosen to maximize A β reduction and the low dose was chosen to achieve considerable, but lower, reduction of A β while lowering the incidence of ARIA. Dose levels were initially based on the results of the fixed-dose cohorts (1, 3, 6 and 10 mg/kg) from Study 103 which demonstrated a time- and dose-dependent reduction of brain amyloid and a dose-dependent reduction of decline for the exploratory endpoints CDR-SB and MMSE. The incidence of ARIA was also dose- and ApoE ϵ 4 carrier-dependent in the fixed-dose cohorts of Study 103. It was hypothesized that dose titration would minimize the incidence of ARIA in Study 302. For these reasons, dosing was initially dependent on ApoE ϵ 4 carrier status with ApoE ϵ 4 carriers titrated to lower doses (3 mg/kg low dose and 6 mg/kg high dose) than ApoE ϵ 4 non-carriers (6 mg/kg low dose and 10 mg/kg high 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 ϵ 4 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 ϵ 4 carriers who received a fixed dose of 10 mg/kg throughout the study. Following this finding, the high dose (after titration) for ApoE ϵ 4 carriers in Study 302 was increased via protocol amendment from 6 mg/kg to 10 mg/kg. The target 14 doses of 10 mg/kg administered over 78 weeks in Study 302 is equivalent to the number of 10 mg/kg doses administered over 54 weeks in the fixed-dose cohort in Study 103 (see Section 6.3.1).

Study Treatments

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. Target doses for both the low- and high-dose treatment arms initially depended on ApoE ϵ 4 carrier status. Protocol version 4 mandated the same target dose, 10 mg/kg, in the high-dose arm for both ApoE ϵ 4 carriers and non-carriers. After implementation of protocol

version 4, subjects enrolled under protocol versions prior to version 4 and assigned to the ApoE ε4 carrier high-dose arm were titrated to 10 mg/kg following receipt of at least 2 doses of 6 mg/kg. The dosing scheme is illustrated in Table 2.

Table 2: 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							
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.

Assignment to Treatment

An automated interactive voice/web response system (IxRS) was used to manage randomization and treatment assignment. Patients were randomized in a 1:1:1 ratio to placebo, low dose, or high dose. Randomization was stratified by site and ApoE ε4 carrier status (carrier or non-carrier) and enrollment was monitored such that 80% of the population included patients with a baseline clinical stage of MCI due to Alzheimer’s disease.

Blinding

A placebo match was not provided for the study, so an unblinded pharmacist managed all aspects of study treatment receipt, dispensing, and preparation. All other study site staff and patients were blinded to treatment assignment during the placebo-controlled period. Efficacy assessments were conducted by two independent health care professionals (HCPs) not involved in patient care or management who were to remain blinded to treatment assignment and any other information that had the potential to reveal treatment assignment, including status of dosing with aducanumab, concomitant therapy, laboratory data, imaging data, or adverse events (AEs). The treating HCP was not allowed to discuss AEs, including occurrence of ARIA, with the independent rating HCPs. The occurrence of certain ARIA events during the titration period required additional monitoring to continue through completion of the titration period. 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.

Reviewer Comment: The occurrence of ARIA has the potential to cause functional unblinding of investigators, patients, and caregivers because ARIA is associated with aducanumab treatment and it prompts differential management of patients, including additional MRIs and dose modification. The potential for this functional unblinding was unavoidable and the applicant has taken steps to address it in the study. This was recognized and reflected in the issuance of FDA agreement to the applicant's request for a special protocol assessment of the protocol. One important safeguard against this potential unblinding is the use of rating HCPs who are independent of patient care and blinded to dosing and adverse events. Patients and caregivers may become functionally unblinded though, which can influence rating scales that require more of their input, such as the ADCS-ADL-MCI. The potential of functional unblinding to influence the efficacy results is an important issue and is addressed in greater detail in Section 7.1.7.

Dose Modification/Dose Discontinuation

Dose modification criteria were established to account for the expected occurrence of ARIA-E and ARIA-H. 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. ARIA dose management was initially informed by results from fixed-dose cohorts of Study 103 and expert recommendations (Sperling et al. 2011) but evolved over time as the scientific field gained experience managing ARIA and as additional data became available from Study 103. Specifically, protocol versions 3 and above enabled more patients to continue treatment with aducanumab and to reach their assigned target dose. Dosing guidelines for different protocol versions are summarized for ARIA-E in Table 3 and ARIA-H in Table 4. Patients who developed ARIA-H coincident with ARIA-E were to follow the more restrictive guideline. If dosing was suspended prior to reaching the target dose the patient must receive at least two doses at the restart dose before titrating to the next dose level and must complete the required number of doses at that dose level per their assigned group.

Table 3: Dose Modification/Discontinuation Rules for ARIA-E by Protocol Version (Study 302)

Clinical Symptom Severity		MRI Severity	Protocol Version ¹		
			Version 1	Version 3	Version 4-6
Asymptomatic		Mild	Continue dosing at same dose and schedule		
		Moderate or Severe	Suspend dosing and restart at next lower dose	Suspend dosing and restart at the same dose	
Symptomatic	Mild or Moderate	Any			

	Severe		Permanently discontinue	
	Serious “other medically important event” ²			
	Serious, except “other than medically important event”		Permanently discontinue	

Created by reviewer, modified from Table 11 in Study 302 Clinical Study Report (CSR)

¹ No patients were consented under Protocol Version 2

² “Other medically important events” include SAEs that were not life-threatening, did not require inpatient hospitalization or prolongation of existing hospitalization, and did not result in significant or permanent disability

Note: Dosing was restarted when ARIA-E and/or clinical symptoms resolved

Note: From protocol versions 3-5, if a second ARIA event (either ARIA-E or ARIA-H) required dose suspension, patients were to restart at the next lower dose. If a third ARIA event required dose suspension, drug was to be permanently discontinued. For protocol version 6, patients were to restart at the same dose after the second or third ARIA event

Table 4: Dose Modification/Discontinuation Rules for ARIA-H Microhemorrhage and Superficial Siderosis by Protocol Version (Study 302)

Clinical Symptom Severity		MRI Severity	Protocol Version ¹	
			Version 1	Version 3-6
Asymptomatic		Mild	Continue dosing at same dose and schedule	
		Moderate	Suspend dosing and restart at next lower dose	Suspend dosing and restart at same dose
		Severe	Permanently discontinue	
Symptomatic	Mild or Moderate	Mild or Moderate	Suspend dosing and restart at next lower dose	Suspend dosing and restart at same dose
		Severe	Permanently discontinue	Permanently discontinue
	Severe	Mild or Moderate		Suspend dosing and restart at same dose
		Severe		Permanently discontinue
	Serious “other medically important event”²	Mild or Moderate		Suspend dosing and restart at same dose
		Severe		Permanently discontinue
	Serious, except “other than	Any		Permanently discontinue

	medically important event"			

Created by reviewer, modified from Table 12 in Study 302 CSR

¹ No patients were consented under Protocol Version 2

² "Other medically important events" include SAEs that were not life-threatening, did not require inpatient hospitalization or prolongation of existing hospitalization, and did not result in significant or permanent disability

Note: Dosing was restarted when ARIA-H stabilized, and clinical symptoms resolved

Note: From protocol version 3-5, if a second ARIA event (either ARIA-E or ARIA-H) required dose suspension, patients were to restart at the next lower dose. If a third ARIA event required dose suspension, drug was to be permanently discontinued. For protocol version 6, patients were to restart at the same dose after the second or third ARIA event

Administrative Structure

A steering committee blinded to treatment assignment was established to provide scientific and medical direction and to oversee the administrative progress of the study. Members of the committee included study medical directors from Biogen and external experts in Alzheimer's disease. An independent Data Monitoring Committee (IDMC) was formed to monitor the overall conduct of the study and review safety on an ongoing basis and could recommend protocol modifications, dose suspension, dose termination, or study termination. The IDMC was also responsible for reviewing the futility analysis. At each meeting the IDMC made a recommendation to continue, stop, or modify the study.

A centralized imaging laboratory was selected to read and interpret PET and MRI scans. The central laboratory was to notify the principal investigator and the applicant of ARIA-E and ARIA-H findings. For the purpose of study conduct, readings from the central reader prevailed over those from the local radiologist.

A central electronic clinical outcomes vendor was selected to ensure standardization of clinical outcome assessments. Selected assessments were reviewed by central raters for consistency. If the central review resulted in feedback to the site rater, the site rater either agreed with the feedback and updated the assessment or provided rationale for not making the update.

Procedures and Schedule

The schedule for key assessments is presented in Table 5. The screening period consisted of three visits within a 60-day period before administration of the first dose. Eligible subjects reported to the study site to receive study treatment every 4 weeks for 76 weeks. The end-of-treatment visit occurred on Week 78 and the follow-up visit occurred on Week 94.

Table 5: Study 302 Schedule of Key Assessments

Assessment	Schedule
Eligibility Criteria	Screening V1, V2 and V3
ApoE Genotyping	Screening V1
Neurological and Physical Examinations	Screening V1, Week 12, 24, 48, 72, 78, 94

Brain MRI	Screening V2, Weeks 14, 22, 30, 42, 54, 66, 78
Study Drug Infusion	Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76
Anti-Aducanumab Ab	Weeks 1, 24, 32, 60, 78, 94
Aducanumab Concentration	Weeks 1, 4, 12, 16, 20, 26, 28, 52, 56, 78, 94
RNA, Serum and Plasma for Biomarkers	Screening V1, Weeks 8, 12, 24, 28, 56, 78, 94
CSF Collection (optional)	Screening V1, Week 78
Amyloid PET	Screening V3, Weeks 26 and 78
Tau PET	Screening V3, Weeks 26 and 78
RBANS	Screening V1
CDR	Screening V1, Weeks 26, 50, 78, 94
MMSE	Screening V1, Weeks 26, 50, 78, 94
ADCS-ADL-MCI, ADAS-Cog 13	Screening V2, Weeks 26, 50, 78, 94
NPI-10	Screening V2, Weeks 26, 50, 78

Created by reviewer, modified from Table 1 and Table 2 in Study 302 protocol

Note: There were three screening visits (V1, V2 and V3) within 60 days of randomization

Note: Amyloid PET and tau PET were assessed in different subgroups of patients

Note: Additional MRIs were collected in response to ARIA

Concurrent Medications

Medications for treatment of Alzheimer's disease, including but not limited to donepezil, rivastigmine, galantamine, and memantine were allowed if patients were receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and were to stay on a stable dose during the study. Patients were instructed to continue the medications they were receiving at enrollment without changes and to avoid starting new medications. An unscheduled visit for collection of all clinical assessments for the primary and secondary endpoints should have occurred before any change in Alzheimer's disease medications.

The following medications were not allowed:

- o Medications with platelet anti-aggregant or anti-coagulant properties, except aspirin at doses ≤ 325 mg per day
- o Non-prescription narcotic medication
- o Immunosuppressive drugs including systemic corticosteroids
- o Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis
- o Any investigational drug

Subject Completion, Discontinuation, or Withdrawal

Patients who completed the 78-week treatment period and follow-up visit were considered to have completed the study.

Patients who discontinued treatment were to remain in the study, attend a follow-up visit 18 weeks after the final visit, and continue protocol-required tests and assessments at a subset of the clinical visits listed in Table 5 until the end of the study or until the patient withdrew consent. The most notable treatment-related reason for study discontinuation was the occurrence of ARIA as outlined in Table 3 and Table 4. Other reasons for discontinuation include withdrawal of consent, medical emergency, AEs that do not resolve, severe infusion reaction, and discretion of the investigator for medical reasons or noncompliance. The reason for discontinuation of study treatment was to be recorded in the patient's case report form (CRF).

Patients who were withdrawn from the study after receiving at least one dose of study treatment were expected to complete the end-of-treatment visit and return to the site for a follow-up visit 18 weeks after receiving their last dose of study treatment. Efficacy assessments were not required if the patients discontinued treatment within 3 months of the previous efficacy assessment and significant changes in cognitive status were not suspected by the investigator. Reasons for withdrawal of patients include withdrawal of consent, unwillingness or inability to comply with the protocol, and discretion of the investigator or applicant. The reason for withdrawal was to be recorded in the patient's CRF.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in CDR-SB at Week 78. The CDR-SB assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews with the patient and a reliable companion or informant. A qualified rater uses interview data and clinical judgment to assign scores for each domain ranging from none=0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3. The personal care domain does not include the 0.5 score. Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity. CDR-SB has been described in the literature (Cederbaum et al. 2013) as a suitable primary endpoint for clinical trials in patients with early Alzheimer's disease due to its psychometric properties and its ability to assess both cognitive and functional disability. CDR-SB is accepted by FDA as an acceptable primary outcome assessment for studies of Alzheimer's disease intended to demonstrate substantial evidence of effectiveness. It has been widely used as the primary efficacy endpoint in clinical trials for other investigational drugs in this population.

CDR-SB assessments were conducted by an independent HCP not involved in patient care or management who remained blinded to treatment assignment. Given the importance of the reliable informant or companion, the inclusion criteria included a stipulation that the informant should be available for the duration of the study and the use of the same informant for the

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duration of the study was encouraged. Raters were required to complete qualification and training prior to being eligible to administer the assessment. All sites were asked to maintain the same rater throughout the study to ensure consistency. If a rater administered the CDR-SB to a patient, that rater was not allowed to administer the other neurocognitive assessments to that patient at any point during the study. A contract research organization (CRO), Medavante, was selected to manage rater training and eligibility and to ensure standardization of clinical outcome assessments with special focus on CDR-SB. Selected assessments were reviewed by central raters for consistency. If the central review resulted in feedback to the site rater, the site rater either agreed with the feedback and updated the assessment or provided rationale for not making the update.

Reviewer Comment: CDR-SB is an integrated scale that adequately and meaningfully assesses both daily function and cognitive effects in early Alzheimer's disease and is consistent with FDA guidance on clinical endpoints in Stage 3 patients. The distinction between cognitive and functional domains for the CDR-SB is somewhat artificial because the effects on cognition are measured in a way that reflect impact on function and are clinically meaningful. The SPA agreement for this protocol indicated FDA's concurrence with the choice of primary endpoint.

Secondary Endpoints

MMSE

The MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, language, and visuospatial functions. The scores from the 11 tests are summed to obtain a total score, which ranges from 0 to 30 with lower scores indicating greater cognitive impairment. It is often used in clinical practice or as a staging instrument for trial inclusion and is also used as an efficacy assessment in clinical trials.

ADAS-Cog 13

The ADAS-Cog is a cognitive assessment consisting of clinical ratings and cognitive tasks that was originally developed for use in clinical trials of patients with later stages of Alzheimer's disease dementia. ADAS-Cog 11 includes 11 tasks measuring disturbances of memory, language, and praxis. Many of the items of the ADAS-Cog 11 are at the measurement floor in patients with mild disease and may not show decline over the length of a typical clinical trial. Therefore, two additional tasks, delayed word recall and number cancellation, were added to create the ADAS-Cog 13 for use in this earlier disease population. The ADAS-Cog 13 includes 9 items that test performance (up to 65 points) and 4 clinician-rated items that test language and memory (up to 20 points) for a total score ranging from 0 to 85, with higher scores indicating greater cognitive impairment. The 13 items assess word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, comprehension

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of spoken language, memory, word-finding, language ability, delayed word recall, and concentration.

The ADAS-Cog was a key clinical endpoint in the trials that led to the approval of the acetylcholinesterase inhibitors. For many of the initial trials of anti-A β antibodies, ADAS-Cog 11 was a co-primary endpoint with a functional outcome such as ADCS-ADL. More recently, another variation of the ADAS-Cog, ADAS-Cog 14, was used as the primary endpoint in the trial for solanezumab in patients with mild dementia due to Alzheimer's disease.

ADCS-ADL-MCI

The ADCS-ADL-MCI is a questionnaire for informants that consists of 17 instrumental items and 1 basic item (getting dressed) intended to reflect activities of daily living. Informants are asked whether the patient attempted each item during the prior 4 weeks and their level of performance. Responses are "Yes," "No," or "Don't Know" with additional sub-ratings depending on the item. The total score ranges from 0 to 53 with lower scores indicating greater impairment. The ADCS-ADL-MCI was adapted from the ADCS-ADL, which was developed for a population with more advanced disease and served as a key endpoint in many of the acetylcholinesterase trials.

The secondary endpoints were assessed by a second HCP who was independent from the rater responsible for administering the CDR-SB. As with CDR-SB, all sites were asked to maintain the same rater throughout the study to ensure consistency. If raters administered the CDR-SB to a patient, they were not allowed to administer the secondary endpoint assessments to that patient at any point during the study.

The applicant performed a principal components analysis of the 48 individual items from CDR-SB, MMSE, ADAS-Cog 13 and ADCS-ADL-MCI using baseline and change from baseline data from Study 301 and Study 302 to assess the degree to which the endpoints capture similar or distinct information. The applicant concluded that the overlap between the items was 5-25% and therefore each scale carries independent information on the clinical state of the patient.

Reviewer Comment: FDA routinely encounters the use of these measures and they are appropriate selections for use in supporting an effect on an acceptable primary measure. The principal components analysis indicated that while there may be some degree of overlap among the 4 clinical endpoints, each also captures distinct information regarding cognitive decline. Effects on each of these endpoints can independently contribute to the persuasiveness of a specific study.

Based on analyses in Appendix II (FDA Statistical Review and Evaluation) of the Advisory Committee Briefing Document, the Advisory Committee accepted as fact that secondary

endpoints were correlated with the primary endpoint and used this correlation as a reason to question the strength of the results of Study 302. The only correlation presented was for the change from baseline for the primary and secondary endpoints. It is important to note that for a progressive disease, correlation between endpoints is expected, not because endpoints are conceptually the same, but because they all change in a similar direction as the disease progresses. Appendix II of the Advisory Committee Briefing Document also notes that correlations are “all easily nominally significant.” Reference to statistical significance is misplaced because statistical significance is influenced by the sample size and is not a measure of the strength of a relationship. Finally, Appendix II of the Advisory Committee Briefing Document presented a principal components analysis on total scores (Figure 32 in the appendix). The appropriate approach is to perform principal components analysis on the individual items of the scales. The final statistical review still includes a presentation of correlations for change from baseline for the primary and secondary endpoints, but no longer includes a principal components analysis and no longer appears to conclude that the four key endpoints do not measure very distinct information.

Dr. Campbell, a measurement expert in the Office of Neuroscience, has reviewed the clinical outcome assessments and concluded in her memo that the assessments capture symptoms and impacts of Alzheimer’s disease that are meaningful to patients. She further concludes that the observed correlations between endpoints do not suggest concern for redundancy or multicollinearity of the outcome assessments.

A more relevant correlation analysis performed on baseline assessments instead of change from baseline reveals a weak degree of correlation between the endpoints, with correlation coefficients ranging from 0.17 and 0.38. Even if one considers change from baseline as the statistical review suggests, correlations in Study 302 are still weak to moderate (0.3 to 0.5). For these reasons, this review concludes that the primary and secondary endpoints capture distinct information and secondary endpoints add to the strength of Study 302.

Tertiary Endpoint

NPI-10 was included as the tertiary clinical efficacy endpoint and was completed by interview with the informant. The NPI-10 assesses the presence, frequency, and severity of 10 neuropsychiatric domains: delusions, hallucinations, dysphoria, apathy, euphoria, disinhibition, agitation/aggression, irritability/liability, anxiety, and aberrant motor behavior. The total score ranges from 0 to 120 with higher scores indicating worse symptoms.

Key Pharmacodynamic Endpoints

Key pharmacodynamic endpoints include the following:

- Change from baseline in amyloid signal as measured by ^{18}F -florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of sites and patients (approximately 400) at Week 26 and Week 78. The SUVR was calculated for a composite of brain regions consisting of frontal, parietal, lateral temporal, sensorimotor, anterior and posterior cingulate, and occipital cortices with whole cerebellum as a reference region
- Change from baseline in CSF levels of $\text{A}\beta_{1-42}$, $\text{A}\beta_{1-40}$, 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 ^{18}F -MK-6240 PET and quantified by a composite SUVR at the Week 78 or end-of-treatment visit in a subset of patients. The SUVR was calculated for 6 composite regions of interest (frontal, temporal, medial temporal, parietal, cingulate, and occipital) with cerebellar cortex as the reference region
- Change in brain volume (whole brain, whole cortex, hippocampus, and lateral ventricle) as measured by MRI at Week 30 and Week 78

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) was finalized on September 11, 2018, before the termination of the study and an addendum was added on November 4, 2019 prior to database lock, in response to the futility declaration of March 21, 2019. The addendum to the SAP did not alter the prespecified primary analysis methods as documented in the September 2018 SAP, except for specifying that the primary analysis would exclude efficacy data collected after March 20, 2019, per agreement with the Division at the October 21, 2019, Type C Meeting. Additionally, no censoring of data was applied to biomarker, PK, and safety data.

Interim Analysis – Blinded Sample Size Reassessment

The sample size 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. The mean difference of 0.5 represents an approximately 25% reduction assuming the placebo mean change in CDR-SB is 2 at Week 78. Sample size was reassessed approximately 3 months before enrollment completion in November of 2017. At the time of this reassessment approximately 10% of the data was available on the primary endpoint from the pooled blinded data from Studies 301 and 302. As a result of the analysis, the sample size was increased from 1350 to 1605 (from 450 to 535 per treatment arm).

Interim Analysis – Futility Assessment

An interim futility analysis was planned to occur after approximately 50% of the patients enrolled in Studies 301 and 302 had the opportunity to complete the Week 78 visit. Futility

criteria were primarily 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 at 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 <20% in both the high-dose and low-dose treatment groups. The SAP specified that other data in addition to the pre-specified criteria could also be considered.

The data cutoff date for the futility analysis was December 26, 2018, at which point 49% of patients from Study 302 had the opportunity to complete the Week 78 visit. 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. An independent, unblinded statistician from a CRO (IQVIA) conducted the futility analysis. The IDMC received the futility analysis package on March 8, 2019, and met with the unblinded statistician 4 days later. The IDMC communicated its recommendation to the Biogen Senior Decision Team, which was independent of the study team, on March 19, 2019. The Biogen Senior Decision Team requested additional analyses which were conducted by unblinded statisticians who were employed by the applicant but not part of the study team. The Biogen Senior Decision Team recommended termination of the studies to the Biogen Executive Decision Team on March 20, 2019, and the Biogen Executive Team made the final decision to terminate all ongoing studies of aducanumab. On March 21, 2019, the applicant publicly announced the discontinuation of the aducanumab program. See Section 7.1.6 for a detailed discussion of the futility analysis and its implications.

Definitions of Statistical Analysis Populations

The following analysis populations were defined:

- Intent-to-Treat (ITT) Population – all randomized subjects who received at least one dose of study treatment and excluding data collected after March 20, 2019
- Per-Protocol Population – all subjects in the ITT population who had no violations of the following inclusion criteria: 6 years of education or work experience, positive PET scan, CDR global score of 0.5, RBANS score of 85 or lower, and MMSE score between 24 and 30. Also, subjects had ≥70% expected infusions and did not make changes to concomitant Alzheimer’s disease medications during the study
- Opportunity to Complete (OTC) Population – subjects in the ITT population who had the opportunity to complete the Week 78 visit by March 20, 2019
- ITT Population during the Double-Blind Period – subjects in the ITT population including

all data collected until April 17, 2019. The applicant began releasing treatment assignments to the CRO on April 18, 2019, to be distributed to the sites upon request.

- Uncensored ITT Population – subjects in the ITT population including all data collected during the study
- ¹⁸F-florbetapir Amyloid PET Analysis Population – all randomized subjects who received at least one dose of study treatment, used ¹⁸F-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

Analysis Method for Primary Endpoint

A mixed model repeated measures (MMRM) model was used to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, Alzheimer's disease medication use at baseline, region, and laboratory ApoE ε4 status.

Missing Data

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.

Adjustments 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 $p > 0.05$ would not 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 were used.

Reviewer Comment: The Advisory Committee accepted as fact the suggestion in Appendix II of the Advisory Committee Briefing Document that the testing sequence does not allow for testing of secondary endpoints for the high dose if the low dose is not statistically significant for the primary endpoint. The applicant disagrees with this suggestion and there was not an opportunity to discuss this issue in depth at the meeting. The applicant has apparently used the same multiplicity adjustment procedure for other registration studies (Tecfidera and Plegridy) and asserts the approach ensures that failure of the low dose does not stop testing of the high

dose. The same neurology statistical review team appeared to accept this interpretation for the Tecfidera review¹, noting, “If statistical significance was not achieved for an endpoint for a particular dose level, all endpoints(s) of a lower rank for that dose level were not considered statistically significant. For each endpoint, the TID group was compared with placebo and if statistically significant ($p \leq 0.050$), the BID group was compared with placebo.”

The source of the confusion appears to be that the applicant planned to apply different levels of Type I error control to the primary and secondary endpoints. 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 different levels of Type I error were not explicitly stated in the SAP, leading the statistical reviewer to conclude in the final statistical review that the plan was “slightly ambiguous.” Unfortunately, a SPA agreement was reached without a shared understanding of the approach.

When evaluating benefit, this clinical review will accept results for secondary endpoints of the high dose. Simply disregarding compelling and clinically meaningful results on well-known and established endpoints in a positive study because of a misunderstanding about language in the statistical analysis plan would be a disservice to the patients and caregivers who devoted their time to generate the data.

Amyloid PET analysis

Amyloid PET 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 comprised 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

¹ See FDA Statistical Review for Tecfidera (NDA 204063), dated October 15, 2012, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204063Orig1s000StatR.pdf

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(aducanumab minus placebo) favors aducanumab. The composite ROI serves as the ROI of primary focus.

The following reference regions were 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.

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 ϵ 4 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 ϵ 4 status, baseline clinical stage, and baseline SUVR value in quartiles. Additional subgroup analyses were performed for all factors in the list above, except for region.

Reviewer Comment: Baseline clinical stage and baseline MMSE are both ways to evaluate disease severity. The distinction between MCI due to Alzheimer's disease and mild Alzheimer's disease is somewhat subjective. Also, only 20% of enrolled patients had mild Alzheimer's disease, further complicating interpretation of potential subgroup effects. The baseline MMSE criterion is more objective and roughly divides the population in half.

Protocol Amendments

The original protocol (Version 1) was issued on April 9, 2015. No patients were consented under Version 2. The main consequence of subsequent protocol versions was to increase the dose level or number of doses received by patients. Notably, Protocol Version 4, dated March 24,

2017, allowed ApoE ε4 carriers randomized to aducanumab high dose to receive the same aducanumab dose received by ApoE ε4 non-carriers (titration to 10 mg/kg). Table 3 and Table 4 outline the most relevant changes to the protocol, including Protocol Version 3 dated July 21, 2016, which modified dosing in relation to ARIA management. Protocol Version 6, dated June 28, 2018, updated the sample size from 450 to 535 per treatment group following the blinded sample size re-estimation.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was performed in accordance with 21 CFR parts 50, 54, 56 and 312 Subpart D, ICH Guideline on GCP (E6) and the ethical principles outlined in the Declaration of Helsinki.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators.

Patient Disposition

A total of 6757 patients were screened for entry into the study and 1643 patients were randomized. The most common reasons reported for screening failure were having a CDR global score, MMSE score, or RBANS score outside the allowed range (62%) or not having a positive amyloid PET scan (16%). There were 5 patients who were randomized but did not receive study treatment, with the most common reason being that the patient should have been classified as a screening failure. Patient disposition is summarized in Table 6. The most common reason for treatment discontinuation is “other.” This category includes patients who terminated the study due to the administrative decision to terminate aducanumab studies based on the interim futility analysis (placebo, 221 (40.3%); low dose, 198 (36.5%); high dose, 187 (34.2%)).

Table 6: Study 302 Patient Disposition

Disposition	Study 302		
No. of patients screened	6757		
No. of patients not randomized	5114		
	Aducanumab Low Dose N=543	Aducanumab High Dose N=547	Placebo N=548

	n (%)	n (%)	n (%)
Patients randomized	547	547	549
ITT population	543 (100%)	547 (100%)	548 (100%)
Per-protocol population	387 (71.3%)	365 (66.7%)	427 (77.9%)
OTC population	329 (60.6%)	340 (62.2%)	313 (57.1%)
¹⁸ F-florbetapir amyloid PET	159 (29.3%)	170 (31.1%)	159 (29.0%)
Discontinued treatment	264 (48.6%)	265 (48.4%)	254 (46.4%)
Adverse event	42 (7.7%)	49 (9.0%)	17 (3.1%)
Consent withdrawn	22 (4.1%)	20 (3.7%)	6 (1.1%)
Other reasons	200 (36.8%)	196 (35.7%)	231 (42.2%)
Discontinued study	252 (46.4%)	252 (46.1%)	260 (47.4%)
Adverse event	13 (2.4%)	20 (3.7%)	10 (1.8%)
Consent withdrawn	32 (5.9%)	26 (4.8%)	15 (2.7%)
Other reasons	207 (38.1%)	206 (37.6%)	235 (42.9%)

Created by the reviewer using ie.xpt and Tables 13, 20 and 50 in Study 302 CSR

Protocol Violations/Deviations

Two-thirds of patients had at least one major protocol deviation during the placebo-controlled period (placebo, 349 (63.7%); low dose, 354 (65.2%); high dose, 388 (70.9%)). The only major protocol deviation with $\geq 5\%$ difference between the high-dose treatment arm and placebo was in the “study procedures” category. The “study procedures” category included a variety of protocol deviations and none seemed to predominate. Overall, the most common categories of major protocol deviations were regarding informed consent (27.8%), study procedures (26.9%), and investigational product compliance (23.7%). These deviations are not expected to affect interpretation of the overall results. During the combined screening and placebo-controlled periods, 101 patients (36 placebo, 29 low dose, 36 high dose) had a major protocol deviation for eligibility or entry criteria. There were 4 patients who did not meet the CDR global score criterion, 2 who did not meet the MMSE criterion and 10 who did not meet the RBANS criterion. These numbers are small relative to the overall population enrolled and balanced across the treatment arms and are therefore not expected to complicate efficacy analyses. A total of 10.1% of patients received disallowed concomitant medications during the placebo-controlled period, but many of these were anti-coagulants or corticosteroids, which were disallowed for safety considerations and were not anticipated to have an impact on the effectiveness of aducanumab. Also, 13 patients were randomized to a carrier status that was discordant with laboratory assay results. There was one patient randomized to placebo who received aducanumab treatment in the visit before the start of the LTE. Single dose administration of aducanumab near the end of the study would not have an impact on the efficacy results.

Table of Demographic Characteristics

Table 7 contains information regarding demographic characteristics for each treatment arm in the ITT population. 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. Overall, 39.8% of patients were enrolled in the United States.

Table 7: 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
Age Group				
≤ 64 years	104 (19.0%)	106 (19.5%)	113 (20.7%)	323 (19.7%)
> 64 – <75 years	255 (46.5%)	262 (48.3%)	257 (47.0%)	774 (47.3%)
≥ 75 years	189 (34.5%)	175 (32.2%)	177 (32.4%)	541 (33.0%)
Race				
White	431 (78.6%)	432 (79.6%)	422 (77.1%)	1285 (78.4%)
Black or African American	1 (0.2%)	6 (1.1%)	4 (0.7%)	11 (0.7%)
Asian	47 (8.6%)	39 (7.2%)	42 (7.7%)	128 (7.8%)
American Indian or Alaska Native	1 (0.2%)	0	0	1 (<0.1%)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other	1 (0.2%)	1 (0.2%)	3 (0.5%)	5 (0.3%)
Ethnicity				
Hispanic or Latino	22 (4.0%)	22 (4.1%)	23 (4.2%)	67 (4.1%)
Not Hispanic or Latino	470 (85.8%)	470 (86.6%)	461 (84.3%)	1401 (85.5%)
Not Reported ¹	56 (10.2%)	51 (9.4%)	62 (11.3%)	169 (10.3%)
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: Table 14 and Table 49 in Study 302 CSR

¹ Data on race and/or ethnicity were not collected because of local regulations.

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Table 8 contains a summary of baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. The disease characteristics are balanced across treatment arms and reflect a population of patients who are early in the course of Alzheimer's disease. By design, the overall population consisted of 80% of patients with MCI due to Alzheimer's disease and 20% with mild Alzheimer's disease dementia. The percentage of the population who were ApoE ε4 carriers is consistent with previous reports. Most patients were receiving concomitant medications for Alzheimer's disease (51.8%). Additionally, 15.3% of patients received any Alzheimer's disease medication and stopped prior to entering the study.

Table 8: Study 302 Disease Characteristics (ITT Population)

Disease Characteristics	Placebo (N=548) n (%)	Treatment Group		
		Aducanumab Low Dose (N=543) n (%)	Aducanumab High Dose (N=547) n (%)	Total (N=1638) n (%)
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%)
Number of Years of Formal Education				
Mean years (SD)	14.5 (3.7)	14.5 (3.6)	14.5 (3.6)	14.5 (3.6)
Median (years)	15.0	15.0	15.0	15.0
Min, Max (years)	5, 29	3, 27	3, 29	3, 29
Number of Years Since Diagnosis of AD				
Mean years (SD)	1.3 (1.4)	1.3 (1.5)	1.3 (1.6)	1.3 (1.5)
Median (years)	0.8	0.8	0.8	0.8
Min, Max (years)	0, 10.0	0, 14.4	0, 16.1	0, 16.1
Concomitant AD medication				
Any AD medication at baseline	282 (51.5%)	281 (51.7%)	285 (52.1%)	848 (51.8%)
Only cholinesterase	235 (42.9%)	230 (42.4%)	228 (41.7%)	693 (42.3%)

inhibitors				
Only memantine	8 (1.5%)	15 (2.8%)	21 (3.8%)	44 (2.7%)
Both cholinesterase inhibitors and memantine	39 (7.1%)	36 (6.6%)	36 (6.6%)	111 (6.8%)
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%)
Baseline ADAS-Cog 13				
Mean (SD)	21.9 (6.7)	22.5 (6.8)	22.2 (7.1)	22.2 (6.9)
Median	21.7	22.3	21.8	21.7
Min, Max	4.7, 45.7	2.0, 46.0	5.3, 57.7	2.0, 57.7
Baseline ADCS-ADL-MCI				
Mean (SD)	42.6 (5.7)	42.8 (5.5)	42.5 (5.8)	42.6 (5.7)
Median	43.0	44.0	43.0	43.0
Min, Max	11, 52	19, 53	5, 53	5, 53

Source: Tables 16, 17 and Table 59 in Study 302 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the period of study treatment, compliance with study treatment was 96.2%. Although compliance was high, protocol-defined dose modification for ARIA, changes to the protocol, and the termination of the study meant that some patients received fewer target doses. For example, only 9% of ApoE ε4 carriers received all 14 doses of aducanumab 10 mg/kg, compared to 37.2% of ApoE ε4 non-carriers. Similarly, 80.1% of ApoE ε4 carriers received any 10 mg/kg doses, compared to 91.1% of ApoE ε4 non-carriers. More patients in the lower dose treatment arm received the maximum dose level (89.7% for ApoE ε4 non-carriers receiving 6 mg/kg and 98.6% for ApoE ε4 carriers receiving 3 mg/kg).

Overall, 14% of patients made changes to their concomitant Alzheimer's disease medications at some point during the study. The number of patients who made changes was similar across treatment arms (placebo, 73 (13.3%); low dose, 74 (13.6%); high dose, 83 (15.2%)).

Efficacy Results – 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 9). The low-dose

treatment arm demonstrated a numerical advantage compared to placebo (-0.26 [-15%]) but failed to reach statistical significance (p=0.0901). The results are consistent with a dose-response relationship.

Table 9: Study 302 Primary Endpoint Analysis

	Placebo (N=548)	Aducanumab Low Dose (N=543)	Aducanumab High Dose (N=547)
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	1.74	1.47	1.35
Standard error	0.115	0.116	0.115
95% CI	(1.513, 1.963)	(1.247, 1.701)	(1.124, 1.573)
Difference from placebo		-0.26	-0.39
95% CI for difference		(-0.569, 0.041)	(-0.694, -0.086)
% difference vs. placebo		-15%	-22%
p-value (compared with placebo)		0.0901	0.0120

Source: Table 22 from Study 302 CSR

Reviewer Comment: The treatment effect is not much different than the estimate used to power the study (-25%). Power calculations assumed a 2-point decline in CDR-SB over 78 weeks, whereas the observed decline in Study 302 was lower (1.74).

A treatment effect size of 1 to 2 on the CDR-SB scale has been quoted in literature (Andrews et al. 2019) as the minimum clinically important difference for CDR-SB. Setting aside concerns about the applicability of the data used in the publication to the population in Study 302, it is important to note that the placebo progression in Studies 301 and 302, 1.56 and 1.74, respectively, was also between 1 and 2. To see a treatment effect the size of the placebo progression in a study like Study 302, a drug would essentially need to halt the disease or even reverse existing cognitive deficits. A cursory review of existing protocols in this population revealed that the treatment effect on CDR-SB observed in Study 302 is consistent with expectation for other drug development programs.

Several SAP-defined and post hoc sensitivity analyses were performed for the primary endpoint. The copy increment from reference method and the jump to reference method were used to test the assumption that missing data were missing at random. Results from these analyses demonstrated that the statistically significant results for the primary endpoint were not sensitive to departures from the missing at random assumption. Notably, a sensitivity analysis for normality revealed that the distribution of the data was skewed, but the primary

analysis results were not sensitive to departures from normality.

Table 10 displays the results of the supplementary analyses of the primary endpoint in some of the key populations as defined in Section 6.1.1. Results in the uncensored population suggest that the magnitude of the treatment effect improves with additional data, including data after patients have stopped dosing for a period of time. Overall, the results support the robustness of the analysis of the primary endpoint in the ITT population.

Table 10: Study 302 Primary Endpoint Analysis (Dataset Sensitivity)

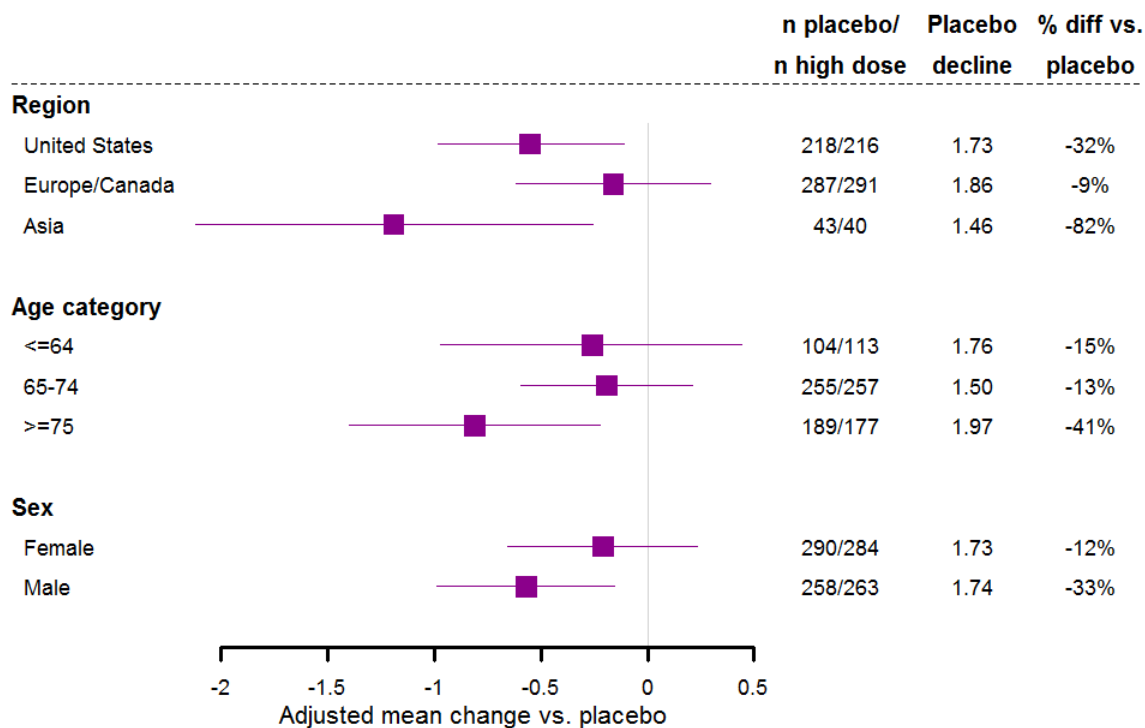
ITT Population during Double-Blind Period				Uncensored ITT Population			OTC Population		
Difference vs. Placebo at Week 78 (%) p-value				Difference vs. Placebo at Week 78 (%) p-value			Difference vs. Placebo at Week 78 (%) p-value		
	PBO Decline (N=548)	Low Dose (N=543)	High Dose (N=547)	PBO Decline (N=548)	Low Dose (N=543)	High Dose (N=547)	PBO Decline (N=313)	Low Dose (N=329)	High Dose (N=340)
CDR-SB	n=340	n=329	n=349	n=408	n=399	n=403	n=288	n=290	n=298
	1.76	-0.23	-0.41	1.79	-0.22	-0.44	1.61	-0.27	-0.36
		-13%	-23%		-12%	-25%		-17%	-22%
		0.1339	0.0061		0.1273	0.0029		0.1188	0.0368

Source: Tables 73, 77, and 79 in Study 302 CSR
p-values are nominal

Subgroup Analysis of the Primary Efficacy Endpoint

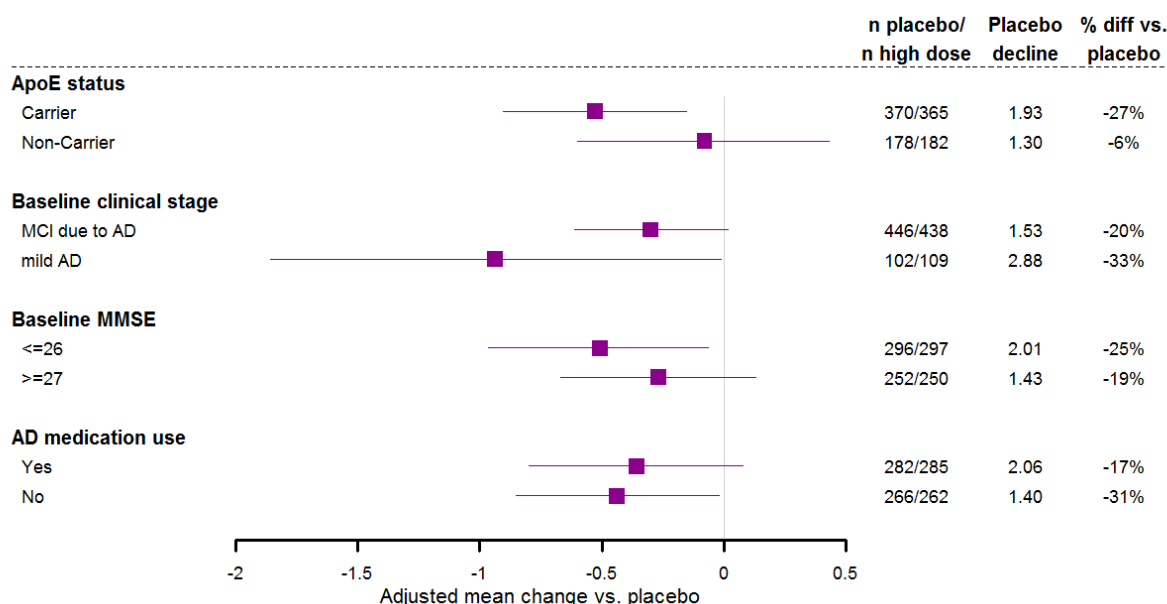
Subgroup analyses were performed on the primary efficacy endpoint for the groups described in Section 6.1.1 and are reported for the high-dose treatment arm in Figure 1 and Figure 2. All results trended in favor of high-dose aducanumab compared to placebo.

Figure 1: Study 302 High Dose Subgroup Analysis of the Primary Efficacy Endpoint (Demographics)



Created by the reviewer using Tables 135, 136, and 137 in Study 302 CSR.

Figure 2: Study 302 High Dose Subgroup Analysis of the Primary Efficacy Endpoint (Baseline Characteristics)



Created by the reviewer using Tables 131 to 134 in Study 302 CSR.

Data Quality and Integrity

There were no major data quality issues identified during the review of Study 302.

Efficacy Results – Secondary endpoints

A summary of the analysis results for the secondary endpoints is provided in Table 11. Statistically significant differences from placebo were observed for the high-dose treatment arm at Week 78 for all secondary endpoints. The low-dose treatment arm demonstrated favorable numerical trends for ADAS-Cog 13 and ADCS-ADL-MCI, but not for MMSE. 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%. Like CDR-SB, the secondary endpoints were also not normally distributed. Supplementary analysis using different datasets, including the OTC dataset, demonstrated similar results to the ITT population. Subgroup analyses for the secondary endpoints showed that all groups favored high-dose aducanumab except for one (MMSE in ApoE ε4 non-carriers). Subgroup findings for ApoE ε4 populations are discussed further in Section 7.1.3.

Table 11: Study 302 Secondary Endpoint Analysis

	Placebo (N=548)	Aducanumab Low Dose (N=543)	Aducanumab High Dose (N=547)
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	-3.3	-3.3	-2.7
Standard error	0.22	0.22	0.21
95% CI	(-3.68, -2.83)	(-3.77, -2.92)	(-3.11, -2.27)
Difference from placebo		-0.1	0.6
95% CI for difference		(-0.65, 0.48)	(0.00, 1.13)
% difference vs. placebo		3%	-18%
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	5.16	4.46	3.76
Standard error	0.40	0.41	0.40
95% CI	(4.37, 5.96)	(3.66, 5.26)	(2.97, 4.55)
Difference from placebo		-0.70	-1.40
95% CI for difference		(-1.76, 0.36)	(-2.46, -0.34)
% difference vs. placebo		-14%	-27%
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	-4.3	-3.5	-2.5
Standard error	0.38	0.38	0.38
95% CI	(-5.02, -3.53)	(-4.29, -2.79)	(-3.27, -1.79)
Difference from placebo		0.7	1.7
95% CI for difference		(-0.27, 1.73)	(0.75, 2.74)
% difference vs. placebo		-16%	-40%
p-value (compared with placebo)		0.1515	0.0006

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

Efficacy Results – Tertiary endpoint

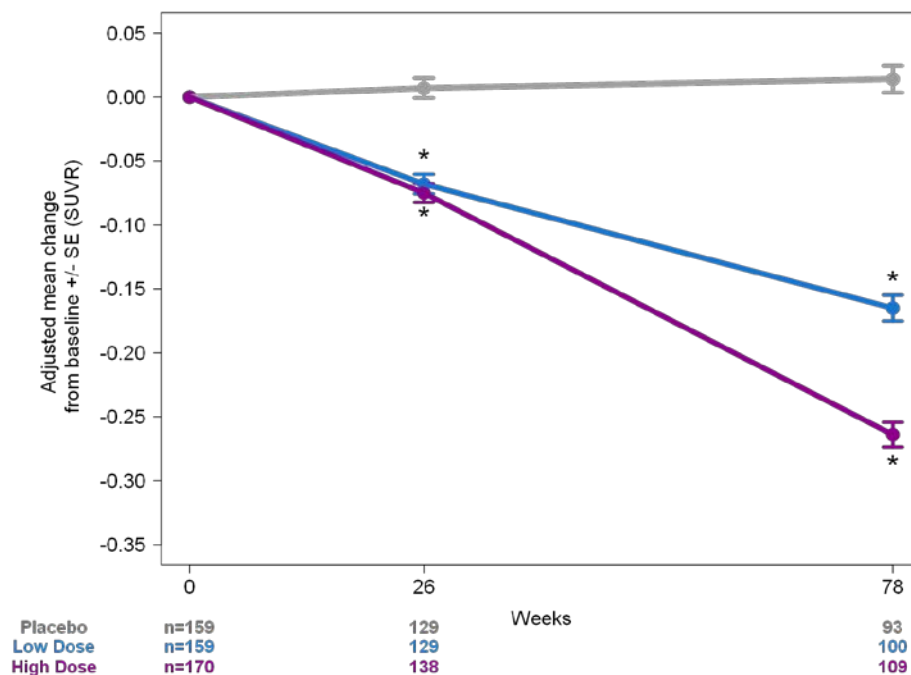
The adjusted mean change from baseline in NPI-10 at Week 78 compared to placebo was -1.3 (-87%, nominal $p = 0.0215$) for aducanumab high dose and -0.5 (-33%, $p=0.3921$) for aducanumab low dose.

Efficacy Results – Pharmacodynamic endpoints

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 $\epsilon 4$ status, and baseline age. The adjusted mean change from baseline relative to placebo 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 3). Consistent and statistically significant 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 statistically significant reduction in SUVR relative to placebo with larger reductions for the high-dose treatment arm compared to the low-dose treatment arm. At Week 78, the difference (95% CI) from placebo in the high-dose treatment arm for ApoE $\epsilon 4$ carriers and ApoE $\epsilon 4$ non-carriers was -0.260 (-0.2915, -0.2280) and -0.298 (-0.3490, -0.2469), respectively. The larger magnitude of reduction in ApoE $\epsilon 4$ non-carriers is consistent with the higher aducanumab exposure achieved in this subgroup. An association between baseline SUVR and magnitude of reduction in SUVR was observed in the high-dose treatment arm at Week 78 with a difference from placebo of -0.205 (-0.2599, -0.1499) in the lowest quartile of baseline SUVR and -0.367 (-0.4361, -0.2970) in the highest quartile of baseline SUVR.

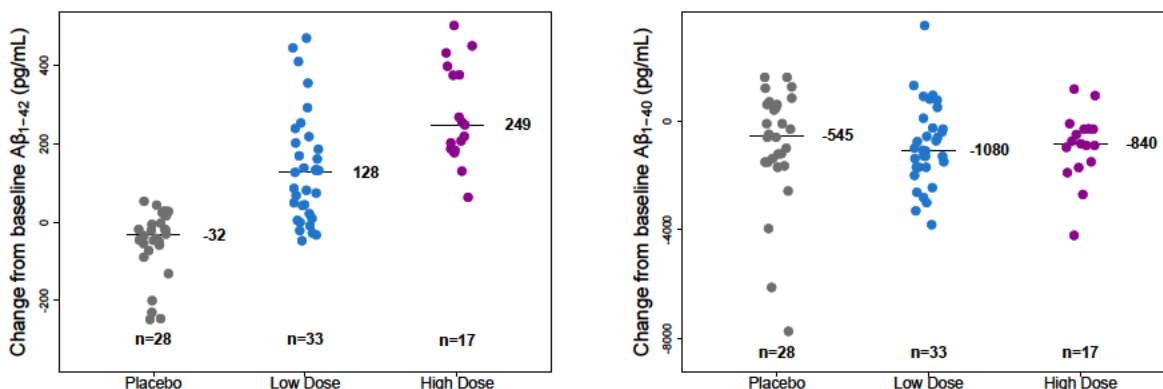
Figure 3: Study 302 Change from Baseline in A β PET Composite SUVR



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

There was a dose-related increase in CSF A β_{1-42} levels with overlap between groups, but no apparent relationship between dose and CSF A β_{1-40} levels (Figure 4). The change in CSF A β_{1-42} levels may reflect an increased input of A β_{1-42} into the CSF, decreased clearance from the CSF due to the prolonged half-life of the aducanumab:A β_{1-42} complex, or dispersion out of aggregated forms.

Figure 4: Study 302 Change from Baseline in CSF $A\beta_{1-42}$ (left) and $A\beta_{1-40}$ (right) at Week 78

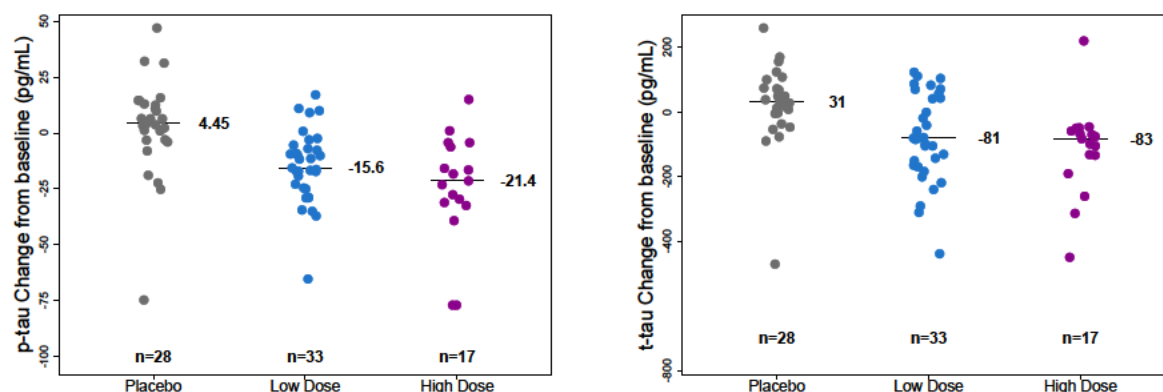


Created by reviewer using adbk.xpt

Change from baseline in markers of downstream Alzheimer's Tau pathophysiology and neurodegeneration are illustrated in Figure 5 and suggest a dose-dependent decrease in both p-Tau and t-Tau with significant variability between patients following aducanumab treatment. There were no differences between either treatment group and placebo for change from baseline at Week 78 in MRI volume measures for whole brain, whole cortex, and hippocampus. There was an increase in change from baseline to Week 78 lateral ventricle volume in both dose groups.

A pooled analysis of Studies 301 and 302 was performed for tau PET and is further described in Section 6.2.2.

Figure 5: Study 302 Change from Baseline in CSF p-Tau (left) and t-Tau (right) at Week 78



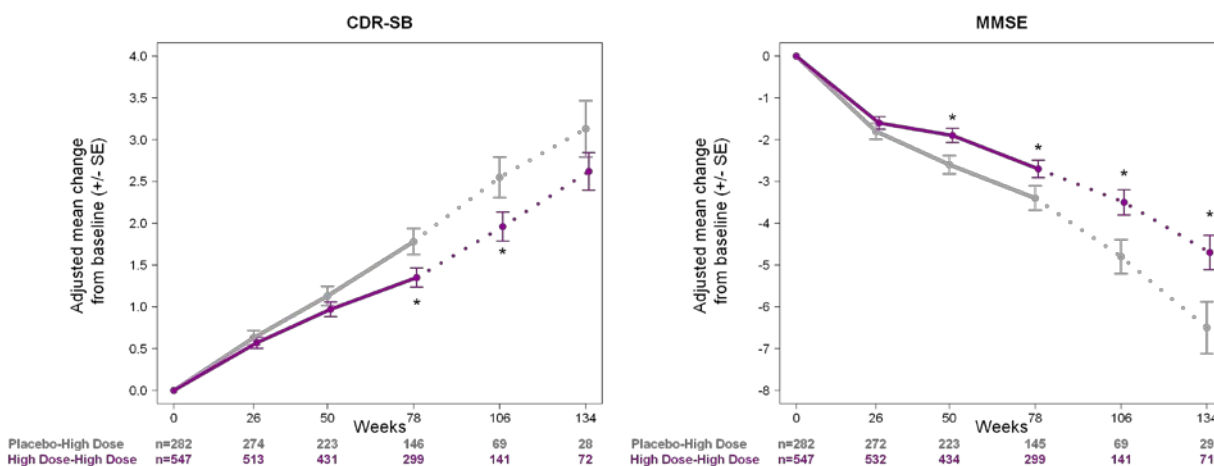
Created by reviewer using adbk.xpt

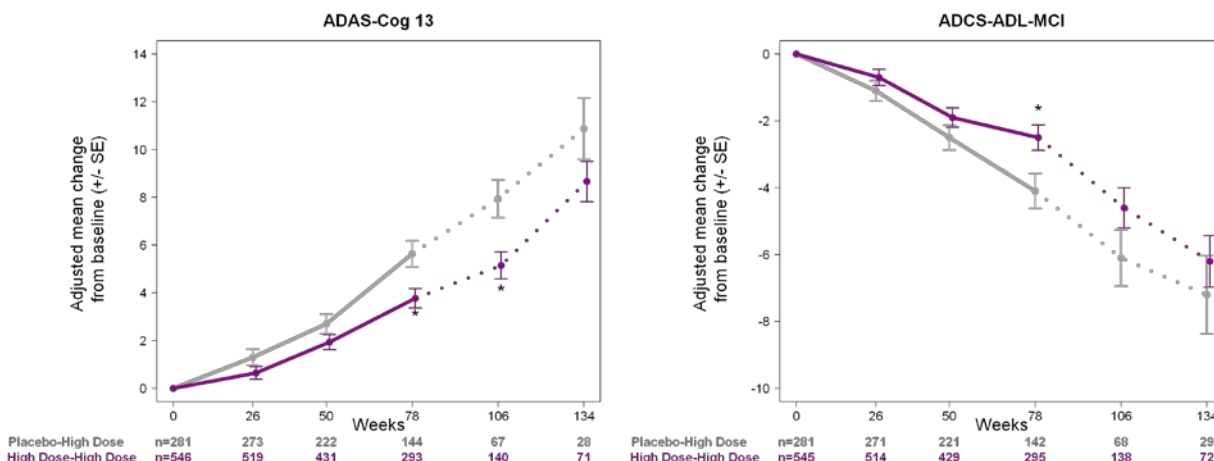
Durability of Response

The durability of clinical response in patients treated with high-dose aducanumab over 134 weeks is illustrated in Figure 6. This analysis compares the results of primary and secondary endpoints in patients randomized to high-dose aducanumab throughout the study to patients randomized to placebo during the placebo-controlled period and high-dose aducanumab during the LTE. Overall, the magnitude of the treatment effect at Week 78 does not appear to diminish during the LTE.

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.

Figure 6: Study 302 Longitudinal Change from Baseline for Clinical Endpoints in High-Dose Aducanumab Treatment Arm through Week 134





Created by reviewer from Tables 31-34 in ISE Appendix G1

* For LTE period, $p < 0.05$ compared with subjects assigned placebo in the placebo-controlled period and high dose in the LTE (Placebo-High Dose) (nominal)

Note: Solid lines represent the placebo-controlled period. Dotted lines represent the LTE

Additional Analyses Conducted on the Individual Trial

Correlation Analysis

Prespecified correlation analyses of individual CDR-SB and brain A β 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 account for potential lag between reduction of brain A β 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.

Reviewer Comment: It has been recognized that brain A β burden is not well correlated with disease progression and there is not an a priori expectation of precisely how reduction in A β burden would relate to changes on clinical scales. It is not even clear if the key metric is a relative reduction in SUVR or an absolute reduction below a certain level. The correlation presented by the applicant is a snapshot of Week 78 data and does not adequately account for the dynamic nature of A β reduction or the potential for downstream effects, or delays between reduction in A β and changes in CDR-SB. The correlation analyses were performed in a subgroup of the overall population (~30-35%) and do not account for other baseline factors, including comorbidities and mixed pathologies, which may affect the relationship. Furthermore, the 25th

to 75th percentiles of the change from baseline of CDR-SB at Week 78 in the overall population are 0 and 2.5, respectively, making it difficult to resolve relationships over this narrow range, especially in small subgroups with limited range of change in SUVR. For these reasons, it is not surprising that despite a treatment effect, there is not a tight correlation between reduction in brain A β plaque levels and CDR-SB at the individual level. Notably, an exposure-response model which considers individual dosing and the time course of SUVR was able to detect a relationship between SUVR and CDR-SB.

Some Advisory Committee members were persuaded by analyses in the statistical review and presentation which showed a univariate analysis using data only from the high-dose treatment arm to suggest a lack of a relationship between SUVR and CDR-SB. Pooling data across dose arms, however, is more appropriate to provide an adequate range of SUVR. Furthermore, when individual data from one dose level is used to quantify the relationship between two endpoints, it is challenging to correctly adjust the imbalances of multiple confounders due to potential nonlinear and complex relationships. Patients with different levels of SUVR reduction within the same high-dose arm in Study 302 had an imbalanced distribution of multiple prespecified covariates. 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 is more appropriate to investigate the relationship between change in SUVR and change in clinical endpoints. The results of this analysis are presented in Section 7.1.2 and reveal a clear positive relationship.

Influence of Placebo Progression in Post-Protocol Version 4 (PV4) Population

Appendix II of the Advisory Committee Briefing Document commented on the “dramatic worsening of placebo Post-PV4 relative to Pre-PV4” and concluded that, “the success could be explained by a higher placebo progression after the implementation of protocol amendment 4 while the study was ongoing.” This argument, illustrated in Figure 5 of Appendix II of the Advisory Committee Briefing Document, and presented on Slide 10 of the FDA statistics presentation was accepted by the Advisory Committee and provided as justification by some committee members for concluding that Study 302 does not support the effectiveness of aducanumab. Because some members of the Advisory Committee found this explanation persuasive, it is important to point out several inaccuracies in the analysis. First, the figure presented in Appendix II of the Advisory Committee Briefing Document was not created using the final dataset submitted in the BLA. It used a working version of the data that had not yet undergone cleaning. Second, there is a typo on slide 10 of the FDA statistics presentation (the numbers 1.37 and 1.25 were transposed). Correction of these two factors eliminate the basis of the argument. Despite updating the analysis with the final dataset, the statistical review reached the same conclusion regarding placebo worsening.

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 and appropriate 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 the Pre-PV4 population and -0.38 for the Post-PV4 population. 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. Additional rationale for why placebo differences, more generally, do not meaningfully explain differences in the results of Studies 301 and 302 is provided in Section 7.1.2.

Reviewer Comment: The similarity of the treatment effect estimates in the Pre-PV4 and Post-PV4 populations may lead some to question the importance of dosing. In other words, if dosing is important, why is there not a substantially larger treatment effect size in the Post-PV4 population? The analyses presented above and in the statistical review are based on the ITT dataset. Due to the early study termination, many patients in the Post-PV4 ITT population were missing Week 50 or Week 78 data. The purported benefit of the dose increase of PV4 is due to the sustained exposure to the 10 mg/kg doses, but due to the termination of the studies, most patients in the Post-PV4 ITT population did not even have the opportunity for this sustained exposure. Inferences about dosing are more appropriately drawn from the OTC dataset, which is limited to patients who had the opportunity to receive all doses. These analyses are presented in Section 7.1.7.

Although the data in the aducanumab program demonstrate the importance of dosing overall, PV4 is simply not the appropriate prism through which to view the entire set of results of Studies 301 and 302. PV4 is not the sole reason for the success of Study 302 and timing of the implementation of the amendment does not explain the different results for the primary endpoint in the two studies.

6.2. Study 301 (221AD301): A Phase 3 Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease

6.2.1. Study Design

Study 301 was identically designed to Study 302. At the time of the futility analysis on December 26, 2018, 57% of patients from Study 301 had the opportunity to complete the Week 78 visit. Please refer to Section 6.1.1 for study design elements as these are applicable to Study 301.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was performed in accordance with 21 CFR parts 50, 54, 56 and 312 Subpart D, ICH Guideline on GCP (E6) and the ethical principles outlined in the Declaration of Helsinki.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators.

Patient Disposition

A total of 6173 patients were screened for the study and 1653 patients were randomized. The most common reasons reported for screening failure were having a CDR global score, MMSE score, or RBANS score outside the allowed range (67%) or not having a positive amyloid PET scan (12%). There were 6 patients who were randomized but did not receive study treatment, with the most common reason being that the patient should have been classified as a screening failure. There were also 5 patients randomized to placebo who received aducanumab treatment in the visit before the start of the LTE. Patient disposition in the study is summarized in Table 12. The most common reason noted for treatment or study discontinuation is “other.” This category includes patients who terminated the study due to the administrative decision to terminate aducanumab studies based on the interim futility analysis (placebo, 166 (30.5%); low dose, 160 (29.3%); high dose, 190 (34.2%)).

Table 12: Study 301 Patient Disposition

Disposition	Study 301		
No. of patients screened	6173		
No. of patients not randomized	4520		
	Aducanumab Low Dose N=547 n (%)	Aducanumab High Dose N=555 n (%)	Placebo N=545 n (%)
Patients randomized	549	556	548
ITT population	547 (100%)	555 (100%)	545 (100%)
Per-protocol population	398 (72.8%)	378 (68.1%)	435 (79.8%)
OTC population	370 (67.6%)	345 (62.2%)	369 (67.7%)
¹⁸ F-florbetapir amyloid PET	198 (36.2%)	183 (33.0%)	204 (37.4%)
Discontinued treatment	221 (40.4%)	280 (50.5%)	219 (40.2%)
Adverse event	45 (8.2%)	63 (11.4%)	28 (5.1%)
Consent withdrawn	9 (1.6%)	16 (2.9%)	14 (2.6%)

Other reasons	167 (30.6%)	201 (36.2%)	177 (32.5%)
Discontinued study	222 (40.6%)	267 (48.1%)	220 (40.4%)
Adverse event	25 (4.6%)	28 (5.0%)	16 (2.9%)
Consent withdrawn	16 (2.9%)	27 (4.9%)	26 (4.8%)
Other reasons	181 (33.1%)	212 (39.2%)	178 (32.7%)

Created by the reviewer using ie.xpt and Tables 13, 20 and 50 in Study 301 CSR.

Reviewer Comment: Patient disposition in Study 301 was largely similar to that in Study 302. Relatively fewer patients in Study 301 discontinued the study because it began before Study 302 and therefore more patients had the opportunity to complete the study at the time of study termination.

Protocol Violations/Deviations

Most patients (60.8%) had at least one major protocol deviation during the placebo-controlled period, but the incidence was similar across treatment groups. The most common categories of major protocol deviations were regarding informed consent (25.9%), study procedures (24.4%), and investigational product compliance (18.0%). These deviations are not expected to affect interpretation of the overall results. During the combined screening and placebo-controlled periods, 83 patients (35 placebo, 21 low dose, and 27 high dose) had a major protocol deviation for eligibility or entry criteria. There were 3 patients who did not meet the CDR global score criterion, 5 who did not meet the MMSE criterion and 13 who did not meet the RBANS criterion. These numbers are small compared to the overall population and balanced across the treatment arms and are therefore not expected to affect the efficacy analyses. A total of 10.9% of patients received disallowed concomitant medications during the placebo-controlled period, but many of these were anti-coagulants or corticosteroids, which were disallowed for safety considerations and were not anticipated to have an impact on the effectiveness of aducanumab. Also, seven patients were randomized to a carrier status that was discordant with laboratory assay results. There were also 5 patients randomized to placebo who received aducanumab treatment in the visit before the start of the LTE. Single dose administration of aducanumab at the end of the study would not have an impact on the efficacy results.

Tables of Demographic and Disease Characteristics

Table 13 contains information regarding demographic characteristics for each treatment arm in the ITT population. 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. Overall, 46.3% of patients were enrolled in the United States.

Table 13: 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
Age Group				
≤ 64 years	130 (23.9%)	116 (21.2 %)	124 (22.3%)	370 (22.5%)
> 64 – <75 years	246 (45.1%)	264 (48.3%)	255 (45.9%)	765 (46.4%)
≥ 75 years	169 (31.0%)	167 (30.5%)	176 (31.7%)	512 (31.1%)
Race				
White	413 (75.8%)	412 (75.3%)	413 (74.4%)	1238 (75.2%)
Black or African American	5 (0.9%)	1 (0.2%)	2 (0.4%)	8 (0.5%)
Asian	55 (10.1%)	55 (10.1%)	65 (11.7%)	175 (10.6%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (0.2%)	0	1 (<0.1%)
Other	3 (0.6%)	4 (0.7%)	3 (0.5%)	10 (0.6%)
Ethnicity				
Hispanic or Latino	13 (2.4%)	11 (2.0%)	13 (2.3%)	37 (2.2%)
Not Hispanic or Latino	489 (89.7%)	492 (89.9%)	499 (89.9%)	1480 (89.9%)
Not Reported ¹	43 (7.9%)	44 (8.0%)	43 (7.7%)	130 (7.9%)
Region				
United States	251 (46.1%)	260 (47.5%)	252 (45.4%)	763 (46.3%)
Rest of the World				
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 and Table 49 in Study 301 CSR

¹ Data on race and/or ethnicity were not collected because of local regulations.

Reviewer Comment: Any differences in the demographics between Studies 301 and 302 were minor and do not explain differences in study outcomes. Study 301 enrolled more patients in the United States (46.3%) than Study 302 (39.8%). The most evident difference in geographic enrollment was that only Study 302 included patients from Poland (12% of the total study

population at 14 sites). The estimated treatment effect for patients in Poland favored placebo over aducanumab and thus this difference does not contribute to the discordant results for the high dose in the two studies.

Other Baseline Characteristics (disease characteristics and important concomitant drugs)

Table 14 contains a summary of baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. The disease characteristics are well-balanced across treatment groups and reflect a population of patients who are early in the course of Alzheimer's disease. By design, the overall population consisted of 80% of patients with MCI due to Alzheimer's disease and 20% with mild Alzheimer's disease dementia. The percentage of the population who were ApoE ε4 carriers is consistent with previous reports. Most patients were receiving concomitant medications for Alzheimer's disease (56.4%). Additionally, 13% of patients received any Alzheimer's disease medication and stopped prior to entering the study.

Table 14: Study 301 Baseline Disease Characteristics (ITT Population)

Disease Characteristics	Placebo (N=545) n (%)	Treatment Group		
		Aducanumab Low Dose (N=547) n (%)	Aducanumab High Dose (N=555) n (%)	Total (N=1647) n (%)
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%)
Number of Years of Formal Education				
Mean years (SD)	14.7 (3.7)	14.6 (3.8)	14.6 (3.7)	14.6 (3.7)
Median (years)	16.0	15.0	15.0	15.0
Min, Max (years)	4, 26	3, 27	4, 27	3, 27
Number of Years Since Diagnosis of AD				
Mean years (SD)	1.1 (1.2)	1.3 (1.6)	1.2 (1.4)	1.2 (1.4)
Median (years)	0.7	0.7	0.8	0.7
Min, Max (years)	0.0, 11.9	0.0, 21.6	0.0, 17.6	0.0, 21.6
Concomitant AD medication				
Any AD medication at	299 (54.9%)	317 (58.0%)	313 (56.4%)	929 (56.4%)

baseline				
Only cholinesterase inhibitors	242 (44.4%)	257 (47.0%)	264 (47.6%)	763 (46.3%)
Only memantine	16 (2.9%)	15 (2.7%)	13 (2.3%)	44 (2.7%)
Both cholinesterase inhibitors and memantine	41 (7.5%)	45 (8.2%)	36 (6.5%)	122 (7.4%)
Baseline CDR-SB				
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				
<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%)
Baseline ADAS-Cog 13				
Mean (SD)	22.5 (6.6)	22.5 (6.3)	22.4 (6.5)	22.5 (6.5)
Median	22.2	22.3	22.0	22.0
Min, Max	4.7, 48.0	8.0, 41.7	6.0, 43.3	4.7, 48.0
Baseline ADCS-ADL-MCI				
Mean (SD)	43.0 (5.6)	42.9 (5.7)	42.9 (5.7)	42.9 (5.7)
Median	44.0	44.0	44.0	44.0
Min, Max	22, 53	21, 53	12, 53	12, 53

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

Reviewer Comment: Any differences in the baseline disease characteristics between Studies 301 and 302 were minor and not expected to explain differences in study outcomes.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The mean percentage of study treatment received was 96.4%. Although compliance with study treatment was high, protocol-defined dose modification for ARIA, changes to the protocol, and the termination of the study meant that some patients received fewer target doses. For example, only 6.1% of ApoE ε4 carriers received all 14 doses of aducanumab 10 mg/kg compared to 33.5% of ApoE ε4 non-carriers. Similarly, 80.2% of ApoE ε4 carriers received any 10 mg/kg doses, compared to 88.6% of ApoE ε4 non-carriers. More patients in the lower dose treatment arm received the maximum dose level (91.7% for ApoE ε4 carriers receiving 6 mg/kg and 99.5% for ApoE ε4 non-carriers receiving 3 mg/kg).

Overall, 11.7% of patients made changes to their concomitant Alzheimer's disease medications at some point during the study. The number of patients who made changes was similar across treatment arms (placebo, 68 (12.5%); low dose, 66 (12.1%); high dose, 58 (10.5%)).

Reviewer Comment: Because of the timing of the studies, the implementation of Protocol Version 3 and 4 occurred earlier in Study 302 than Study 301. Therefore, patients in the high-dose treatment arm in Study 302 were more likely to receive a full treatment course of 10 mg/kg.

Efficacy Results – 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 numeric difference of -12% in favor of the aducanumab low-dose treatment arm compared to placebo was observed (Table 15). Study 301 was a negative study, so sensitivity analyses were not performed, and subgroup analyses are not reported here.

Table 15: Study 301 Primary Endpoint Analysis

	Placebo (N=545)	Aducanumab Low Dose (N=547)	Aducanumab High Dose (N=555)
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	1.56	1.38	1.59
Standard error	0.108	0.108	0.111
95% CI	(1.344, 1.768)	(1.164, 1.590)	(1.370, 1.805)
Difference from placebo		-0.18	0.03
95% CI for difference		(-0.469, 0.110)	(-0.262, 0.326)
% difference vs. placebo		-12%	2%
p-value (compared with placebo)		0.2250	0.8330

Source: Table 22 from Study 301 CSR

Reviewer Comment: The placebo decline in Study 301 (1.56) was smaller than in Study 302 (1.74). The treatment differences for the low dose, although not statistically significant, were remarkably consistent in the two studies and suggest the outcomes between the two studies are only partially discordant, namely for the high-dose treatment arms.

Table 16 displays the results of the supplementary analyses of the primary endpoint in different populations as described in Section 6.1.1. Results in the uncensored population with the most data provide the most favorable results for aducanumab but are still negative.

Table 16: Study 301 Primary Endpoint Analysis (Dataset Sensitivity)

ITT Population during Double-Blind Period				Uncensored ITT Population			OTC Population		
Difference vs. Placebo at Week 78 (%) p-value				Difference vs. Placebo at Week 78 (%) p-value			Difference vs. Placebo at Week 78 (%) p-value		
	PBO Decline (N=545)	Low Dose (N=547)	High Dose (N=555)	PBO Decline (N=545)	Low Dose (N=547)	High Dose (N=555)	PBO Decline (N=369)	Low Dose (N=370)	High Dose (N=345)
CDR-SB	n=369	n=362	n=335	n=414	n=421	n=398	n=332	n=331	n=293
	1.57	-0.17	-0.02	1.60	-0.20	-0.08	1.46	-0.12	0.08
		-11%	-1%		-13%	-5%		-8%	5%
		0.2351	0.8719		0.1530	0.5851		0.4527	0.6326

Source: Tables 74, 76 and 78 in Study 301 CSR

Data Quality and Integrity

There were no major data quality issues identified during the review of Study 301.

Efficacy Results – Secondary endpoints

Although Study 301 was a negative study, a summary of the analysis results for the secondary endpoints is provided in Table 17 for comparison to results from Study 302.

Table 17: Study 301 Secondary Endpoint Analysis

	Placebo (N=545)	Aducanumab Low Dose (N=547)	Aducanumab High Dose (N=555)
Baseline MMSE			
n	545	547	555
Mean	26.4	26.4	26.4
Change from Baseline in MMSE at Week 78			
n	332	334	297
Adjusted mean	-3.5	-3.3	-3.6
Standard error	0.21	0.21	0.21
95% CI	(-3.94, -3.13)	(-3.75, -2.93)	(-4.02, -3.19)
Difference from placebo		0.2	-0.1
95% CI for difference		(-0.35, 0.74)	(-0.62, 0.49)
% difference vs. placebo		-6%	3%
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	5.14	4.56	4.55
Standard error	0.38	0.38	0.39
95% CI	(4.40, 5.88)	(3.82, 5.30)	(3.79, 5.31)
Difference from placebo		-0.58	-0.59
95% CI for difference		(-1.58, 0.42)	(-1.61, 0.43)
% difference vs. placebo		-11%	-11%
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	-3.8	-3.1	-3.1
Standard error	0.35	0.35	0.35
95% CI	(-4.48, -3.12)	(-3.76, -2.39)	(-3.81, -2.42)
Difference from placebo		0.7	0.7
95% CI for difference		(-0.19, 1.64)	(-0.25, 1.61)
% difference vs. placebo		-18%	-18%
p-value (compared with placebo)		0.1225	0.1506

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

Reviewer Comment: Results for the secondary endpoints for the low-dose treatment arms in Studies 301 and 302 are remarkably similar and suggest a numerical difference in favor of aducanumab, further suggesting that the outcomes between the two studies are only partially discordant, namely for the high-dose treatment arms. The results for ADAS-Cog 13 and ADCS-ADL-MCI were numerically favorable in the high-dose arm and directionally inconsistent with the results for the primary endpoint.

Efficacy Results – Tertiary 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 $p=0.0460$) for aducanumab low dose.

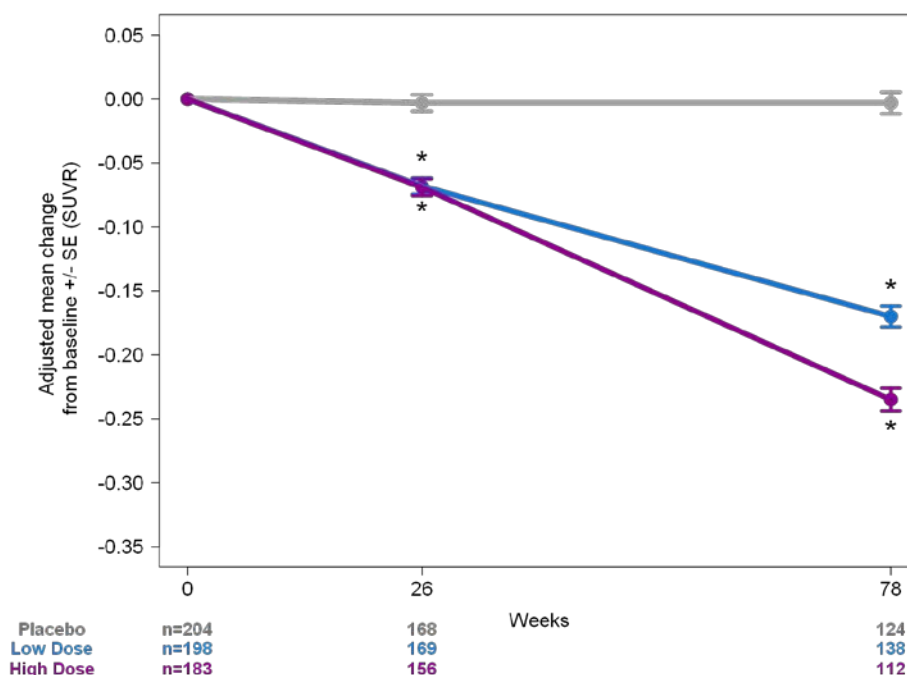
Efficacy Results – Pharmacodynamic endpoints

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 $\epsilon 4$ status, and baseline age. The adjusted mean change from baseline relative to placebo 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 due to

similar dosing during titration. At Week 78, the adjusted mean change from placebo was -0.167 ($p < 0.0001$) for the low dose and -0.232 ($p < 0.0001$) for the high dose, indicating time- and dose-dependent relationships (Figure 7). Consistent relationships were found for other brain regions and when using additional reference regions. No correlation was observed between change from baseline CDR-SB at Week 78 and change from baseline SUVR at Week 78.

Adjusted mean changes from baseline in brain amyloid for all subgroups of interest demonstrated statistically significant reduction in SUVR relative to placebo with larger reductions for the high-dose treatment arm compared to the low-dose treatment arm. At Week 78, the difference (95% CI) from placebo in the high-dose treatment arm for ApoE $\epsilon 4$ carriers and ApoE $\epsilon 4$ non-carriers was -0.231 (-0.2569, -0.2047) and -0.234 (-0.2824, -0.1849), respectively. Reductions in both groups were lower in magnitude than the corresponding reductions observed in Study 302. The magnitude of reduction was also similar in the two groups, despite the expectation that ApoE $\epsilon 4$ non-carriers would have a larger reduction due to the anticipated higher aducanumab exposure. An association between baseline SUVR and magnitude of reduction in SUVR was observed in the high-dose treatment arm at Week 78 with a difference from placebo of -0.127 (-0.1643, -0.0898) in the lowest quartile of baseline SUVR and -0.335 (-0.3945, -0.2765) in the highest quartile of baseline SUVR.

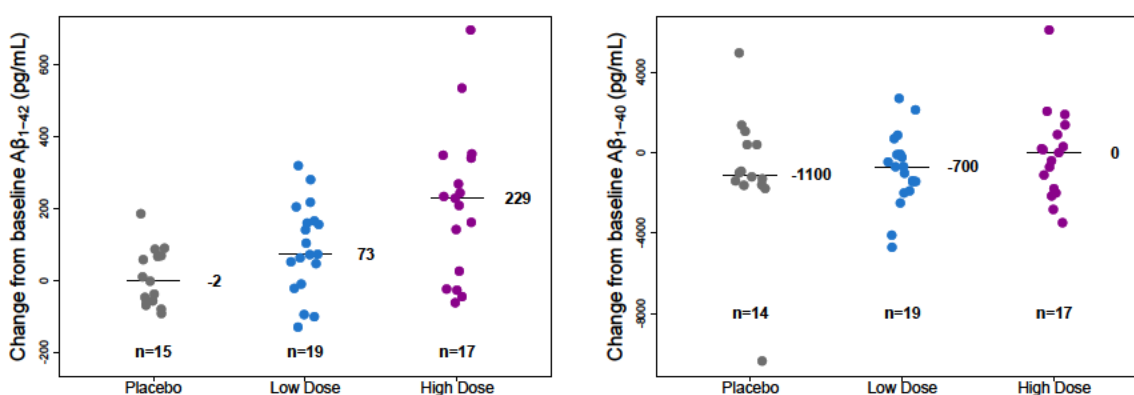
Figure 7: Study 301 Change from Baseline in A β PET Composite SUVR



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

There was an apparent dose-related increase in CSF $A\beta_{1-42}$ levels, but some overlap between groups (Figure 8). The high-dose treatment arm exhibited no median change in $A\beta_{1-40}$ compared to decreases in the placebo and low-dose arms, but there was considerable overlap between groups.

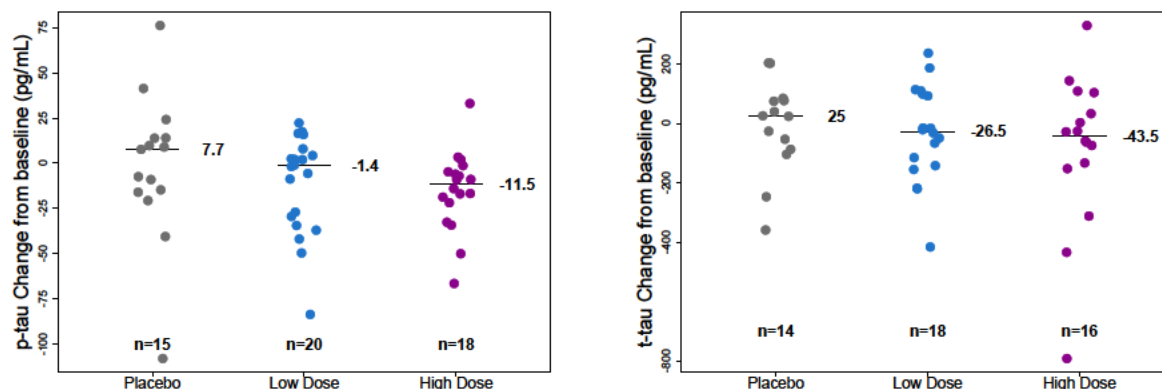
Figure 8: Study 301 Change from Baseline in CSF $A\beta_{1-42}$ (left) and $A\beta_{1-40}$ (right) at Week 78



Created by reviewer using adbk.xpt

Change from baseline in markers of downstream Alzheimer's Tau pathophysiology and neurodegeneration are illustrated in Figure 9. Dose-dependent trends were consistent with those observed in Study 302, but with smaller decreases following aducanumab treatment. There were no differences between either treatment group and placebo for change from baseline at Week 78 in MRI volume measures for whole brain, whole cortex and hippocampus. There was an increase in change from baseline to Week 78 lateral ventricle volume in both dose groups.

Figure 9: Study 301 Change from Baseline in CSF p-Tau (left) and t-Tau (right) at Week 78

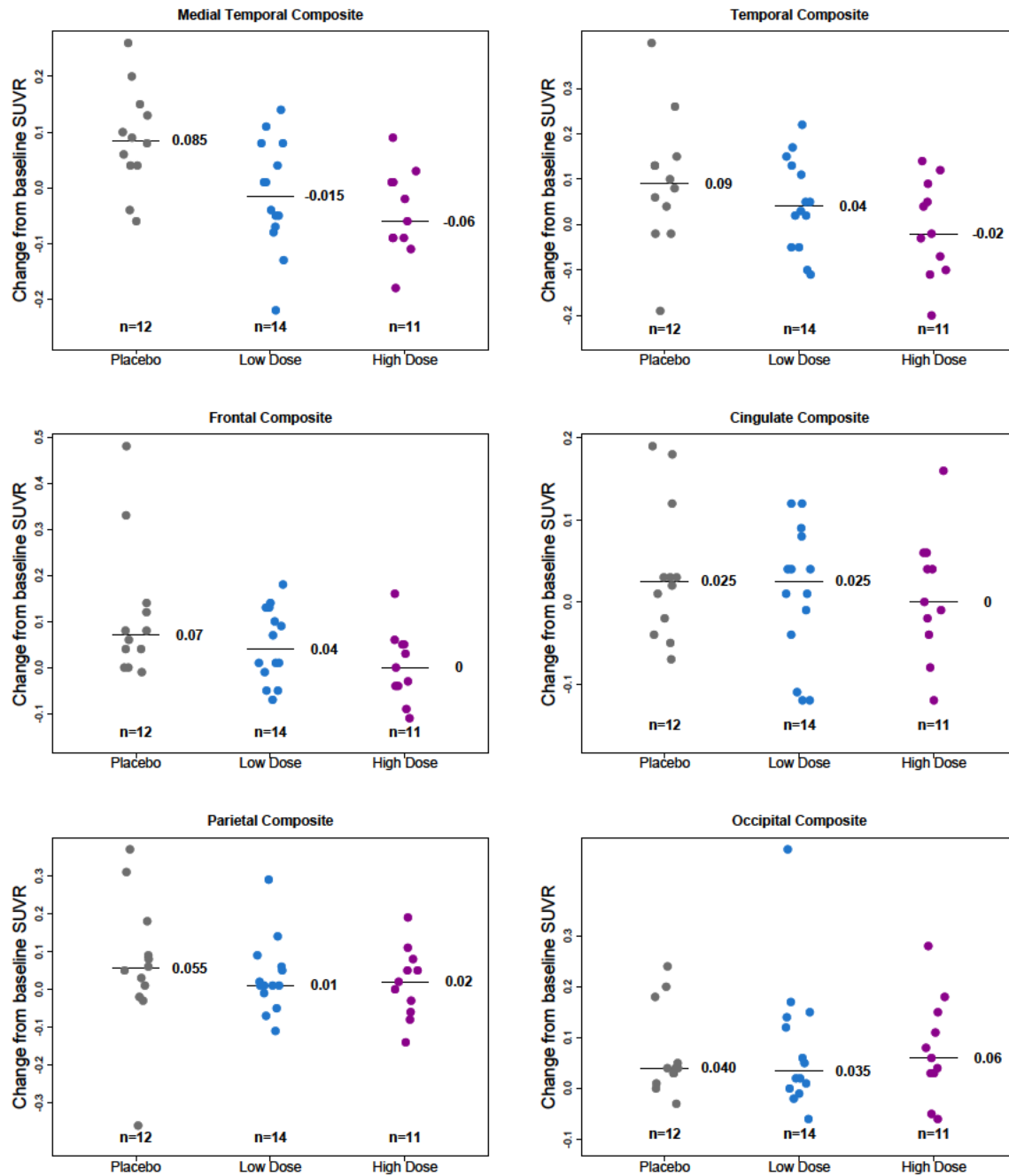


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Reviewer Comment: The change from baseline in SUVR at Week 78 was similar for the low-dose arms in Studies 301 and 302, but lower for the high dose in Study 301 (-0.232) than in Study 302 (-0.278). This is consistent with the expectation that patients in Study 301, especially those enrolled early in the studies as in the PET subpopulation, achieved lower aducanumab exposure than patients in Study 302. Similar trends are observed for CSF biomarkers, but it is more difficult to draw conclusions because of the limited sample size and considerable variability.

A pooled analysis of Studies 301 and 302 was performed for tau PET measurements because the number of patients with tau PET imaging was small (31 in Study 301 and 6 in Study 302). Measurement of tau PET was introduced relatively late in the studies and therefore this subpopulation includes more patients in the high-dose arms who had the opportunity to receive the 10 mg/kg dose. Post-baseline samples were collected earlier in some patients (mean visit time of 13.6 months) before they received the full course of aducanumab treatment. For example, the mean cumulative dose for the pooled high-dose group for tau PET data was 86 mg/kg compared to 122 mg/kg for the high dose group of patients in Study 301 who contributed p-Tau data. The observations for different brain regions are illustrated in Figure 10. Dose-dependent reductions in brain tau SUVR were observed in the medial temporal, temporal, and frontal composite regions with trends favoring active treatment for the cingulate and parietal composite brain regions.

Figure 10: Study 301 and Study 302 Pooled Analyses: Change from Baseline in Tau PET



Created by reviewer using adtau.xpt

Durability of Response

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.

6.3. Study 103 (221AD103): A Randomized, Double-Blinded, Placebo-Controlled Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB037 in Subjects with Prodromal or Mild Alzheimer's Disease

6.3.1. Study Design

Overview and Objective

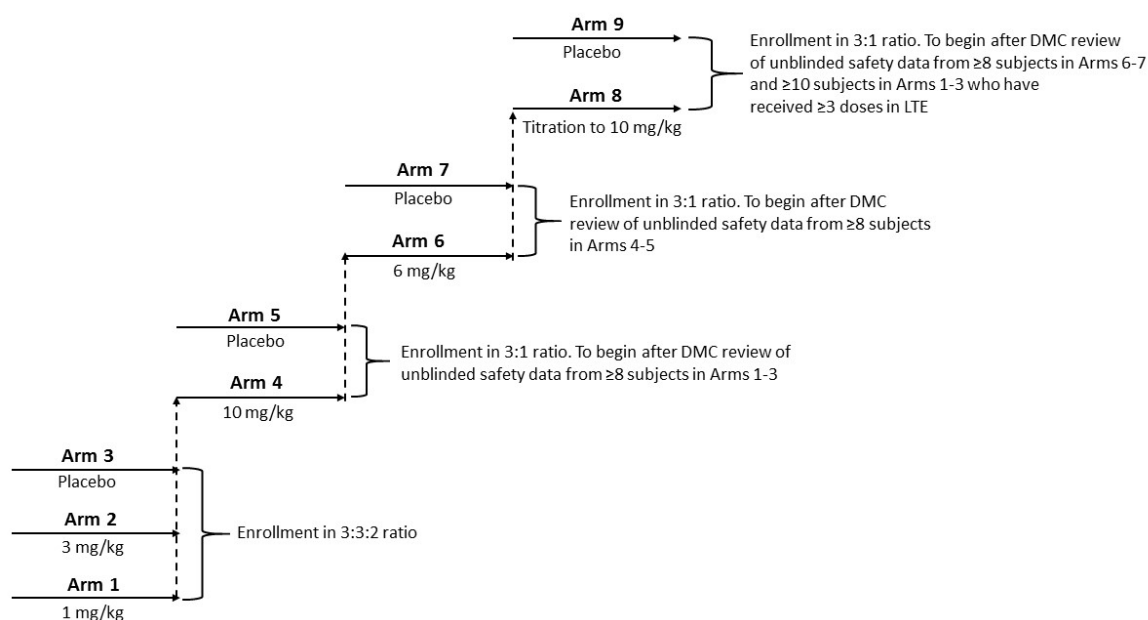
Study 103 was the first multiple-dose study of aducanumab in patients with Alzheimer's disease. The primary objective of the study was to evaluate the safety and tolerability of multiple doses of aducanumab in subjects with prodromal or mild Alzheimer's disease dementia. Although described as a safety and tolerability study, Study 103 was a randomized, double-blind, multicenter study which incorporated many of the elements of Study 301 and Study 302, including efficacy and pharmacodynamic assessments in a similar patient population.

Trial Design

Study Design

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 study was conducted in 27 sites in the United States. A schematic of the staggered, parallel-group design of the study is illustrated in Figure 11. Initially, Arms 1-3 were enrolled in parallel. Upon review of ongoing unblinded safety data in a subset of patients enrolled in Arms 1-3, Arms 4-5 were enrolled in parallel, then Arms 6-7, and then Arms 8-9. Patients were randomized into each treatment group within Arms 1-3, Arms 4-5, Arms 6-7 and Arms 8-9, with each cohort including 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.

Figure 11: Study 103 Schematic



Created by reviewer, modified from Figure 2 in Study 103 protocol

Note: Safety data from the single ascending dose study (Study 101) was also considered for dose escalation.

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.

Diagnostic Criteria

Patients with mild Alzheimer's disease fulfilled the clinical criteria as defined by the 2011 NIA-AA framework (McKhann et al. 2011). The clinical criteria for prodromal patients were consistent with those described for MCI due to Alzheimer's disease in the 2011 NIA-AA framework. Patients were also required to have evidence of brain Aβ pathology by visual read of a PET scan.

Key Inclusion Criteria

1. Male or female patients age 50 to ≤90 years
2. Positive amyloid PET scan
3. Must consent to ApoE genotyping
4. Must meet the following core clinical criteria:
 - Prodromal Alzheimer's disease

- o MMSE ≥ 24
 - o A spontaneous memory complaint
 - o Free recall score ≤ 27 on the Free and Cued Selective Reminding Test (FCSRT)
 - o CDR global score of 0.5
 - o Absence of significant levels of impairment in other cognitive domains
 - o Essentially preserved activities of daily living and an absence of dementia
- Mild Alzheimer's disease
 - o MMSE between 20-26, inclusive
 - o CDR global score of 0.5 or 1.0
 - o Meet NIA-AA core clinical criteria for probable Alzheimer's disease
- 5. Has one informant/care partner able to provide accurate information about the subject's cognitive and functional abilities and should be available for the duration of the study

Key Exclusion Criteria

1. Any medical or neurological condition (other than Alzheimer's disease) that may be a contributing cause of the subject's cognitive impairment
2. Any medication that may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing
3. Clinically significant unstable psychiatric illness within 6 months prior to screening
4. Brain MRI performed at screening that shows evidence of any of the following: 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
5. Contraindications to having a brain MRI or PET scan
6. History of bleeding disorder
7. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤ 325 mg daily)
8. Uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic heart failure, or clinically significant conduction abnormalities
9. Participation in any active immunotherapy study targeting A β , any passive immunotherapy study targeting A β within 48 weeks of screening or any study with purported disease-modifying effect in Alzheimer's disease within 24 weeks of screening

Reviewer Comment: The population enrolled in Studies 301 and 302 is essentially represented within Study 103. Study 103 also includes patients at a later stage of the disease continuum. Specifically, the entry criteria for Study 103 allows for enrollment of patients with an MMSE as

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low as 20 (compared to 24 in Studies 301 and 302) and a CDR global score of 0.5 or 1 (compared to only 0.5 in Studies 301 and 302).

Dose Selection

Dosing was originally based on results from nonclinical studies, the PKPD relationship of mouse chimeric aducanumab on brain amyloid in mice, safety and PK data from the single ascending dose study in subjects with mild to moderate Alzheimer's disease, and the projected PKPD relationship in humans. The intended doses were 1 mg/kg, 3 mg/kg, up to 10 mg/kg, and up to 30 mg/kg. Based on review of ongoing safety data and IDMC recommendations, the actual 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.

Study Treatments

IV infusions of aducanumab or placebo were administered approximately every 4 weeks over 52 weeks for a total of 14 doses. Fixed doses were administered in Arms 1-7 (Figure 11). Titration in Arm 8 consisted of 1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, 6 mg/kg for the next 5 doses and 10 mg/kg thereafter (3 doses) for a 44-week titration period.

Reviewer Comment: 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).

Assignment to Treatment

IxRS was used to manage randomization and treatment assignment. The randomization ratios for different arms are included in Figure 11. Randomization was stratified by ApoE ε4 status (carrier or non-carrier) except for Arms 8-9 which included only ApoE ε4 carriers. The ratio of ApoE ε4 carriers was to be no more than 2:1 and no less than 1:2.

Blinding

An unblinded pharmacist managed all aspects of study treatment receipt, dispensing, and preparation. All other study site staff and patients were blinded to treatment assignment during the placebo-controlled period. The rater who conducted the CDR for a patient was not allowed to complete any other rating scales for the same patient. For the LTE period, patients

were to remain blinded to their treatment assignment. Investigators were blinded to whether the patient received a titrated dose of study treatment.

The Biogen study team was blinded until the interim analysis of the Week 26 data. Information from Arms 1-5 was unblinded after all patients in these arms completed evaluation at the Week 26 visit, information from Arms 6-7 was unblinded after all patients in these arms completed evaluation at the Week 26 visit, and information from Arms 8-9 was unblinded after all patients in these arms completed evaluation at the Week 26 visit.

Reviewer Comment: There was no central review of ratings, but the rater who conducted CDR was not able to complete other rating assessments.

Dose Modification/Dose Discontinuation

Dose modification criteria were established to account for the expected occurrence of ARIA-E or ARIA-H. 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. Dosing guidelines evolved during the study and are summarized in Table 18, Table 19, and Table 20 for ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis, respectively. The investigator was allowed to choose a more conservative course of action than specified. Patients who developed ARIA-H coincident with ARIA-E were to follow the more restrictive guideline.

Table 18: Dose Modification/Discontinuation Rules for ARIA-E by Protocol Version (Study 103)

Clinical Symptom Severity		MRI Severity	Protocol Version ¹			
			Version 2 and 3	Version 4-8	Version 9-11	
Asymptomatic		Mild	Suspend dosing and restart at next lower dose	Continue dosing at same dose and schedule		
		Moderate or Severe		Suspend dosing and restart at next lower dose	Suspend dosing and restart at same dose and titrate to target	
Symptomatic	Mild	Any	Permanently discontinue			
	Moderate					
	Severe/Serious “other medically important event” ²			Permanently discontinue		

	Serious, except “other than medically important event”				Permanently discontinue

Created by reviewer, modified from Table 11 in Study 103 CSR

¹ Participant enrollment began under Protocol Version 2

² “Other medically important events” include SAEs that were not life-threatening, did not require inpatient hospitalization or prolongation of existing hospitalization, and did not result in significant or permanent disability

Note: Dosing was restarted when ARIA-E and/or clinical symptoms resolved

Table 19: Dose Modification/Discontinuation Rules for ARIA-H (Microhemorrhage) by Protocol Version (Study 103)

Clinical Symptom Severity		MRI Severity	Protocol Version ¹		
			Version 2 and 3	Version 4-8	Version 9-11
Asymptomatic		Mild	Continue dosing at same dose and schedule		
		Moderate	Permanently Discontinue	Permanently Discontinue	Suspend dosing and restart at the same dose
		Severe			Permanently discontinue
Symptomatic	Mild	Mild		Suspend dosing and restart at next lower dose	Suspend dosing and restart at the same dose
		Moderate		Permanently Discontinue	Permanently discontinue
		Severe			Suspend dosing and restart at the same dose
	Moderate/Severe	Mild or Moderate			Permanently discontinue
		Severe			Suspend dosing and restart at the same dose
	Serious “other medically important event” ²	Mild or Moderate			Permanently discontinue
		Severe			Suspend dosing and restart at the same dose
	Serious, except other than medically important event”	Any			Permanently discontinue

Created by reviewer, modified from Table 12 in Study 103 CSR

¹ Participant enrollment began under Protocol Version 2

² “Other medically important events” include SAEs that were not life-threatening, did not require inpatient hospitalization or prolongation of existing hospitalization, and did not result in significant or permanent disability

Note: Dosing was restarted when ARIA-E and/or clinical symptoms resolved

Note: As of Protocol Version 9, mild on MRI = 1 to 4 cumulative microhemorrhages; moderate on MRI = 5 to 9 cumulative microhemorrhages; severe on MRI ≥10 cumulative microhemorrhages

Table 20: Dose Modification/Discontinuation Rules for ARIA-H (Superficial Siderosis) by Protocol Version (Study 103)

Clinical Symptom Severity		MRI Severity	Protocol Version ¹				
			Version 2-4	Version 5-8	Version 9-11		
Asymptomatic		Mild	Permanently discontinue	Suspend dosing and restart at the next lower dose	Continue dosing at same dose and schedule		
		Moderate		Permanently discontinue	Suspend dosing and restart at same dose		
					Severe	Permanently discontinue	
Symptomatic	Mild	Mild		Suspend dosing and restart at the next lower dose	Suspend dosing and restart at same dose		
		Moderate		Permanently discontinue	Permanently discontinue		
		Severe			Suspend dosing and restart at same dose		
	Moderate/Severe	Mild or Moderate			Permanently discontinue		
		Severe			Suspend dosing and restart at same dose		
	Serious “other medically important event” ²	Mild or Moderate			Permanently discontinue		
		Severe			Suspend dosing and restart at same dose		
	Serious, except “other than medically important event”	Any			Permanently discontinue		

Created by reviewer, modified from Table 13 in Study 103 CSR

¹ Participant enrollment began under Protocol Version 2

² “Other medically important events” include SAEs that were not life-threatening, did not require inpatient hospitalization or prolongation of existing hospitalization, and did not result in significant or permanent disability

Note: Dosing was restarted when ARIA-E and/or clinical symptoms resolved

Note: As of Protocol Version 9, mild on MRI = 1 cumulative area of superficial siderosis; moderate on MRI = 2 cumulative areas of superficial siderosis; severe on MRI >2 superficial siderosis

Reviewer Comment: ARIA management was more conservative in Study 103 than Studies 301 and 302. Protocol Versions 4 through 8 of Study 103 were generally similar to Version 1 of Studies 301 and 302. ARIA management rules starting in Version 9 of the Study 103 protocol were essentially the same as Protocol Version 3 in Studies 301 and 302.

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Administrative Structure

An IDMC was formed to monitor the overall conduct of the study and was the same IDMC used for Studies 301 and 302. At each closed session of the IDMC meeting, unblinded data was reviewed and the IDMC made recommendations to continue, modify, or stop the study. The IDMC played a key role reviewing safety, tolerability, and PK data and recommending dose levels to be studied in subsequent arms.

A centralized imaging laboratory was selected to read and interpret PET and MRI scans. The central laboratory was to notify the PI and the applicant of ARIA-E and ARIA-H findings. For the purposes of study conduct, readings from the central reader prevailed over those from the local radiologist.

The applicant used a CRO (ePharmaSolutions) to provide monitoring of neurocognitive assessments and training and oversight to ensure rating consistency.

Procedures and Schedule

The schedule for key assessments is presented in Table 21. The screening period consisted of four visits within a 60-day period before administration of the first dose of study treatment. Eligible subjects reported to the study site to receive study treatment every 4 weeks for 52 weeks. The final study visit was 18 weeks after the final dose.

Table 21: Study 103 Schedule of Key Assessments

Assessment	Schedule
Eligibility Criteria	Screening V1
ApoE Genotyping	Screening V1
Neurological and Physical Examinations	Screening V1, Day 1, Weeks 4, 8, 12, 22, 40, 52, 70
Study Drug Infusion	Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52
Anti-Aducanumab Ab	Day 1, Weeks 4, 8, 12, 20, 28, 36, 44, 52, 70
Aducanumab Concentration (Arms 1-7)	Day 1, Weeks 4, 6, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 42, 44, 48, 52, 70
Aducanumab Concentration (Arms 8-9)	Day 1, Weeks 4, 6, 8, 12, 14, 16, 20, 22, 24, 28, 30, 32, 36, 40, 42, 44, 48, 50, 52, 70
CDR	Screening V1, Weeks 26, 54, 70
MMSE	Screening V1, Weeks 24, 52, 70
CSF Collection (optional)	Screening, Week 3, Week 51
Amyloid PET	Screening V3, Weeks 26, 54, 70

Created by reviewer, modified from Table 1 and Table 2 in Study 103 protocol
Note: There were four screening visits (V1, V2, V3 and V4) within 60 days of randomization

Concurrent Medications

Medications for treatment of Alzheimer's disease were allowed if patients were on a stable dose for 4 weeks prior to and during screening and were to stay on a stable dose while in the study. Medications for chronic diseases were also allowed if patients had been stable on the medication for 4 weeks prior to and during screening. Patients were instructed to continue the medications they were receiving at enrollment and avoid starting any new medications during the study. If a patient's medication was to be changed during the study, the applicant could have been consulted to determine whether the patient's study treatment should be suspended.

The following medications were not allowed:

- Medications with platelet anti-aggregant or anti-coagulant properties, except aspirin at doses ≤ 325 mg per day
- Immunosuppressive drugs including systemic corticosteroids
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis
- Any investigational drug

Subject Completion, Discontinuation, or Withdrawal

Patients who completed the 54-week treatment period were considered completers.

Patients who discontinued treatment could remain in the study and continue protocol-defined assessments. The main treatment-related reason for study discontinuation was the occurrence of ARIA as outlined in Table 18, Table 19, and Table 20. Other reasons for discontinuation include withdrawal of consent, medical emergency, and discretion of the investigator for medical reasons or noncompliance. The reason for discontinuation of study treatment was to be recorded in the patient's CRF.

Patients who withdrew from the study after receiving at least one dose of study treatment were encouraged to complete all scheduled safety evaluations or the end-of-treatment visit. Reasons for withdrawal of patients include withdrawal of consent, unwillingness or inability to comply with the protocol, and discretion of the investigator or applicant. The reason for withdrawal was to be recorded in the patient's CRF.

Patients who discontinued study treatment or withdrew from the placebo-controlled part of the study may have been replaced. Replacement subjects were to be randomized into a treatment group within the same group (i.e., Arms 1-3, Arms 4-5, Arms 6-7, or Arms 8-9) as the subject who withdrew.

Study Endpoints

The primary endpoint was safety and tolerability as measured by incidence of adverse events and monitored via several clinical assessments. The secondary endpoint, for which the study was powered, was the change from baseline in amyloid signal as measured by ¹⁸F-florbetapir PET at Week 26. The change from baseline in amyloid signal at Week 54 was considered an exploratory endpoint. Notably, change from baseline in CDR-SB and MMSE were also included as exploratory endpoints. For a description of CDR-SB and MMSE, please refer to Section 6.1.1. The rater who conducted the CDR for a given patient was not allowed to complete any other rating scales for that patient. Raters had to be certified before they could perform assessments and sites were encouraged to use the same rater to administer a given test across all visits. Central review of ratings was not performed.

Statistical Analysis Plan

The SAP was finalized on February 7, 2014, and modified on August 5, 2016, to specify the analysis plan for Arms 8-9 and the integrated plan for Arms 1-9 and on May 30, 2018, to specify details for the analyses of the LTE.

Interim Analyses

The SAP specified three interim analyses for the purpose of planning future studies of aducanumab. The three analyses were to be conducted: (1) after all subjects in Arms 1-5 had completed the Week 26 visit, (2) after all subjects in Arms 1-7 had completed the Week 26 visit, and (3) after all subjects in Arms 1-5 had completed the Week 54 visit. The Biogen study team were unblinded at these interim analyses. Data evaluated during these analyses included subject disposition, dosing information, safety data, change from baseline in amyloid signal and change from baseline in CDR and MMSE.

Definitions of Statistical Analysis Populations

The following relevant populations include:

- Pharmacodynamic (PD) Analysis Population – all subjects who were randomized, received at least one dose of study treatment, and have both baseline and at least one post-baseline PET SUVR assessment
- Efficacy Analysis Population – all subjects who were randomized, received at least one dose of study treatment, and have both baseline and at least one post-baseline CDR or MMSE assessment for at least one scheduled timepoint

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- Per-Protocol Population – all subjects who were randomized, received at least one dose of study treatment, had at least 80% study treatment compliance, and did not take any disallowed medications

Sample Size Considerations

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%.

Analysis Method for Clinicals Endpoints (CDR-SB and MMSE)

CDR-SB and MMSE were analyzed by analysis of covariance (ANCOVA) adjusting for their baseline values and ApoE ε4 carrier status at Week 24 and Week 52 separately. A MMRM model was used as a sensitivity analysis. Placebo data were pooled across Arms 3, 5, 7, and 9.

Missing Data

Values for missing data were not imputed for the ANCOVA analysis.

Adjustments for Multiplicity

This study was designed as a safety and tolerability study, so there were no adjustments for multiplicity.

Subgroup Analyses

Subgroup analyses for PET SUVR were performed for ApoE ε4 status (carrier or non-carrier), baseline clinical stage (prodromal or mild AD), and baseline composite SUVR ($\leq$ median or $>$ median). Subgroup analysis for clinical endpoints was not conducted.

Protocol Amendments

Enrollment began under Protocol Version 2, dated April 20, 2012. Many of the protocol amendments specified changes to dose levels to be studied or extended the study duration. Protocol Version 8, dated July 13, 2015, modified the titration regimen in Arm 8 from 1 mg/kg to 6 mg/kg to 1 mg/kg to 10 mg/kg. Table 18, Table 19, and Table 20 outline the changes to the protocol which modified dosing in relation to ARIA management.

6.3.2. Study Results

Compliance with Good Clinical Practices

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The applicant asserts that the study was performed in accordance with 21 CFR parts 50, 54, 56, and 312 Subpart D, ICH Guideline on GCP (E6) and the ethical principles outlined in the Declaration of Helsinki.

Financial Disclosure

The applicant has adequately disclosed financial interests or agreements with clinical investigators as outlined in the guidance for industry Financial Disclosures by Clinical Investigators.

Patient Disposition

A total of 197 patients were randomized into the study and 196 received at least one dose of study treatment. One patient was randomized to the aducanumab 3 mg/kg treatment arm but was withdrawn from the study before receiving study treatment because he met the exclusion criterion of uncontrolled hypertension. Patient disposition is summarized in Table 22. Treatment and study discontinuation was highest in the fixed-dose 10 mg/kg treatment arm due to discontinuation rules outlined in Table 18, Table 19, and Table 20. Of the 7 patients who discontinued the study from the 10 mg/kg fixed-dose treatment arm for “other reasons,” 6 were simply because they did not require a follow-up visit due to their treatment being discontinued for longer than 18 weeks.

Table 22: Study 103 Patient Disposition

Disposition	Study 103					
	Aducanumab 1 mg/kg N=31 n (%)	Aducanumab 3 mg/kg N=32 n (%)	Aducanumab 6 mg/kg N=30 n (%)	Aducanumab 10 mg/kg N=32 n (%)	Aducanumab Titration N=23 n (%)	Placebo N=48 n (%)
Patients randomized	31	33	30	32	23	48
PD analysis population	26 (84%)	29 (91%)	24 (80%)	28 (88%)	18 (78%)	42 (88%)
Efficacy analysis population	30 (97%)	32 (100%)	29 (97%)	30 (94%)	22 (96%)	46 (96%)
Discontinued treatment	7 (23%)	6 (19%)	5 (17%)	12 (38%)	4 (17%)	10 (21%)
Adverse event	3 (10%)	2 (6%)	3 (10%)	10 (31%)	2 (9%)	3 (6%)
Consent withdrawn	2 (6%)	1 (3%)	1 (3%)	1 (3%)	0	0
Other reasons	2 (6%)	3 (9%)	1 (3%)	1 (3%)	2 (9%)	7 (14%)
Discontinued study	8 (26%)	6 (19%)	4 (13%)	11 (34%)	3 (13%)	10 (21%)

Adverse event	3 (10%)	1 (3%)	0	3 (9%)	0	3 (6%)
Consent withdrawn	2 (6%)	1 (3%)	2 (7%)	1 (3%)	0	0
Other reasons	3 (10%)	4 (12%)	2 (7%)	7 (22%)	3 (13%)	7 (14%)

Source: Table 36 in Study 103 CSR

Protocol Violations/Deviations

Overall, 30% of patients had at least one major protocol deviation during the placebo-controlled period, but the incidence was similar across treatment arms. The most common categories of major protocol deviations were regarding study procedures criteria (15%) and informed consent (14%). These deviations are not expected to affect interpretation of the overall results. During the screening period there were 6 patients who did not meet the inclusion criteria for MMSE but were randomized. Two of these patients were in the placebo arm and none were in the fixed-dose 10 mg/kg arm. One patient randomized to placebo mistakenly received 2 doses of aducanumab 1 mg/kg. Two doses of aducanumab 1 mg/kg would not have an impact on the efficacy results for the placebo arm.

Table of Demographic Characteristics

Table 23 contains information regarding demographic characteristics for each treatment arm in the ITT population. 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.

Table 23: 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
Age Group							
≥ 51 - ≤60 years	3 (6%)	2 (6%)	4 (13%)	2 (7%)	2 (6%)	1 (4%)	14 (7%)
≥ 61 - ≤70 years	13 (27%)	9 (29%)	10 (31%)	11 (37%)	6 (19%)	6 (26%)	55 (28%)
≥ 71 - ≤80 years	26 (54%)	16 (52%)	14 (44%)	8 (27%)	19 (59%)	12 (52%)	95 (48%)
≥ 81 - ≤90 years	6 (13%)	4 (13%)	4 (13%)	8 (27%)	5 (16%)	4 (17%)	31 (16%)
>90 years	0	0	0	1 (3%)	0	0	1 (<1%)
Race							
White	48 (100%)	31 (100%)	31 (97%)	28 (93%)	30 (94%)	23 (100%)	191 (97%)
Black or African American	0	0	0	2 (7%)	0	0	2 (1%)
Asian	0	0	0	0	1 (3%)	0	1 (<1%)
American Indian or Alaska Native	0	0	0	0	1 (3%)	0	1 (<1%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
Other ¹	0	0	1 (3%)	0	0	0	1 (<1%)
Ethnicity							
Hispanic or Latino	1 (2%)	2 (6%)	1 (3%)	0	1 (3%)	1 (4%)	6 (3%)
Not Hispanic or Latino	47 (98%)	29 (94%)	31 (97%)	30 (100%)	30 (94%)	22 (96%)	189 (96%)

Source: Table 14 in Study 103 CSR

¹ Data on race and/or ethnicity were not collected because of local regulations.

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Table 24 contains a summary of baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. The disease characteristics represent a population similar to Studies 301 and 302 but with more mild patients as evidenced by 23% of patients with a CDR global score of 1 and 39% of patients with baseline MMSE less than 24. 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 24: Study 103 Disease Characteristics (ITT Population)

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 (%)
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%)
Number of Years of Formal Education							
Mean years (SD)	15.5 (2.98)	15.5 (3.15)	15.5 (2.42)	16.1 (2.76)	15.2 (2.35)	14.5 (3.33)	15.4 (2.84)
Median (years)	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Min, Max (years)	12, 24	12, 27	12, 21	12, 23	10, 20	5, 21	5, 27
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%)
Memantine	12 (25%)	6 (19%)	5 (16%)	8 (27%)	5 (16%)	3 (13%)	39 (20%)
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 CDR global score							
0.5	40 (83%)	22 (71%)	22 (69%)	25 (83%)	24 (75%)	18 (78%)	151 (77%)
1.0	8 (17%)	9 (29%)	10 (31%)	5 (17%)	8 (25%)	5 (22%)	45 (23%)
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 Table 15 and Table 16 in Study 103 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the period of study treatment, compliance with study treatment was ≥94% in all treatment arms. Because of dose modifications due to ARIA, only 14 patients (44%) in the aducanumab fixed-dose 10 mg/kg arm received all 14 infusions compared to 26 patients (54%) in the placebo arms. Similarly, 63% of patients receiving aducanumab 10 mg/kg fixed-dose were on treatment for ≥48 weeks, compared to 86% of placebo patients.

Overall, 21 patients (11%) either changed the dose or initiated treatment with cholinesterase inhibitors and/or memantine during the placebo-controlled period but the number was reasonably balanced across the treatment arms.

Efficacy Results – Clinical Endpoints

The results for CDR-SB and MMSE are presented in Table 25. 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 (Table 26). Subgroup analysis was not performed due to the small sample size in the treatment arms.

Table 25: Study 103 Clinical Endpoints (CDR-SB and MMSE) Analyses by ANCOVA

	Placebo (N=46)	1 mg/kg (N=30)	3 mg/kg (N=32)	6 mg/kg (N=29)	10 mg/kg (N=30)	Titration (N=22)
Baseline CDR-SB						
n	44	28	30	27	28	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
Adjusted mean	1.89	1.69	1.33	1.09	0.63	0.70
Standard error	0.350	0.441	0.413	0.423	0.446	0.499
95% CI	(1.198, 2.581)	(0.819, 2.564)	(0.517, 2.149)	(0.258, 1.930)	(-0.251, 1.511)	(-0.287, 1.686)
Difference from placebo		-0.20	-0.56	-0.80	-1.26	-1.19
95% CI for difference		(-1.308, 0.912)	(-1.612, 0.499)	(-1.855, 0.264)	(-2.356, -0.163)	(-2.343, -0.037)
% difference vs. placebo		-11%	-30%	-42%	-67%	-63%
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
Adjusted mean	-2.5	-2.2	-0.8	-2.0	-0.6	-1.0
Standard error	0.59	0.74	0.74	0.73	0.74	0.86
95% CI	(-3.63, -1.28)	(-3.66, -0.75)	(-2.20, 0.69)	(-3.44, -0.54)	(-2.01, 0.92)	(-2.70, 0.71)
Difference from placebo		0.2	1.7	0.5	1.9	1.5
95% CI for difference		(-1.61, 2.11)	(-0.14, 3.54)	(-1.36, 2.29)	(0.06, 3.75)	(-0.53, 3.45)
% difference vs. placebo		-8%	-68%	-20%	-76%	-60%
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

Table 26: Study 103 Clinical Endpoints (CDR-SB and MMSE) Analyses by MMRM

	Placebo (N=46)	1 mg/kg (N=30)	3 mg/kg (N=32)	6 mg/kg (N=29)	10 mg/kg (N=30)	Titration (N=22)
Baseline CDR-SB						
n	48	31	32	30	32	23
Mean	2.69	3.40	3.50	3.32	3.14	3.24
Change from Baseline in CDR-SB at Week 54						
n	39	23	27	26	23	21
Adjusted mean	1.88	1.82	1.42	1.20	0.80	1.14
Standard error	0.337	0.424	0.403	0.420	0.424	0.481
95% CI	(1.210, 2.541)	(0.981, 2.653)	(0.627, 2.218)	(0.367, 2.025)	(-0.041, 1.633)	(0.193, 2.094)

Difference from placebo		-0.06	-0.45	-0.68	-1.08	-0.73
95% CI for difference		(-1.122, 1.005)	(-1.483, 0.578)	(-1.730, 0.371)	(-2.141, -0.018)	(-1.866, 0.403)
% difference vs. placebo		-3%	-24%	-36%	-57%	-39%
p-value (compared with placebo)		0.9136	0.3869	0.2035	0.0464	0.2047
Baseline MMSE						
n	48	31	32	30	32	23
Mean	24.7	23.6	23.2	24.4	24.8	24.7
Change from Baseline in MMSE at Week 52						
n	40	25	26	26	25	21
Adjusted mean	-2.5	-2.2	-1.2	-2.0	-0.5	-1.1
Standard error	0.58	0.73	0.71	0.72	0.72	0.83
95% CI	(-3.60, -1.32)	(-3.64, -0.75)	(-2.59, 0.23)	(-3.45, -0.61)	(-1.94, 0.88)	(-2.74, 0.56)
Difference from placebo		0.3	1.3	0.4	1.9	1.4
95% CI for difference		(-1.56, 2.11)	(-0.52, 3.09)	(-1.37, 2.23)	(0.13, 3.74)	(-0.59, 3.34)
% difference vs. placebo		-12%	-52%	-16%	-76%	-56%
p-value (compared with placebo)		0.7708	0.1615	0.6366	0.0356	0.1680

Source: Table 9 and Table 10 in ISE appendix G5
p-values are nominal

Reviewer Comment: Differences between the results for the two methods are minor. The MMRM results will be considered in the integration of efficacy to maintain consistency with the statistical approach in Studies 301 and 302.

The statistical review and Advisory Committee focused on the observation that the p-value for CDR-SB crossed 0.05 for certain sensitivity analyses, such as when accounting for post-baseline starting of Alzheimer's medications or excluding the titration placebo arm. This finding is not surprising given the small size of the study and the proximity of the p-value to 0.05 to begin with. Study 103 is not meant to replace Study 301 or carry the same weight. More important is that the estimate of the treatment effect did not substantially change for different sensitivity analyses.

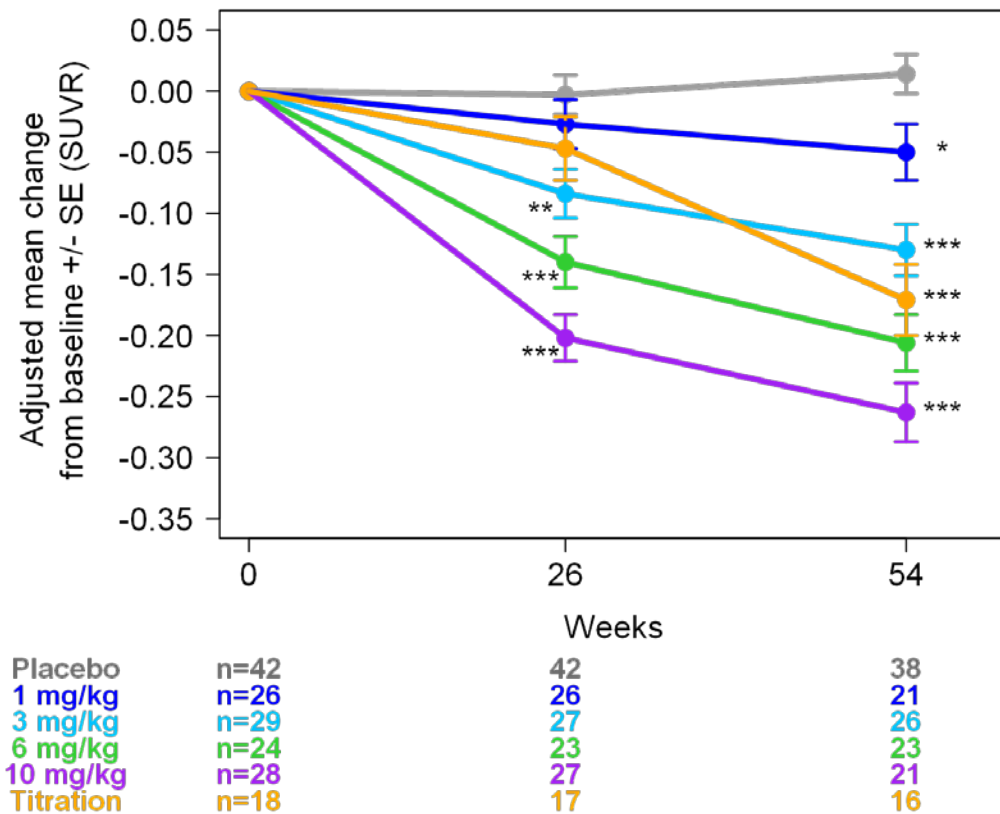
Data Quality and Integrity

There were no major data quality issues identified during the review of Study 103.

Efficacy Results – Pharmacodynamic Endpoints

Change from baseline in brain amyloid signal as measured by SUVR was analyzed with an ANCOVA model adjusting for baseline SUVR and ApoE ϵ 4 status. Statistically 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 12). 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 ($p < 0.0001$).

Figure 12: Study 103 Change from Baseline in A β PET Composite SUVR



Created by reviewer from Table 22 in Study 103 CSR

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

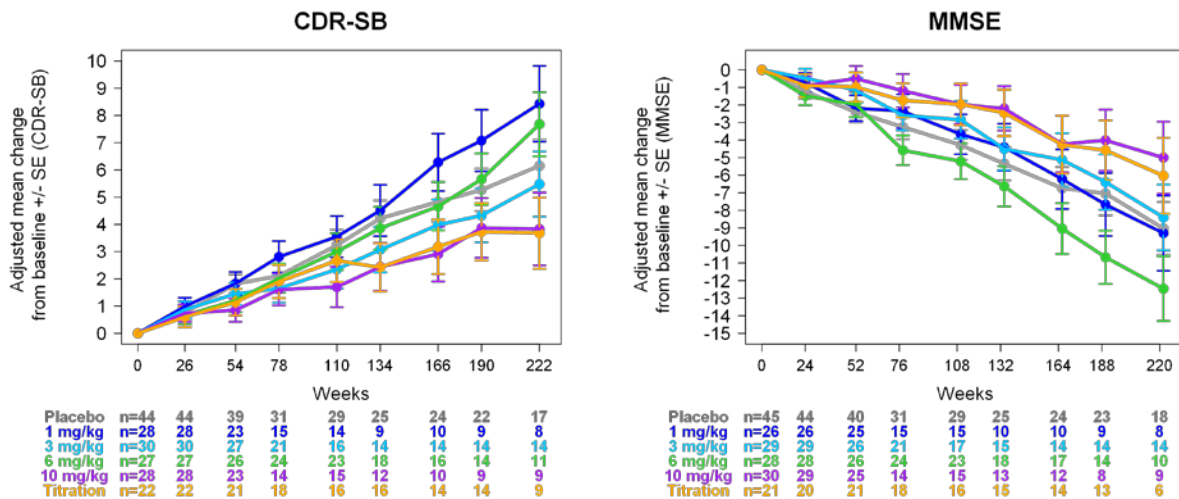
Reviewer Comment: The reduction in A β PET composite SUVR compared to placebo for the fixed-dose 10 mg/kg arm at Week 54 (-0.277) using an MMRM analysis was similar to the

reduction at Week 78 in Study 302 (-0.278). Therefore, it is reasonable to compare clinical outcomes from Study 103 at Week 54 to those of Studies 301 and 302 at Week 78.

Durability of Response

The durability of response in patients treated with aducanumab in Study 103 over 4.25 years is illustrated in Figure 13. For patients receiving 10 mg/kg throughout the study, the adjusted mean change from baseline in CDR-SB at Week 222 (3.68) was similar to the value in placebo patients between Week 110 (3.24) and Week 134 (4.22). Despite a substantial reduction in brain amyloid, patients in the 6 mg/kg arm progressed similar to or more than patients in the placebo arm.

Figure 13: Study 103 Longitudinal Change from Baseline for Clinical Endpoints through Week 222



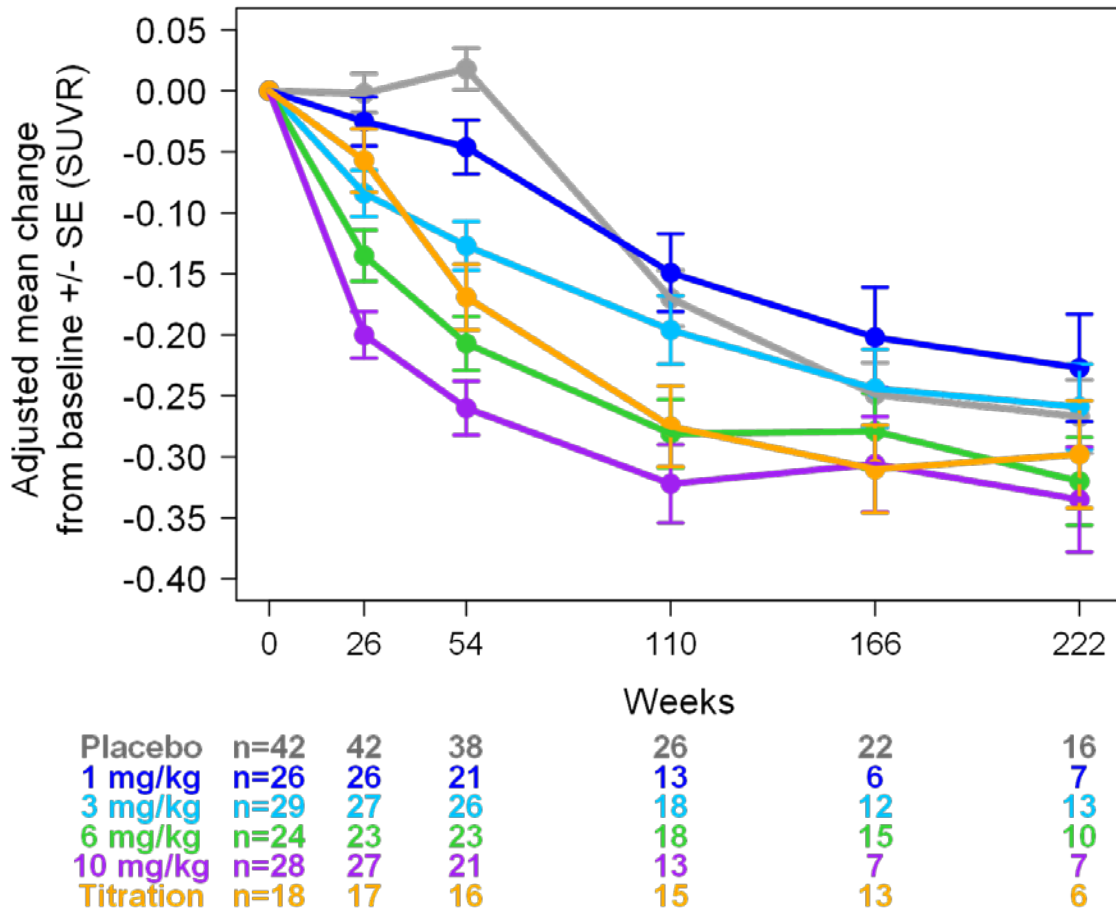
Source: Created by reviewer from Tables 66 and 73 in Study 103 CSR

Subjects in placebo arm received 3 mg/kg or a titration regimen of 3 to 6 mg/kg or 1 to 3 to 6 to 10 mg/kg in LTE

Subjects in 1 mg/kg arm received 3 mg/kg in LTE

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 (Figure 14). For patients who switched from placebo in the placebo-controlled period to aducanumab treatment in the LTE, SUVR declined as expected.

Figure 14: Study 103 Longitudinal Change from Baseline in A β PET Composite SUVR through Week 222



Created by reviewer from Tables 60 in Study 103 CSR

Note: Subjects in placebo arm received 3 mg/kg or a titration regimen of 3 to 6 mg/kg or 1 to 3 to 6 to 10 mg/kg in LTE

Note: Subjects in 1 mg/kg arm received 3 mg/kg in LTE

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy endpoint in Studies 301 and 302 was the change from baseline in CDR-SB at Week 78. Study 103 was designed primarily as a safety and tolerability study but included CDR-SB as an exploratory endpoint. Studies 301 and 302 were large, contemporaneous, and

identically designed studies and therefore directly comparable. Study 103 included many of the elements of the other two studies with some minor differences: the sample size was considerably smaller, patient recruitment was entirely within the United States, and the entry criteria allowed for enrollment of patients later in the disease continuum. Differences in study design and patient demographics are provided in Section 6.

The aducanumab fixed-dose 10 mg/kg treatment arm in Study 103 is the relevant arm to compare to the high-dose arms of Studies 301 and 302. Although the primary endpoint was assessed earlier in Study 103 than Studies 301 and 302 (54 weeks vs. 78 weeks), the planned number of 10 mg/kg doses received during the treatment period was the same. The appropriateness of the comparison is also supported by the similar reduction in amyloid burden observed in the studies (Table 31).

A summary of the results for CDR-SB across studies is contained in Table 27. The statistically significant result in favor of high-dose aducanumab in Study 302 is consistent with the result from the fixed-dose 10 mg/kg treatment arm in Study 103. Direct comparison of the magnitude of the treatment effect between the two studies is complicated by the differences described earlier as well as the greater degree of decline in placebo patients in Study 103 in a shorter period of time. Study 302 and Study 103 are also consistent in their demonstration of an apparent dose-response relationship. Importantly, the dose-response relationships are consistent with the dose- and exposure-response relationships for changes in amyloid burden and other biomarkers. The fixed-dose 1 mg/kg arm is the only treatment arm in the two studies that does not notably change brain amyloid load and is also the only dose that has marginal numerical effects on CDR-SB.

The results of Studies 301 and 302 were only partially discordant. The low-dose aducanumab treatment arms provided very similar and numerically favorable estimates of change from baseline in CDR-SB at Week 78. Across the 3 studies, 7 out of 8 treatment arms that resulted in a reduction of amyloid burden numerically favored aducanumab treatment. It may be posited that aducanumab treatment itself causes a small bias in favor of treatment perhaps due to functional unblinding to ARIA. This possibility was explored (Section 7.1.7) and ultimately found to be lacking. Of course, the result for the primary endpoint in the high-dose treatment arm in Study 301 is an important finding and in isolation raises questions about the effectiveness of aducanumab. But in the context described above, it is not unreasonable to consider whether the high dose in Study 301 is an aberration. Section 7.1.7 will explore the discordant results in Studies 301 and 302 in detail.

The treatment effect in Study 302 (-22%) is consistent with the effect size used to power the study (-25%). Furthermore, the treatment effect size may accrue over time because aducanumab targets the underlying pathophysiology of the disease.

Table 27: Summary of Findings for CDR-SB in Studies 103, 301 and 302

	Study 301			Study 302			Study 103					
Dose group	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	Titration	10 mg/kg
N, ITT population	545	547	555	548	543	547	48	31	32	30	23	32
n at Week 78 or 54	333	331	295	288	290	299	39	23	27	26	21	23
Change from baseline	1.56	1.38	1.59	1.74	1.47	1.35	1.88	1.82	1.42	1.20	1.14	0.80
Difference from placebo (%)		-0.18 (-12%)	0.03 (2%)		-0.26 (-15%)	-0.39 (-22%)		-0.06 (-3%)	-0.45 (-24%)	-0.68 (-36%)	-0.73 (-39%)	-1.08 (-57%)
p-value		0.2250	0.8330		0.0901	0.0120		0.9136	0.3869	0.2035	0.2047	0.0464

Source: Table 13 in the Summary of Clinical Efficacy

7.1.2. Secondary and Other Endpoints

MMSE was the first secondary endpoint in the hierarchy for Studies 301 and 302 and the only other clinical endpoint that was collected in all three studies. Results are presented in Table 28 and are generally similar to those for CDR-SB except that the low-dose treatment effects in Studies 301 and 302 do not consistently favor aducanumab. Also, the 3 mg/kg and 6 mg/kg treatment arms in Study 103 are not consistent with a dose-response relationship.

Table 28: Summary of Findings for MMSE in Studies 103, 301 and 302

	Study 301			Study 302			Study 103					
Dose group	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	Titration	10 mg/kg
N, ITT population	545	547	555	548	543	547	48	31	32	30	23	32
n at Week 78 or 52	332	334	297	288	293	299	40	25	26	26	21	25
Change from baseline	-3.5	-3.3	-3.6	-3.3	-3.3	-2.7	-2.5	-2.2	-1.2	-2.0	-1.1	-0.5
Difference from placebo (%)		0.2 (-6%)	-0.1 (3%)		-0.1 (3%)	0.6 (-18%)		0.3 (-12%)	1.3 (-52%)	0.4 (-16%)	1.4 (-56%)	1.9 (-76%)
p-value		0.4795	0.8106		0.7578	0.0493		0.7708	0.1615	0.6366	0.1680	0.0356

Source: Table 14 in the Summary of Clinical Efficacy

Results for ADAS-Cog 13 and ADCS-ADL-MCI are presented in Table 29 and Table 30, respectively. The findings are consistent with those of CDR-SB in two respects: (1) the high-dose arm in Study 302 demonstrated a statistically significant and clinically meaningful reduction in

decline and (2) the low-dose arms in both studies show a consistent numerical trend in favor of aducanumab. Unlike CDR-SB, the results for these two secondary endpoints numerically favor aducanumab in the high-dose treatment arm in Study 301 and the magnitude of the treatment effects are similar to those observed in the low-dose treatment arms. The principal components analysis presented by the applicant demonstrates that each of the 3 secondary endpoints captures distinct information regarding cognitive decline. Therefore, the strongly positive results on the secondary endpoints in Study 302 reinforce the persuasiveness of the findings on the primary endpoint.

Table 29: Summary of Findings for ADAS-Cog 13 in Studies 301 and 302

	Study 301			Study 302		
Dose group	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose
N, ITT population	545	547	555	548	543	547
n at Week 78 or 54	331	332	294	287	289	293
Change from baseline	5.140	4.558	4.552	5.162	4.461	3.763
Difference from placebo (%)		-0.583 (-11%)	-0.588 (-11%)		-0.701 (-14%)	-1.400 (-27%)
p-value		0.2536	0.2578		0.1962	0.0097

Source: Table 16 in the Summary of Clinical Efficacy

Table 30: Summary of Findings for ADCS-ADL-MCI in Studies 301 and 302

	Study 301			Study 302		
Dose group	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose
N, ITT population	545	547	555	548	543	547
n at Week 78 or 54	331	330	298	283	286	295
Change from baseline	-3.8	-3.1	-3.1	-4.3	-3.5	-2.5
Difference from placebo (%)		0.7 (-18%)	0.7 (-18%)		0.7 (-16%)	1.7 (-40%)
p-value		0.1225	0.1506		0.1515	0.0006

Source: Table 17 in the Summary of Clinical Efficacy

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 appear to 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 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. Although the study was not designed to specifically assess dose-response, the trend observed for clinical outcomes in Study 302 is consistent with the dose-response relationship for brain amyloid and consistent with the dose-response relationship for both brain amyloid and clinical outcomes observed in Study 103.

The change from baseline in amyloid signal as measured by PET and quantified by a composite SUVR was a key pharmacodynamic marker collected using the same methods across all three studies. The results of these studies and the accompanying PKPD modeling demonstrate a robust relationship between aducanumab exposure and reduction in amyloid signal. Interestingly, the high-dose arm in Study 301 yielded a reduction in SUVR commensurate with the 6 mg/kg dose in Study 103, rather than the high dose in Study 302 or the 10 mg/kg dose in Study 103. This observation alone cannot explain the negative outcome of Study 301 but provides an avenue for further exploration. Specifically, it supports the hypothesis that dosing in Study 301 was lower than in Study 302 and that this lower dosing contributed in part to the discordant results.

Table 31: Summary of Findings for Amyloid PET Composite SUVR in Studies 103, 301 and 302

	Study 301			Study 302			Study 103					
Dose group	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	Titration	10 mg/kg
N, PET population	204	198	183	159	159	170	46	29	32	30	19	31
n at Week 78 or 54	124	138	112	93	100	109	38	21	26	23	16	21
Change from baseline	-0.003	-0.170	-0.235	0.014	-0.165	-0.264	0.017	-0.047	-0.130	-0.208	-0.170	-0.259
Difference from placebo		-0.167	-0.232		-0.179	-0.278		-0.064	-0.147	-0.225	-0.187	-0.276
p-value		<1e-4	<1e-4		<1e-4	<1e-4		0.0231	<1e-4	<1e-4	<1e-4	<1e-4

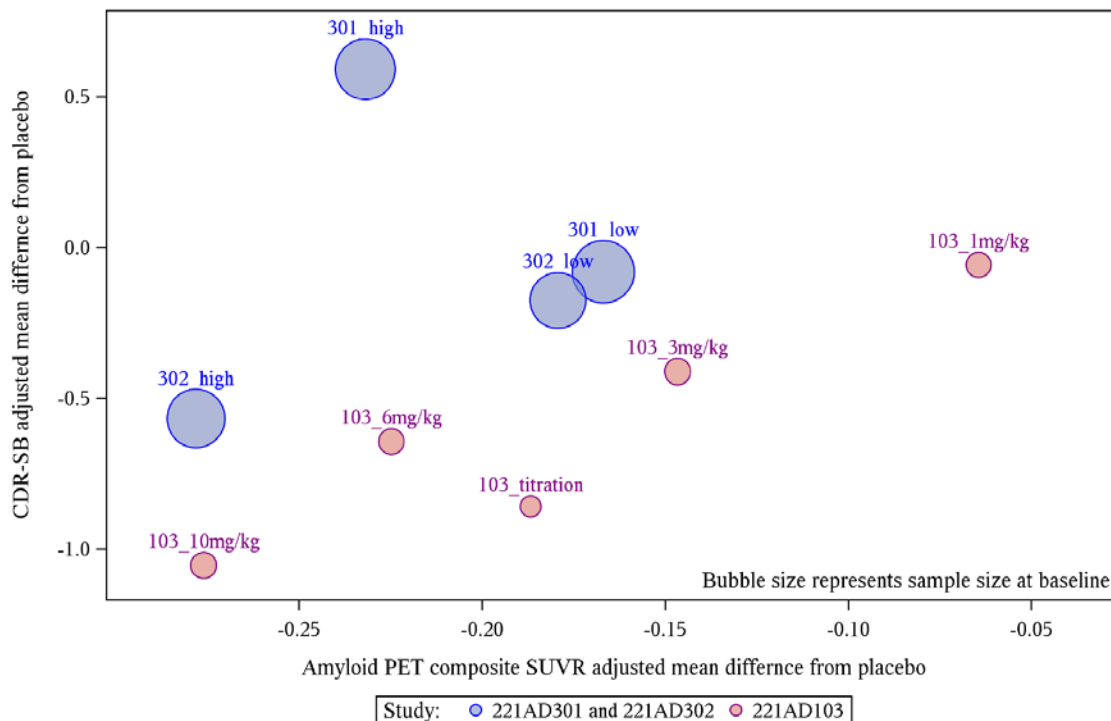
Source: Table 15 in the Summary of Clinical Efficacy

Note: Study 103 results are based on an MMRM model with the same covariates as the primary prespecified ANCOVA model

The group-level correlation between change from baseline on A β PET and CDR-SB across the three studies is illustrated in Figure 15. It is noteworthy that due to differences in study design, Week 78 was used for Studies 301 and 302 and Week 54 was used for Study 103. There are also other differences in study design, analysis, and study populations that affect the interpretation

of such an analysis. But from a qualitative perspective, the analysis is consistent with there being a relationship between brain amyloid reduction and treatment effect for CDR-SB. Figure 15 also highlights the apparently aberrant performance of the high dose in Study 301. The Office of Clinical Pharmacology (OCP) also concludes that there is a clear association between A β plaque reduction and treatment effect for CDR-SB. In addition, OCP has reviewed data from publicly accessible sources for multiple compounds under development and concludes that the relationship observed for aducanumab is consistent with the relationship observed in other clinical development programs.

Figure 15: Group-Level Correlation Between Adjusted Mean Difference from Placebo in A β PET Composite SUVR and CDR-SB



Source: Figure 61 in ISE

7.1.3. Subpopulations

A pooled analysis across trials is not provided because Study 301 is a negative trial and the sample size for Study 103 is small. Subgroup analysis for Study 302 is presented in Section 6.1.2. Treatment effects favored aducanumab for the various subpopulations considered.

One factor of interest is ApoE ϵ 4 carriage because it is the most relevant known genetic risk factor for the development of Alzheimer's disease and is thought to affect disease pathogenesis via both amyloid-dependent and amyloid-independent mechanisms. Potential differences in treatment effect due to ApoE ϵ 4 carriage are therefore biologically plausible and not evidence

of “inconsistency” in the data as suggested in the statistical review. The only subgroup across the primary and secondary endpoints with a point estimate of the treatment effect that did not favor aducanumab was MMSE in ApoE ϵ 4 non-carriers. In Figure 2, the trend for a lower response in ApoE ϵ 4 non-carriers is also evident for CDR-SB. This might be viewed as unexpected, given that ApoE ϵ 4 non-carriers had the opportunity to be exposed to the 10 mg/kg dose throughout the study. The applicant provided additional analyses using the OTC and uncensored datasets which question the robustness of this finding. For example, 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 ϵ 4 carriers and -19% for ApoE ϵ 4 non-carriers. In the uncensored ITT population, the percent decline versus placebo for CDR-SB was -26% for ApoE ϵ 4 carriers and -20% for ApoE ϵ 4 non-carriers. Interestingly, in the disease progression model developed by the applicant, ApoE ϵ 4 carrier status was not a clinically meaningful covariate on the rate of progression after incorporating a mixture model to describe different subpopulations of progressors. Also, brain amyloid is similarly reduced in ApoE ϵ 4 carriers and ApoE ϵ 4 non-carriers, suggesting the underlying pharmacodynamic effect is similar in the two populations. In sum, the data suggest a treatment effect exists for ApoE ϵ 4 carriers and ApoE ϵ 4 non-carriers although there might be a more modest effect in ApoE ϵ 4 non-carriers. A definitive conclusion cannot be drawn from the data.

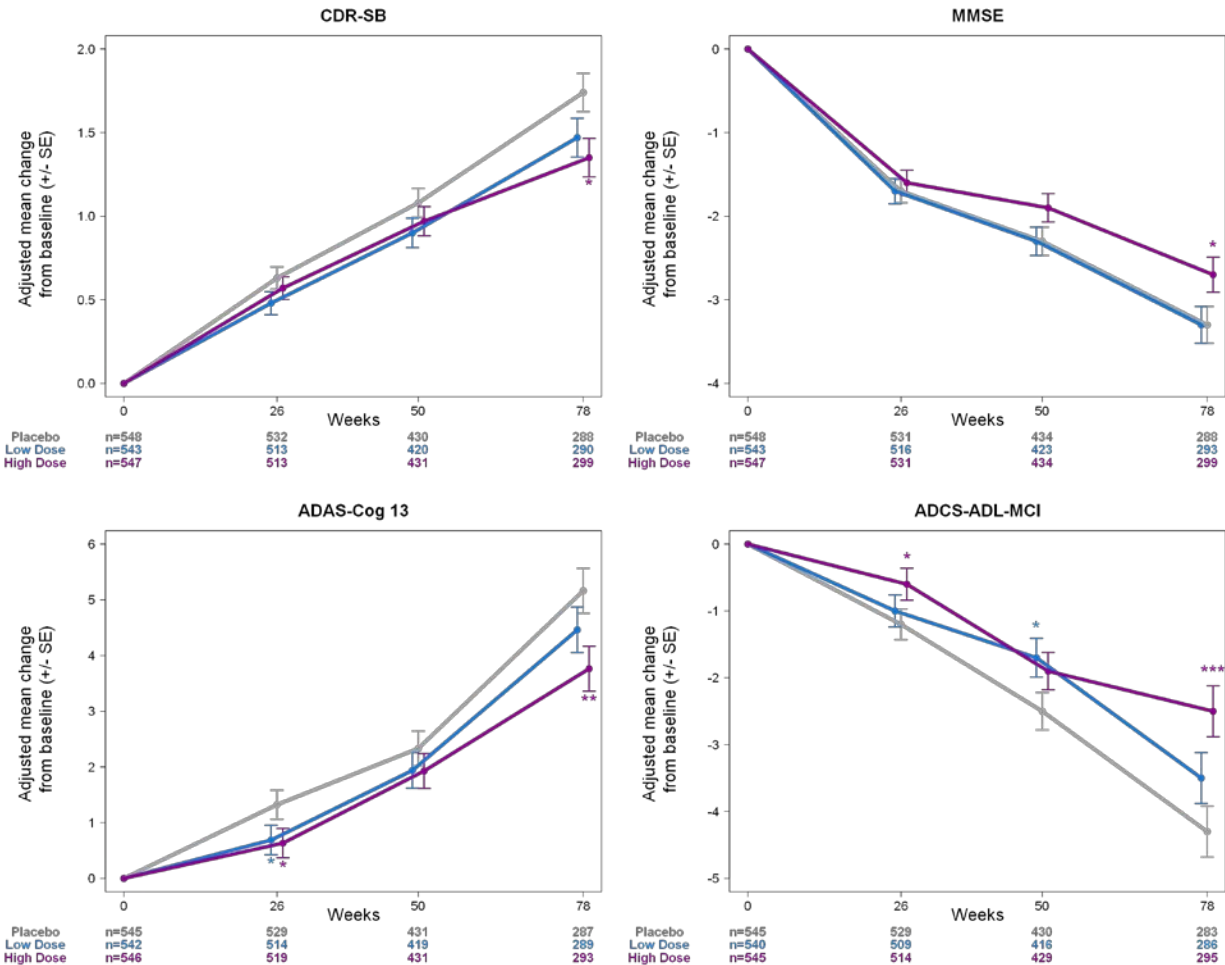
7.1.4. Dose and Dose-Response

The results of Study 103 and 302 were indicative of a dose-response relationship for reduction of brain amyloid and treatment effect for clinical endpoints (see Sections 6.1.2 and 6.2.2). The role of dose is discussed in detail in Section 7.1.7. Further considerations of the concentration- and dose-response relationships are also provided in 7.1.7 and in the clinical pharmacology review. Notably, the clinical pharmacology review team has concluded that exposure-response relationships for clinical endpoints were established in both Study 302 and Study 301, although the magnitude of the drug effect on disease progression slopes were different in the two studies.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Week 78 is the earliest time in Study 302 when statistically convincing evidence of a clinically meaningful effect is observed across all clinical endpoints (Figure 16). There were a few instances at Week 26 or 50 where the adjusted mean change from baseline for ADAS-Cog 13 or ADCS-ADL-MCI crossed the bounds to nominal significance, but the effect was not sustained.

Figure 16: Study 302 Clinical Endpoints Adjusted Mean Change from Baseline over Time



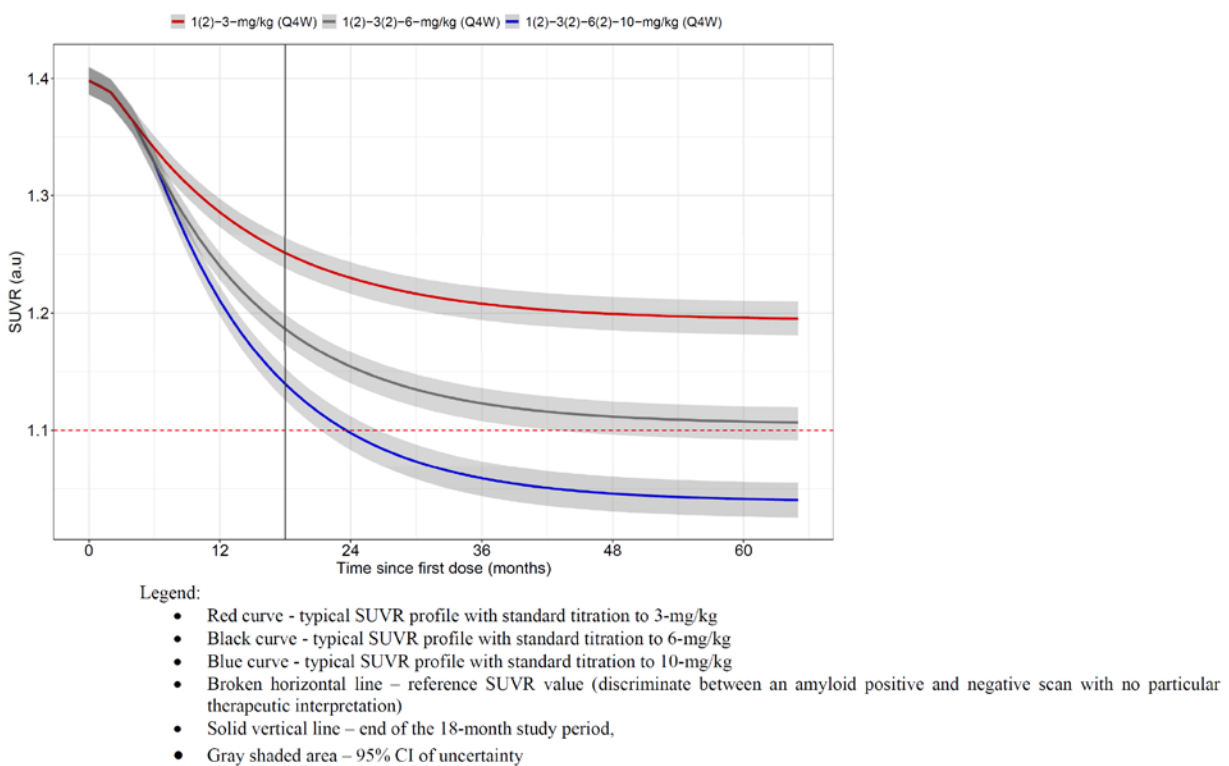
Created by reviewer from Figures 4, 7, 9 and 11 in Study 302 CSR

*p<0.05, **p<0.01, ***p<0.001

Although the precise relationship between reduction in amyloid plaque and clinical outcomes is unknown, consideration of the time-course of SUVR for the proposed dosing regimen is instructive (Figure 17). The first key observation is that the reduction in brain amyloid is delayed with respect to initiation of treatment. Based on the understanding of the mechanism of action of aducanumab and the disease process, one can reasonably assume that the effect on tau reduction is even further delayed, although the staging of events is not discernible from the data collected in the studies. Second, the pharmacodynamic effect of aducanumab on amyloid plaque reduction is increasing during the trial and does not reach maximum effect until more than a year after the double-blind treatment period. Furthermore, dose interruptions due to ARIA would further prolong the time to achieve maximum effect on amyloid levels. Together, these observations are consistent with an effect on clinical outcomes that did not clearly emerge until the end of the study, with favorable trends observed at earlier time points.

Moreover, these findings suggest that the effect should be durable and may increase over time. On the other hand, these same observations raise the possibility that patients receiving aducanumab treatment progressed as normal during the early portion of the trial before therapeutic levels of amyloid reduction were reached, thereby making it more difficult to demonstrate effectiveness in the studies. The fixed-dose of 10 mg/kg in Study 103 reduced amyloid plaque to a similar extent as the high dose in Study 302, but in a shorter period of time. Accordingly, a treatment effect on clinical endpoints was observed earlier in Study 103.

Figure 17: Typical Profile of SUVR for Planned Titration and No Dose Interruptions



Source: Figure 8 in Summary of Clinical Pharmacology

The persistence of clinical efficacy with continuous treatment is informed by the LTE periods of Studies 103 and 302. Specifically, the LTE period of Study 103 included patients with continuous aducanumab treatment for approximately 4.25 years. Although clinical endpoints continue to decline in all groups, the magnitude of the treatment effects observed at the conclusion of the placebo-controlled periods do not appear to diminish over time with high-dose aducanumab treatment (Figure 6 and Figure 13). Consistent with predictions (Figure 17), there is a further reduction of amyloid with continuous treatment, as observed in Study 103 (Figure 14).

The persistence of clinical benefit after treatment has been stopped is indirectly assessed by the efficacy results using the uncensored ITT population (Table 16) because this data set includes assessments after the March 20, 2019, termination of study treatment. The mean time (range) elapsed from the time of last dose to the last assessment in the high-dose aducanumab treatment arm was 13 weeks (1 to 67 weeks) during the placebo-controlled period. The magnitude of the treatment effect is consistent with the estimate derived from the ITT population. These results should be viewed with caution, however, because of the termination of the studies and the subsequent unblinding of some patients.

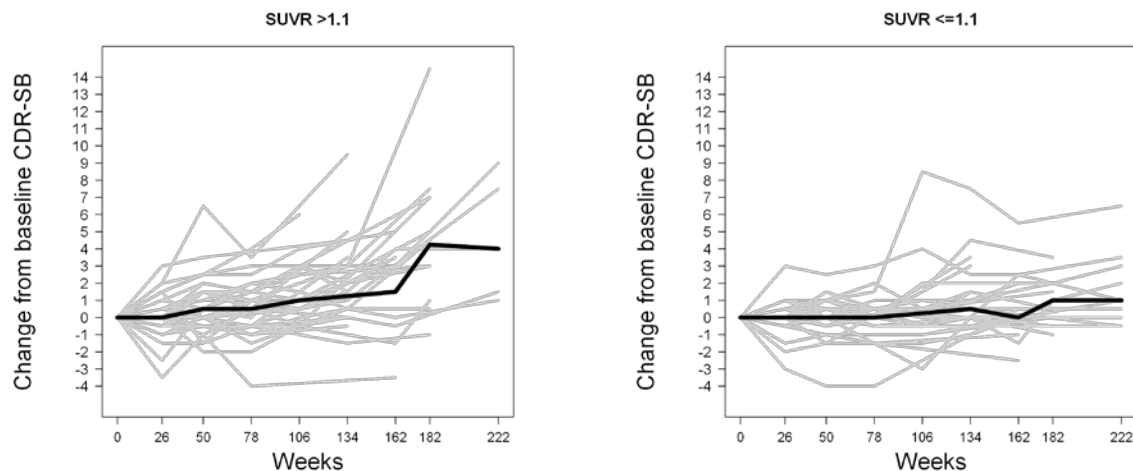
The termination of aducanumab studies in March of 2019 followed by the subsequent resumption of dosing in subjects who opted to enroll in a redosing study, Study 304, also offers a unique opportunity to investigate the persistence of benefit after cessation of treatment. Study 304 is an ongoing, single-arm, open-label study to assess the long-term safety and efficacy of aducanumab in participants who were actively participating in Studies 103, 205, 301, or 302. The first patient enrolled into Study 304 on March 13, 2020, and interim data, consisting only of baseline values, was available up to October 21, 2020. The median gap in treatment for patients entering Study 304 was 1.5 years. For study participants who did not enter the LTE period of Study 302, but enrolled in Study 304, a numerical advantage on all 4 clinical endpoints was maintained during the treatment gap in participants who received high-dose aducanumab in Study 302 (n=58) compared to those receiving placebo (n=70). For study participants who did enter the LTE period of Study 302 and enrolled in Study 304, there was not a consistent difference between endpoints in the group of patients who were randomized to high-dose aducanumab throughout the placebo-controlled and LTE periods (n=101) compared to patients who were randomized to placebo in the placebo-controlled period and high-dose aducanumab in the LTE (n=39). In all groups, clinical decline during the treatment gap was evident.

The persistence of effect on brain amyloid following treatment discontinuation was informed by a comparison of SUVR at the Study 304 baseline visit to the last nonmissing SUVR assessment in Study 301 or Study 302 for patients who received high-dose aducanumab in the placebo controlled and LTE periods. The mean change from baseline in SUVR at the last Study 301/302 visit was -0.285 (n=35). During the treatment gap, the SUVR increased by 0.022, which corresponds to a change from baseline of -0.263 (n=35). The baseline SUVR assessment for Study 301/302 was used as the baseline value for both calculations. These results suggest that the effect of aducanumab on reduction of brain amyloid persists after treatment cessation.

The relationship between brain amyloid reduction and maintenance of treatment effect on clinical endpoints was also investigated with data from Study 304. 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 (Figure 18) suggest that patients who achieved $\text{SUVR} \leq 1.1$ 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.

Figure 18: Individual CDR-SB Change from Baseline by End of Study 302 Amyloid SUVR



Source: Created by reviewer from adcfbeff.xpt
Solid black lines represent median values

There are several important limitations of the data and analyses from Study 304. There is no guarantee that participants in Study 304 are representative of the participants enrolled in Study 302 and the baseline characteristics are likely not balanced between groups used for comparisons. For example, there is likely selection bias in the participants who chose to enroll in the study. Also, the enrollment in Study 304 is weighted towards patients in the United States at this time. The analyses do not account for the potential for intercurrent events to occur in the gap period, including a change in concomitant Alzheimer's medications or the impact of the COVID-19 pandemic. There may have also been a change in the rater from Study 302 to Study 304. For these reasons and more, the explorations of the data provided above do not meaningfully contribute to the evidence used to support the effectiveness of aducanumab. On the other hand, there were no trends in the data which diminish the persuasiveness of the results observed in placebo-controlled periods of the studies.

7.1.6. Early Termination and Interpretation of Study 301 and Study 302

The applicant announced the early termination of Studies 301 and 302 on March 21, 2019, based on the results of a prespecified futility analysis of interim data. A detailed timeline of the interactions leading to the futility declaration is included in Section 6.1.1. The futility criteria were based on conditional power, which was defined by the applicant as the chance that the primary efficacy endpoint analysis will be statistically significant in favor of aducanumab at the

planned final analysis, given the data at the interim analysis. Conditional power was calculated assuming that the future unobserved effect would be equal to the maximum likelihood estimate of the pooled observed interim data from Studies 301 and 302. Pooling of the data assumes that the treatment effect would be similar in the two studies. The studies were to be considered futile if both studies had conditional power less than 20% for both the high-dose and low-dose treatment groups. The SAP specified that other data, in addition to the prespecified futility criteria, could also be considered. At the June 14, 2019, Type C meeting the applicant asserted that if the conditional power had been less than 20% for CDR-SB, but greater than 90% for either MMSE or ADAS-Cog 13, the studies could have continued.

The futility analysis was planned to occur after approximately 50% of the patients enrolled in the studies had the opportunity to complete the Week 78 visit. Data from patients who were enrolled in the studies but did not yet have the opportunity to complete the Week 78 visit were not included in the calculation of conditional power.

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. Table 32 provides the results of the futility analysis and shows that the futility criteria were met. The results also clearly demonstrate divergent estimates of treatment effect for the high-dose treatment arm in the two studies for all three endpoints. In other words, the assumption that the treatment effect would be similar in the two studies was not realized.

Table 32: Conditional Power for Change from Baseline in CDR-SB, MMSE and ADAS-Cog13 at Week 78 (Interim Futility Dataset)

	Study 301			Study 302		
	Diff vs. placebo (%) Conditional Power			Diff vs. placebo (%) Conditional Power		
	Placebo decline (N=324)	Low Dose (N=320)	High Dose (N=301)	Placebo decline (N=258)	Low Dose (N=269)	High Dose (N=276)
CDR-SB	1.45	-0.15 (-10%) 12.9%	0.22 (15%) 0%	1.53	-0.10 (-7%) 10.7%	-0.28 (-18%) 11.8%
MMSE	-3.2	0.3 (-9%) 5.7%	-0.4 (13%) 0%	-3.0	-0.1 (3%) 0.3%	0.6 (-20%) 24.9%
ADAS-Cog 13	4.827	-0.472 (-10%) 9.8%	-0.058 (-1%) 3.3%	5.488	-0.311 (-6%) 9.0%	-1.089 (-20%) 55.2%

Source: Table 5 in ISE

Upon review of the futility analysis and prior to the June 14, 2019, Type C meeting, the Division asked the applicant to recalculate the conditional power assuming the future unobserved effect would be equal to the maximum likelihood estimates for each individual study independently. The results are provided in Table 33 and show that the futility criteria would not have been met

with this analysis. Estimates of the treatment effect for all three endpoints in the high-dose arm in Study 302 numerically favor aducanumab treatment. For these reasons, the futility decision is not an accurate reflection of the individual studies.

Table 33: Conditional Power (Non-Pooled Analysis) for Change from Baseline in CDR-SB, MMSE and ADAS-Cog13 at Week 78 (Interim Futility Dataset)

	Study 301			Study 302		
	Diff vs. placebo (%) Conditional Power			Diff vs. placebo (%) Conditional Power		
	Placebo decline (N=324)	Low Dose (N=320)	High Dose (N=301)	Placebo decline (N=258)	Low Dose (N=269)	High Dose (N=276)
CDR-SB	1.45	-0.15 (-10%) 11.23%	0.22 (15%) 0%	1.53	-0.10 (-7%) 4.4%	-0.28 (-18%) 58.6%
MMSE	-3.2	0.3 (-9%) 12.4%	-0.4 (13%) 0%	-3.0	-0.1 (3%) 0.02%	0.6 (-20%) 78.2%
ADAS-Cog 13	4.827	-0.472 (-10%) 8.1%	-0.058 (-1%) 0.3%	5.488	-0.311 (-6%) 3.7%	-1.089 (-20%) 72.4%

Source: Table 6 in ISE

It is important to note that rigorous, per-protocol collection of blinded data continued between the time of the data cutoff in December 2018 and the futility announcement in March 2019. Subsequently, the primary analysis per the SAP was conducted on the more complete ITT dataset including assessments collected before March 21, 2019. On face, Study 302 was a positive study which might be considered exceptionally persuasive on several of the instruments used to evaluate efficacy. Study 301 remained a negative study. To a casual observer, the turnabout from futility to a positive study might suggest that the data collected after the futility announcement was completely incongruent with the data used to make the futility decision or that some new analysis was performed on the data. Although the treatment effect did improve over time (e.g., -18% to -22% for the high dose in Study 302), one can see from Table 33 that Study 302 was trending positively and had a reasonable likelihood of success if run to conclusion. It is not surprising that the treatment effect would improve over time, as protocol amendments implemented during the studies had the effect of increasing the exposure to aducanumab, although other factors also clearly contributed.

Before further consideration could be given to Studies 301 and 302 it was imperative to evaluate the effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses. 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. Two approaches were used to virtually complete the studies. Both approaches estimated parameters from a target dataset, simulated patient-level data, and fit an MMRM model to the simulated data. The primary approach supplemented the existing observed data

with simulated assessments for the data that were censored due to the early termination of the trials. Another approach fully simulated studies to explore the range of plausible results if many trials like Studies 301 and 302 were run from start to completion. Overall, simulation results were highly consistent with the primary analysis of the observed data. Similar results were obtained using all data (ITT) or only data in patients who had the opportunity to complete the Week 78 visit.

The results of this exercise established the following:

- The early termination of the aducanumab program does not compromise the interpretability of the efficacy results of Studies 301 and 302
- The appropriate dataset for further consideration is the ITT population consisting of all randomized subjects who received at least one dose of study treatment and excluding data collected after March 20, 2019.

Thus, the final analysis results presented earlier in Table 27 to Table 30 simply provide the final, interpretable results of trials that were terminated early but analyzed in accordance with the prespecified analysis.

7.1.7. Analysis of Discordant Results in Study 301 and Study 302

Once the results of Studies 301 and 302 were deemed interpretable, the review team was met with a unique situation of having a large and complicated, but incomplete and partially discordant, data set suggestive of the possible effectiveness of aducanumab.

Upon initial review, the one positive study (Study 302) and one negative study (Study 301) were given equal weight and consideration. Despite divergent outcomes in the primary endpoint, there were some key similarities between the two studies. As noted earlier, the low-dose aducanumab treatment arms, while not statistically significant, demonstrated consistent numerical effects favoring aducanumab in the studies. Also, aducanumab produced a time- and dose-dependent reduction in brain amyloid burden. Upon closer review of the individual studies, Study 302 appeared to be a strongly positive study on many distinct and important clinical measures, robust to sensitivity analyses, and supported by well-characterized biomarker data. Simulations performed by the clinical pharmacology review team suggest the probability of observing such a pattern of results in Study 302 by chance if aducanumab is similar to placebo is very small (less than 1 in 10 million). In the context of a positive Study 302, the dose-response relationship observed in Study 103, and the numerically favorable results of similar magnitude in the low-dose groups in both studies, the high dose in 301, and specifically the primary endpoint, tends to stand apart. Also, the magnitude of the effect on CDR-SB in the high-dose group in Study 301 underwent the greatest change from the futility analysis (15%) to the final analysis (2%), suggesting instability in the estimate.

Given the enormous unmet medical need, it was agreed by the applicant and Division at the June 14, 2019, Type C Meeting that extensive resources should be brought to bear on achieving a maximum understanding of the existing data.

By their nature, these analyses are post hoc and exploratory and therefore carry with them the appropriate caveats and caution in their interpretation. To address these concerns, any exploration of the data was to be rigorous, limited in scope, and based on well-defined hypotheses. To the maximum degree possible, the analyses were pre-specified. An important distinction is that these analyses were not aimed at obtaining independent support from Study 301. Study 301 is a negative study. The results of the analyses had the potential to cast doubt on the persuasiveness of Study 302. The purpose of these analyses is to provide maximum understanding of the partially discordant results of Studies 301 and 302.

Demographics and Baseline Disease Characteristics

A first step to establish the foundation for future investigation was to rule out any glaring differences in the characteristics of the patients enrolled in the two studies, especially in the high-dose arms. Prior to the June 14, 2019, Type C Meeting, the Division requested the applicant to investigate this possibility even though differences were not expected due to the identical design and timing of the studies. The individual studies are reviewed in Sections 6.1.2 and 6.2.2 and no major differences in demographics or baseline disease characteristics between the studies were noted.

A population exposure-CDR-SB model developed by the applicant revealed that observable baseline factors do not explain much of the variability in disease progression. This suggests that even if there were small differences in observed baseline characteristics, they are unlikely to explain the discordant results in the high dose arms. Most of the variability between patients in disease progression is due to unknown factors that should be balanced by randomization.

Influence of Study Participants with Rapid Progression

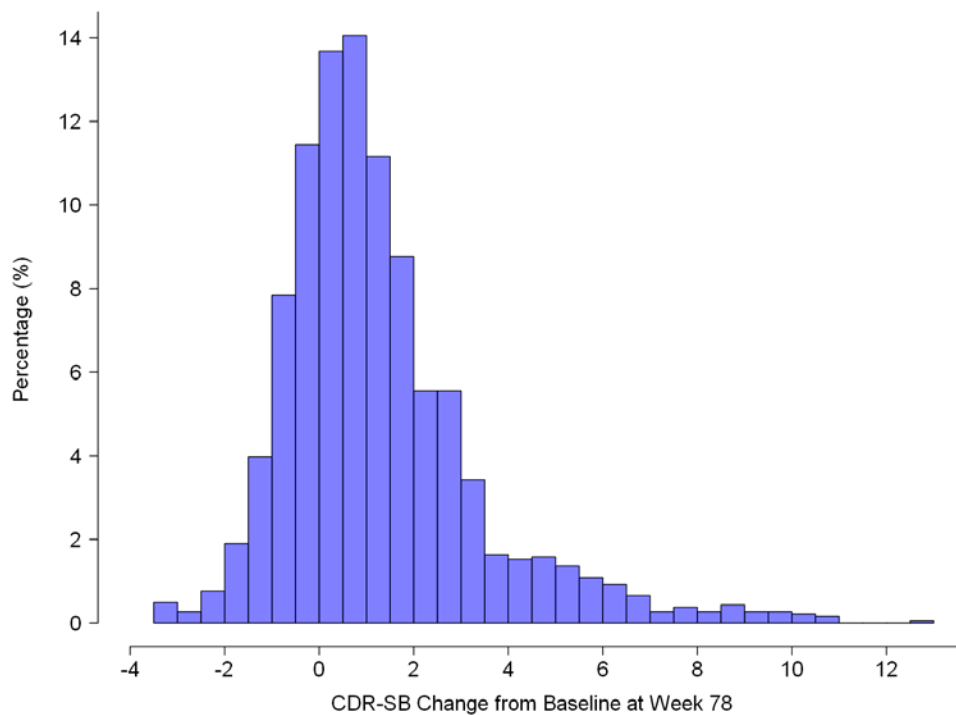
Investigation of individual treatment responses, particularly identification of participants with a rapid rate of disease progression, was an area of focus due to the following considerations:

- Diagnostic plots of the primary endpoint analysis demonstrated that the distribution of the change from baseline in CDR-SB was skewed.
- At the time of the futility analysis, the high-dose treatment arm in Study 301 was unique in that aducanumab-treated patients had greater cognitive decline (15% on CDR-SB) than patients receiving placebo. A credible indication that aducanumab treatment was

accelerating cognitive decline in Study 301 would undermine the results of Study 302. It was therefore particularly important to interrogate the nature of the decline in aducanumab high-dose patients in Study 301.

A graphical review of the data revealed that CDR-SB change from baseline at Week 78 was right-skewed with a small percentage of patients having relatively large increases (Figure 19). Some degree of right-skewness is expected as the mean baseline CDR-SB was approximately 2.5 on a scale that ranges from 0 to 18. Also, the existence of a small proportion of patients with a rapid rate of disease progression has been noted in the literature (Abu-Rumeileh et al. 2018; Schmidt et al. 2012). 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.

Figure 19: Distribution of Change from Baseline in CDR-SB at Week 78 in Pooled Treatment Arms in Studies 301 and 302



Created by reviewer using adqs.xpt

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 except for the high-dose group in Study 301 (Table 34). A similar degree of progression was observed in these patients across the secondary endpoints.

Table 34: Number of Patients with Rapid Progression (CDR-SB Change from Baseline of >8 at Week 78)

	Placebo	Low Dose	High Dose	Total
Study 301	4	5	9	18
Study 302	4	4	5	13

Source: Table 34 in ISE

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 (Table 35). Minor differences were observed at the lower dose in Study 301. Likewise, results of Study 302 were not sensitive to exclusion of rapid progressors (Table 36). The analysis was repeated for other cutoff values to define rapid progressors and the results were similar.

Table 35: Study 301 Change from Baseline in CDR-SB, MMSE and ADAS-Cog13 at Week 78 Excluding Rapid Progressors (CDR-SB Change from Baseline > 8)

	Study 301 (excluding rapid progressors)			Study 301 (ITT)		
	Placebo decline (N=541)	Diff vs. placebo (%)		Placebo decline (N=545)	Diff vs. placebo (%)	
		Low Dose (N=542)	High Dose (N=546)		Low Dose (N=547)	High Dose (N=555)
CDR-SB	1.47	-0.19 (-13%)	-0.09 (-6%)	1.56	-0.18 (-12%)	0.03 (2%)
MMSE	-3.5	0.2 (-6%)	0.1 (-3%)	-3.5	0.2 (-6%)	-0.1 (3%)
ADAS-Cog 13	5.033	-0.607 (-12%)	-0.818 (-16%)	5.140	-0.583 (-11%)	-0.588 (-11%)
ADCS-ADL-MCI	-3.7	0.8 (-22%)	1.0 (-27%)	-3.8	0.7 (-18%)	0.7 (-18%)

Source: Table 3 in Appendix C in ISE

Table 36: Study 302 Change from Baseline in CDR-SB, MMSE and ADAS-Cog13 at Week 78 Excluding Rapid Progressors (CDR-SB Change from Baseline > 8)

	Study 302 (excluding rapid progressors)	Study 302 (ITT)

	Placebo decline (N=544)	Diff vs. placebo (%)		Placebo decline (N=548)	Diff vs. placebo (%)	
		Low Dose (N=539)	High Dose (N=542)		Low Dose (N=543)	High Dose (N=547)
CDR-SB	1.66	-0.29 (-17%)	-0.42 (-25%)	1.74	-0.26 (-15%)	-0.39 (-22%)
MMSE	-3.2	-0.1 (3%)	0.6 (-19%)	-3.3	-0.1 (3%)	0.6 (-18%)
ADAS-Cog 13	4.996	-0.729 (-15%)	-1.335 (-27%)	5.162	-0.701 (-14%)	-1.400 (-27%)
ADCS-ADL-MCI	-4.1	0.7 (-17%)	1.9 (-46%)	-4.3	0.7 (-16%)	1.7 (-40%)

Source: Table 2 in Appendix C in ISE

The applicant investigated potential group- and individual-level factors that may have contributed to the rapid clinical decline in the 31 patients defined as rapid progressors. Demography, baseline disease characteristics, comorbidities, concomitant medication use, imaging biomarkers, and exposure were explored at the group level, but a distinct pattern for rapid progressors did not emerge. There was a trend for lower baseline whole cortex volume, increased lateral ventricle volume, and higher baseline ADA-Cog 13 scores in rapid progressors but there was considerable overlap with the overall population.

Even though the high-dose arm in Study 301 was the only aducanumab-treatment arm with a relatively higher number of rapid progressors, it was important to investigate whether aducanumab treatment itself was the cause of rapid progression. Of the 23 rapid progressors who received aducanumab, 10 had an adverse event of ARIA-E, ARIA-H, or superficial siderosis, although most were mild or moderate and asymptomatic. For the two patients in Study 301 who received high-dose aducanumab and had symptomatic ARIA, the symptoms occurred late in the treatment after significant clinical decline had already occurred. Other AEs were also reviewed, but there was no consistent pattern with respect to rapid 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. With rapid progressors excluded from the analysis, the high-dose aducanumab arm in Study 301 suggests a numerical trend in favor of aducanumab, consistent with every other aducanumab treatment arm. It is also important to note that 8 of the 9 rapid progressors from the high-dose arm in Study 301 were included in the futility data cut. This further casts doubt on the appropriateness of the futility determination, as the numerical trend in favor of placebo over high-dose aducanumab in Study 301 may be due to a small imbalance in rapid progressors rather than a systematic worsening across aducanumab-treated patients.

Influence of ARIA and ARIA Management

The potential impact of ARIA and ARIA management on efficacy results was investigated for the following reasons:

- The occurrence of ARIA has the potential to cause functional unblinding of investigators, patients, and caregivers because ARIA is associated with aducanumab treatment and it prompts differential management of patients
- ARIA management evolved over the course of the studies (see Section 6.1.1)
- An initial review of the data revealed that the number of patients with symptomatic ARIA was higher for the high-dose arm in Study 301 (65) than for the high-dose arm in Study 302 (45)

Functional unblinding was therefore considered a potential explanation for the positive results observed in Study 302. An indication of a systematic bias due to functional unblinding would therefore undermine the strength of Study 302.

The incidence and radiographic severity of ARIA was generally similar between Study 301 and Study 302. A small imbalance in symptomatic ARIA was noted for patients in the high-dose arms and a post hoc analysis suggested that the primary endpoint was sensitive to exclusion of patients with symptomatic ARIA in Study 301. Upon further review, it was determined that this sensitivity was almost entirely due to two patients who were rapid progressors and experienced symptomatic ARIA. As noted in the previous section, rapid clinical decline occurred prior to the occurrence of ARIA in these patients. 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.

Given the similar incidence of ARIA between the two studies, potential unblinding due to ARIA is likely to affect both studies equally. As such, the following analyses are not likely to directly address the discordant results in the two studies but are presented more as sensitivity analyses. It is important to reiterate that steps were taken in the protocol to minimize functional blinding, specifically the use of an independent rater who was blinded to patient management, including occurrence of ARIA and dose modifications. Also, an ARIA incidence of approximately 10% in the placebo arm indicates that an ARIA event does not directly imply unblinding.

To address the potential effect of functional unblinding due to ARIA, the applicant compared the results of the primary analysis using the ITT dataset 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 do not suggest a systematic bias due to functional unblinding (Table 37). The treatment difference for the high-dose arm in Study 302 was higher (33% vs. 22% for CDR-SB) after

excluding observations post-ARIA. It is worth noting that all 4 patients in Study 302 who were rapid progressors and experienced ARIA also received the high-dose. The occurrence of ARIA in these patients tended to happen early in the course of treatment, so exclusion of post-ARIA observations likely influenced this finding. It also demonstrates that rapid progressors can have an outsized effect when interpreting subgroups.

Table 37: Change from Baseline in CDR-SB, MMSE, ADAS-Cog 13 and ADCS-ADL-MCI at Week 78: All Observations vs. Exclusion of Observations Post-ARIA

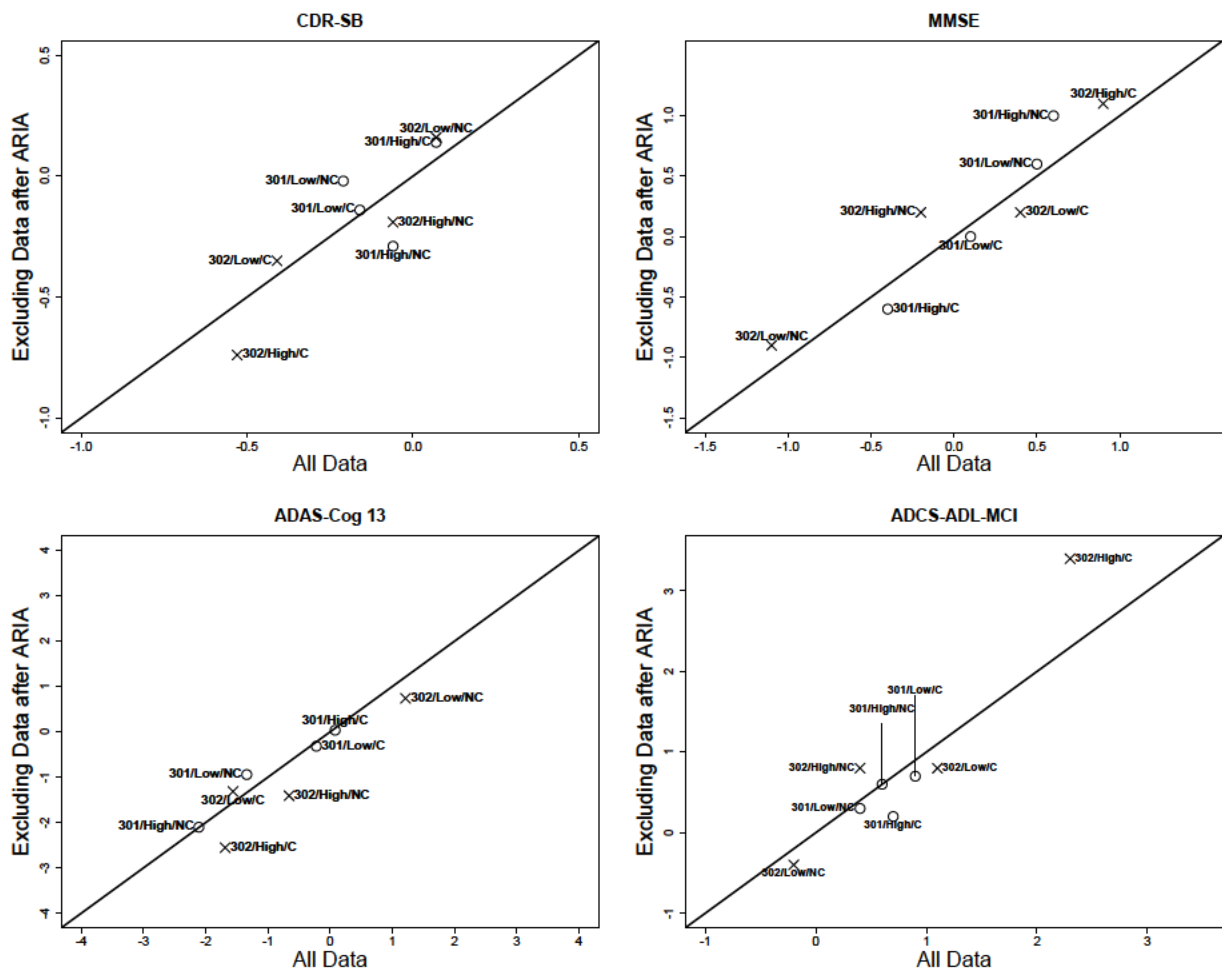
	Study 301			Study 302		
	Placebo decline (N=545)	Diff vs. placebo (%)		Placebo decline (N=548)	Diff vs. placebo (%)	
		Low Dose (N=547)	High Dose (N=555)		Low Dose (N=543)	High Dose (N=547)
CDR-SB						
All observations	n=333 1.56	N=331 -0.18 (-12%)	N=295 0.03 (2%)	N=288 1.74	N=290 -0.26 (-15%)	N=299 -0.39 (-22%)
Post-ARIA observations excluded	n=298 1.55	N=240 -0.11 (-7%)	N=181 0.00 (0%)	N=254 1.72	N=194 -0.19 (-11%)	N=172 -0.57 (-33%)
MMSE						
All observations	N=332 -3.5	N=334 0.2 (-6%)	N=297 -0.1 (3%)	N=288 -3.3	N=293 -0.1 (3%)	N=299 0.6 (-18%)
Post-ARIA observations excluded	N=297 -3.6	N=242 0.2 (-6%)	N=182 -0.1 (3%)	N=254 -3.4	N=195 -0.1 (3%)	N=172 0.8 (-24%)
ADAS-Cog 13						
All observations	N=331 5.140	N=332 -0.583 (-11%)	N=294 -0.588 (-11%)	N=287 5.162	N=289 -0.701 (-14%)	N=293 -1.400 (-27%)
Post-ARIA observations excluded	N=296 5.143	N=240 -0.507 (-10%)	N=180 -0.669 (-13%)	N=254 5.306	N=193 -0.628 (-12%)	N=169 -2.193 (-41%)
ADCS-ADL-MCI						
All observations	N=331 -3.8	N=330 0.7 (-18%)	N=298 0.7 (-18%)	N=283 -4.3	N=286 0.7 (-16%)	N=295 1.7 (-40%)
Post-ARIA observations excluded	N=296 -3.6	N=239 0.5 (-14%)	N=183 0.3 (-8%)	-4.3	N=190 0.5 (-12%)	N=171 2.6 (-60%)

Source: Table 33 in ISE and Output # 128, 129 and 130 in ISE Appendix F

The applicant also assessed the treatment effect at Week 78 for groups defined by dose, study, and ApoE ε4 carrier status including and excluding observations after occurrence of ARIA. The results are presented graphically in Figure 20. If a systematic bias were present, one would expect the points to consistently fall on one side of the line of unity. Instead, the results show an even scatter around the line of unity, suggesting no systematic bias due to ARIA.

The potential impact of ARIA is inherently confounded with dosing through protocol-specified dose modifications due to ARIA. Therefore, it is challenging to independently assess the impact of ARIA and dosing. Approaches to address the potential effect of dosing on outcomes will be further discussed in the following section.

Figure 20: Treatment Effect Estimate of Change from Baseline in CDR-SB, MMSE, ADAS-Cog 13 and ADCS-ADL-MCI at Week 78 Grouped by Study, Dose, and ApoE Carrier Status, and Including or Excluding Post-ARIA Observations. (× - Study 302, o – Study 301, C – carrier, NC – non-carrier; solid line is line of unity)



Created by reviewer using output # 219-226 in ISE Appendix F

Influence of Dosing

Dosing was an obvious area of investigation to understand the discordant results for the high dose arms between Study 301 and Study 302. The critical role of dosing for amyloid-targeting therapies became increasingly evident during the aducanumab clinical program. The lack of adequate dosing was acknowledged as a contributing factor to the failure of previous clinical trials.

The importance of dose was also directly established in the aducanumab program by Study 103 which demonstrated a dose-dependent reduction in brain amyloid and reduction of decline on clinical outcome measures.

The motivation to investigate the potential importance of dosing in the interpretation of Studies 301 and 302 is further supported by the conduct of these clinical studies, including the following considerations:

- The protocols for Studies 301 and 302 were amended twice during the studies to increase the dose or to allow for patients to continue dosing after occurrence of ARIA:
 - Protocol Version 3 modified ARIA management rules so that patients were more likely to be able to continue dosing or achieve target dose levels.
 - Protocol Version 4 increased the target dose for ApoE ϵ 4 carriers in the high-dose arm from 6 mg/kg to 10 mg/kg.
- 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.
- The timing of the protocol amendments was such that patients enrolled later in the studies were more likely to achieve higher aducanumab exposures.

In fact, before any investigation of the results of Studies 301 and 302 began, the Division asked the applicant about the role of dosing in preliminary comments to the June 14, 2019, Type C Meeting.

Dosing in Studies 301 and 302

One challenge in comparing dosing over time or between studies is identifying an appropriate dosing metric. Steady-state is achieved after 4 consecutive doses and dose interruptions can have long-term consequences on amyloid reduction (Figure 17). There was also heterogeneity in the dosing profiles due to changes in the protocol and dose modifications due to adverse events. It may be possible that achieving consistent exposure early in the study is more important than reaching the target dose later in the study. It is worth noting that patients receiving lower doses had more consistent dosing compared to patients receiving higher doses.

For these reasons, multiple measures of dosing were characterized, including cumulative dose, number of doses at target dose, and number of uninterrupted doses at target dose.

Through the implementation of protocol amendments, exposure to aducanumab increased over the course of Studies 301 and 302. Protocol Version 3 modified ARIA management rules so that patients who experienced ARIA were more likely to continue dosing or achieve target dose levels. Protocol Version 4 increased the target dose for all ApoE ϵ 4 carriers in the high-dose arm from 6 mg/kg to 10 mg/kg. To quantify the actual increase in dose due to these protocol amendments, patients were dichotomized into groups based on the timing of their consent to Protocol Version 4 or higher prior to Week 16 (i.e., Pre-PV4 or Post-PV4). Week 16 was chosen because patients who consented by this time had the opportunity to receive all 14 doses of 10 mg/kg according to the protocol amendment. The mean cumulative dose received up to Week 78 for the high-dose arms was lower in the Pre-PV4 group (104.4 mg/kg in Study 301 and 109.5 mg/kg in Study 302) compared to the Post-PV4 group (129.8 mg/kg in Study 301 and 127.8 mg/kg in Study 302). As expected, the mean cumulative dose received up to Week 78 was similar in the Pre-PV4 (58.8 mg/kg in Study 301 and 59.9 mg/kg in Study 302) and Post-PV4 (59.8 mg/kg in Study 301 and 57.8 mg/kg in Study 302) groups for the low-dose arms because Protocol Version 4 did not change dosing for the low-dose arms. In the high-dose arms, the mean number of 10 mg/kg doses received up to Week 78 was lower in the pre-PV4 groups (6.5 in Study 301 and 7.3 in Study 302) compared to the post-PV4 groups (10.8 in Study 301 and 10.5 in Study 302).

Due to the timing of the initiation of the studies and the pace of enrollment, more patients in Study 302 were able to benefit from the amendments in Protocol Versions 3 and 4 (81.3% and 55.9%, respectively) compared with patients in Study 301 (73.4% and 49.1%, respectively). For example, the mean cumulative dose received up to Week 78 in the high-dose arms was 114.7 mg/kg in Study 302 compared with 110.6 mg/kg in Study 301. The difference between studies is more evident at the extremes where 100 patients in Study 302 received all 14 doses of 10 mg/kg compared to 82 in Study 301. The difference in dosing between studies is smaller than the difference in dosing over time in the studies as described in the previous paragraph.

The potential impact of differences in dosing between studies is evident in the amyloid PET analysis populations. The mean cumulative dose received up to Week 78 was higher in the high-dose arm of Study 302 (118.3 mg/kg) compared to Study 301 (109.1 mg/kg). This relatively small difference in dosing corresponded with a 16% smaller reduction in brain amyloid at Week 78 in Study 301 (-0.232) compared to Study 302 (-0.278). It is also noteworthy that the CSF biomarker changes for the high-dose arm in Study 301 were consistently smaller than the changes observed in Study 302 (see Sections 6.1.2 and 6.2.2).

Response in Dosing Subgroups Based on Stratified Randomization

Modifications in dosing due to protocol changes, ApoE ϵ 4 status, and ARIA management suggest that randomized dose (i.e., low or high) does not fully capture the level of aducanumab exposure. To further investigate the relationship between dose and response, subgroups were formed for each study based on stratified randomization (low/high dose and ApoE ϵ 4 carrier/non-carrier) and by enrollment (Pre-PV4 vs. Post-PV4) to form a total of 16 distinct groups (Table 38). The advantage of this approach is that it largely preserves randomization and the primary analysis method can be used when estimating treatment differences. Mean cumulative dose at Week 78 was calculated for patients in each subgroup. The expected cumulative dose at Week 78 assuming no dose interruptions is 56 mg/kg, 98 mg/kg, and 160 mg/kg for randomized target dose levels of 3 mg/kg, 6 mg/kg, and 10 mg/kg. The 16 randomized groups were categorized as low, medium, or high in Table 38 and roughly correspond with the target levels. Using this categorization, it becomes evident that some groups in the randomized high-dose arms (i.e., pre-PV4 ApoE ϵ 4 carriers) achieved actual aducanumab dosing similar to groups randomized to the low dose (i.e., ApoE ϵ 4 noncarriers).

Table 38: Dosing in Subgroups Defined by Study, Randomized Dose Group, ApoE ϵ 4 Status, and Pre- and Post-Protocol Version 4

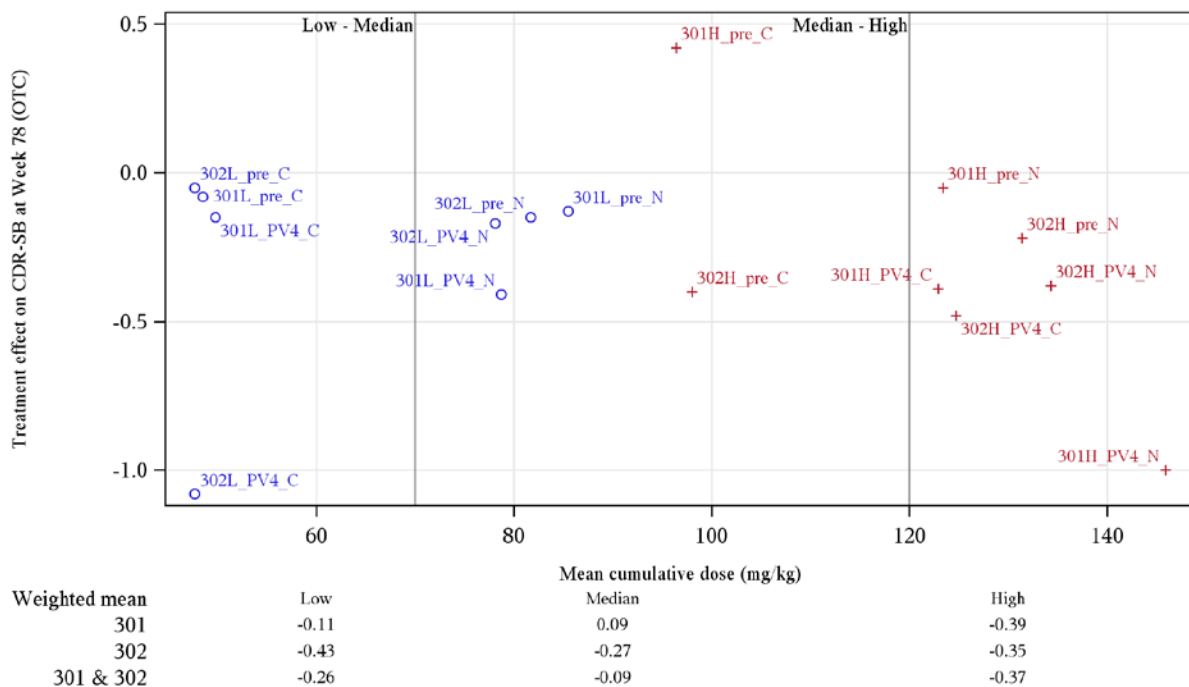
Dosing Regimen (Study/Dose/Protocol Version/ApoE ϵ 4 status)	Mean Cumulative Dose at Week 78 (mg/kg)	Exposure Categorization
301 high pre-PV4 carrier	96.4	Medium
301 high post-PV4 carrier	122.9	High
301 high pre-PV4 non-carrier	123.4	High
301 high post-PV4 non-carrier	145.9	High
302 high pre-PV4 carrier	98.0	Medium
302 high post-PV4 carrier	124.7	High
302 high pre-PV4 non-carrier	131.4	High
302 high post-PV4 non-carrier	134.3	High
301 low pre-PV4 carrier	48.5	Low
301 low post-PV4 carrier	49.8	Low
301 low pre-PV4 non-carrier	85.5	Medium
301 low post-PV4 non-carrier	78.7	Medium
302 low pre-PV4 carrier	47.7	Low
302 low post-PV4 carrier	47.7	Low
302 low pre-PV4 non-carrier	81.7	Medium
302 low post-PV4 non-carrier	78.1	Medium

Adapted from Table 38 in ISE
PV=Protocol Version

Mean differences of CDR-SB between aducanumab treatment and placebo were calculated for each of the 16 subgroups listed in Table 38 and are plotted against mean cumulative dose in Figure 21. The relationship between mean cumulative dose and treatment effect is weak with considerable variability between the groups. On the other hand, it is noteworthy that the weighted mean treatment effect among randomized groups from Study 301 in the “high”

exposure category is -0.39. This estimate is consistent with the weighted mean estimate from Study 302 in the “high” exposure category (-0.35) and with the primary analysis of the high-dose arm Study 302 in (-0.39). These results suggest that groups of patients in Study 301 who had the opportunity to receive higher exposure to aducanumab show a response to aducanumab treatment similar in character to Study 302.

Figure 21: Treatment Difference in CDR-SB at Week 78 Vs. Mean Cumulative Dose by Study, Randomized Dose Group, ApoE ε4 Carrier Status, and Protocol Version



Source: Figure 41 in ISE

Notes: Blue circles are groups randomized to low dose. Red + are groups randomized to high dose. The label for each point represents the study, dose (L = low, H = high), Protocol Version (pre = pre-PV4, PV4 = post-PV4), ApoE ε4 status (C = carrier, N = non-carrier).

Response in Dosing Subgroups Based on Individual Dosing

Within the randomized subgroups presented in the previous section there may still be meaningful heterogeneity with respect to individual aducanumab dose or exposure. Therefore, in a separate analysis, subgroups were defined by levels of individual aducanumab dosing. Analyses were conducted on the subset of patients who had the opportunity to complete 78 weeks of treatment so as not to confound cumulative dosing with time in the study. A disadvantage of this approach, however, is that it primarily includes patients enrolled early in the study and does not fully address changes in exposure that occurred over time. The purpose of the following analyses was to test the hypothesis that patients in Study 301 who were exposed to higher levels or doses of aducanumab were more likely to show benefit. An initial

view of the data (Table 39) from the high-dose arm in Study 301 suggests a trend between increasing cumulative dose and numerically greater treatment difference vs. placebo. Placebo here corresponds to the overall placebo response.

Table 39: Treatment Difference in CDR-SB at Week 78 by Cumulative Dose Threshold for High Dose in Study 301

Cumulative Dose Threshold (mg/kg)	Number of Subjects	Treatment Difference vs. Placebo
< 100*	401	-4%
≥ 100	223	4%
≥ 110	206	1%
≥ 120	178	-6%
≥ 130	157	-10%
≥ 140	133	-14%
≥ 150	98	-24%
≥ 160	75	-30%

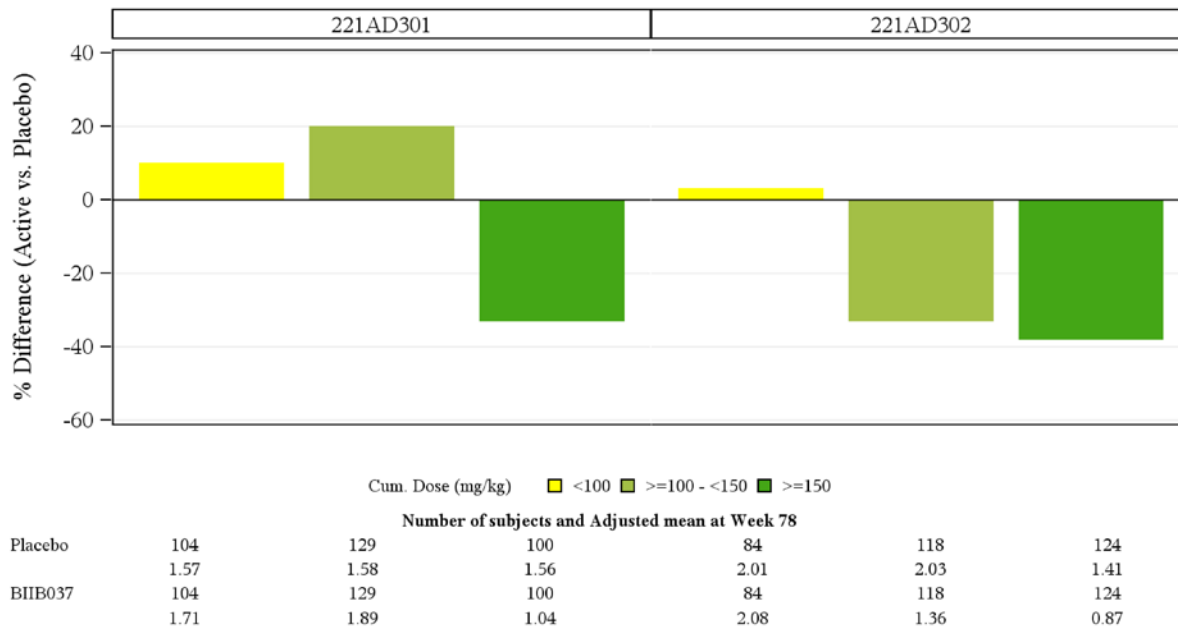
Source: Appendix G7 Table 16 in ISE

* Patients in high dose were combined with low dose group

A limitation of this approach is that subgroups are created by post-randomization outcomes (i.e., cumulative dose) and may not be balanced on other relevant factors. For example, the ≥160 mg/kg group in Table 39 is made up of approximately 75% ApoE ε4 non-carriers whereas the overall placebo group is approximately 33% ApoE ε4 non-carriers. Therefore, a propensity score matching analysis was used to balance placebo and aducanumab groups on baseline demographic and disease characteristics. To explore the relationship between individual aducanumab dosing within the high-dose arm and treatment response, three independent groups of low, intermediate, and high exposure were formed. Three groups were chosen so that each group included approximately ≥100 aducanumab-treated patients.

The treatment differences at Week 78 for CDR-SB between aducanumab and propensity score matched placebo subgroups based on cumulative dose are illustrated in Figure 22. The results for Study 302 show the expected pattern with subgroups exposed to higher cumulative doses exhibiting the largest treatment effect and the subgroup with limited exposure showing a response similar to placebo. For Study 301, the high cumulative dose subgroup performs similarly to Study 302. The discrepancy is primarily in the intermediate exposure subgroup which appears to show an advantage of placebo over aducanumab. Dosing cannot explain this observation.

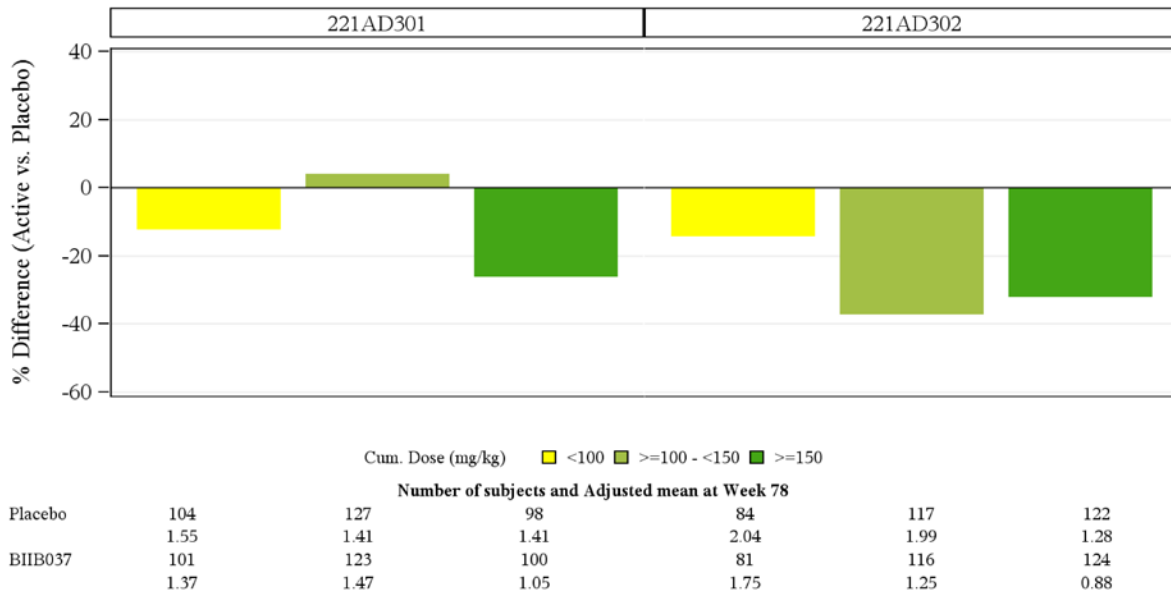
Figure 22: CDR-SB Adjusted Mean Change from Baseline % Difference from Propensity-Matched Placebo at Week 78 in Subgroups by Cumulative Dose in Studies 301 and 302



Source: Figure 52 in ISE
* BIIB037 refers to aducanumab

Previous analyses have demonstrated the outsized effect rapid progressors can have on interpretation of treatment differences. This effect is also notable when interpreting subgroups of data. Figure 23 shows the results of the same analyses, but with the rapid progressors removed. Again, the high cumulative dose group in Study 301 continues to indicate a favorable response to aducanumab treatment in line with the corresponding group in Study 302. This finding is robust to the existence of rapid progressors. Instead of showing a favorable response for placebo compared to aducanumab, the intermediate exposure group indicates a response similar to placebo.

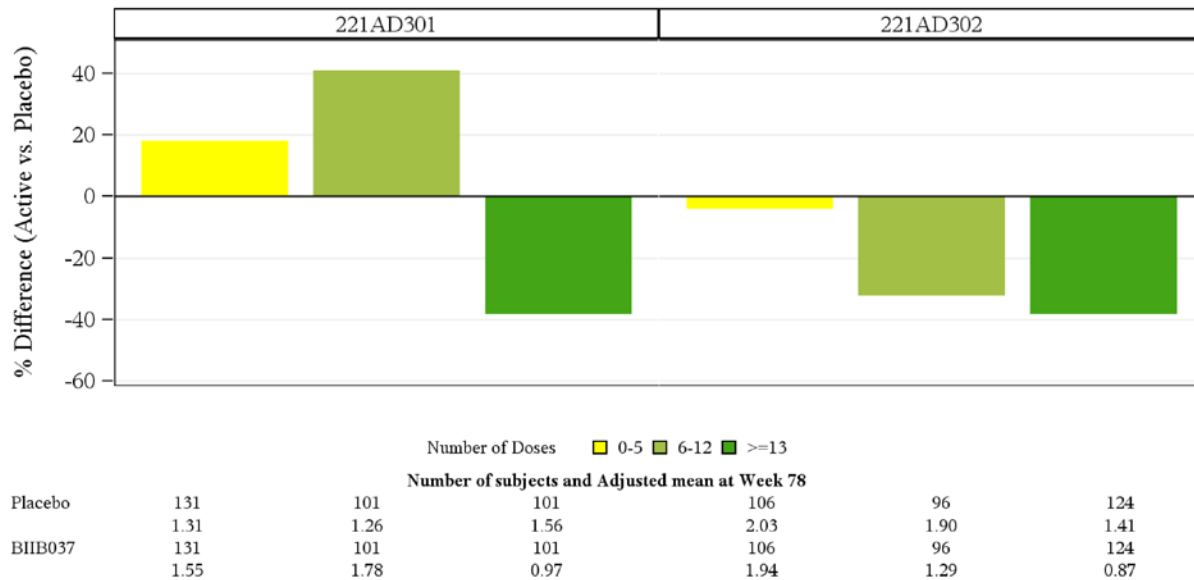
Figure 23: CDR-SB Adjusted Mean Change from Baseline % Difference from Propensity-Matched Placebo at Week 78 in Subgroups by Cumulative Dose in Studies 301 and 302 (Rapid Progressors Removed)



Source: Figure 53 in ISE
* BIIB037 refers to aducanumab

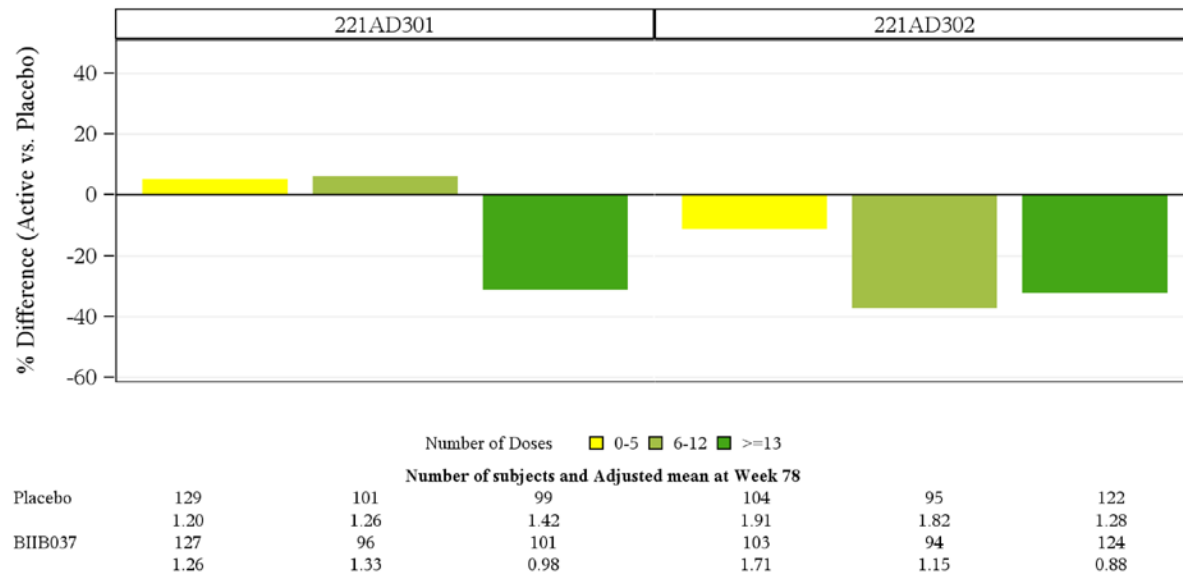
The same analyses were also performed using the number of uninterrupted steady-state doses at 10 mg/kg and the number of doses at 10 mg/kg without regard for interruption as the dosing metrics. These results showed a similar pattern to results using the cumulative dose. using the number of doses at 10 mg/kg without regard for interruptions are illustrated in Figure 24 and Figure 25 (with rapid progressors removed).

Figure 24: CDR-SB Adjusted Mean Change from Baseline % Difference from Propensity-Matched Placebo at Week 78 in Subgroups by Number of 10 mg/kg Doses in Studies 301 and 302



Source: Figure 49 in ISE
* BIIB037 refers to aducanumab

Figure 25: CDR-SB Adjusted Mean Change from Baseline % Difference from Propensity-Matched Placebo at Week 78 in Subgroups by Number of 10 mg/kg Doses in Studies 301 and 302 (Rapid Progressors Removed)



Source: Figure 50 in ISE
* BIIB037 refers to aducanumab

It is noteworthy that the treatment difference observed in the high exposure group in Study 301 does not appear to be driven by the placebo response. The adjusted mean change from baseline in this group in Study 301 is approximately 1 unit, similar to the approximately 0.88 change observed in Study 302. It is still possible that patients in the high exposure group in Study 301 have other characteristics not considered in the propensity score analysis that make them more likely to have a favorable response. For example, the fact that they remained in the study and received most of their expected doses might also make them more likely to be responders. As a supplementary analysis, only placebo patients in the per-protocol population (i.e., received $\geq 70\%$ expected infusion) were included in the propensity matching pool. A favorable treatment effect was still observed in the high exposure group in Study 301.

The difference in dosing between the two studies is also illustrated in Figure 24. A total of 124 patients in Study 302 received ≥ 13 doses of 10 mg/kg compared to 101 patients in Study 301. Conversely, more patients (131) in Study 301 received 0-5 doses of 10 mg/kg compared to Study 302 (106 patients). As noted before, this difference in dosing between studies is modest. Simple arithmetic calculations suggest that if dosing in Study 301 had been similar to Study 302, the overall treatment effect from the primary analysis in Study 301 would only improve by 1-2%.

The primary discrepancy between Study 301 and Study 302 in these analyses is the group of patients with cumulative dose or number of 10 mg/kg doses in the intermediate range. It is worth noting that this group includes the most heterogeneity in terms of dosing profiles. Even with this heterogeneity, pharmacokinetic and PET data indicate that the aducanumab exposure and amyloid reduction in this subgroup are in excess of observations in the low-dose arm in the study. Therefore, if one accepts that the low doses in Studies 301 and 302 consistently demonstrate a numerical effect in favor of aducanumab, one expects to observe at least a numerically favorable outcome in this intermediate exposure subgroup in Study 301. Given the multitude of findings suggesting a dose-response relationship and a directionally favorable effect of aducanumab, the fact that this is not the case in this one subset raises the possibility that this observation may simply be due to chance or some other unknown factor unrelated to aducanumab.

Overall, the analyses on dose indicate the following:

- Dosing is an important consideration for interpretation of the efficacy result of aducanumab in Studies 301 and 302
- Patients in Study 301 with higher exposure to the 10 mg/kg dose demonstrated treatment effects similar to patients in Study 302
- Lower exposure to the target dose of 10 mg/kg in Study 301 was a small but contributing factor for the discordant results with Study 302. Factors other than dosing may also contribute to the difference

It may be tempting to misinterpret the considerations presented in Section 7.1.7 as “explaining why Study 301 was negative.” This was not the intention of this work and such an explanation is not necessary to establish the effectiveness of aducanumab. At the June 14, 2019, Type C Meeting, the Division clearly stated that, “available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness supporting the approval of aducanumab.” Rather, the Division noted that analyses “may have a role in supporting the results of Study 302,” or “may be understood well enough... to not represent evidence that the drug is ineffective.” The analyses presented in this section are exploratory by design but limited in scope and focused on pre-defined areas of interest. The rapid progressor analysis indicated that a small imbalance in the number of rapid progressing patients in the high-dose arm in Study 301 had a disproportionate impact on the estimate of the treatment effect using the primary analysis method. An examination of dosing in Study 301 indicates that patients with higher exposure to the 10 mg/kg dose in Study 301 had similar responses to patients in Study 302. These two factors contribute to the overall understanding of Study 301 and together indicate that the results of Study 301 do not meaningfully detract from the persuasiveness of Study 302. There were no findings from the exploration that represented evidence that aducanumab is clearly not effective.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The population enrolled in Studies 103, 301, and 302 did not include patients at either end of the Alzheimer’s disease continuum and there is some uncertainty with respect to the generalizability of benefit across the entire spectrum of Alzheimer’s disease. There is a general expectation, however, that initiating treatment with an anti-amyloid agent earlier in the disease, before detectable functional impairment (i.e., Stage 1 and Stage 2), may provide the best opportunity to delay or halt the pathophysiological processes that lead to the clinical deficits of Alzheimer’s disease. Intervention with an anti-amyloid therapy later in the disease, in patients with moderate and severe dementia, may be expected to provide less benefit, as downstream pathological processes may dominate. The application does not contain clinical data in either population to directly assess the effectiveness of aducanumab at either end of the disease continuum. On the other hand, Alzheimer’s disease is defined in part by the presence of amyloid pathology, and the pharmacodynamic effect of aducanumab on reduction of brain amyloid plaque should occur across the disease continuum, providing the potential for clinical benefit.

One patient population with Alzheimer’s disease not explicitly studied in the aducanumab program is individuals who have a mutation that causes dominantly inherited Alzheimer’s disease (DIAD). This population was not specifically excluded from enrollment, but the number

of individuals with DIAD enrolled in the studies is too small to draw any conclusions in this subgroup. Current clinical trials in this patient population typically target an early stage of the disease, before functional impairment, so the considerations for Stage 1 and Stage 2 discussed above apply.

Individuals with Down syndrome represent another important population which might also benefit from treatment with aducanumab. Alzheimer's disease pathophysiology in individuals with Down syndrome is likely driven by an overexpression of the gene for amyloid precursor protein located on chromosome 21, thus the pathology in this population is similar to that found in DIAD and sporadic Alzheimer's disease. One challenge is assessing changes in cognition and function in a population with intellectual disability. Also, people with Down syndrome have a higher incidence of cerebral amyloid angiopathy, which is associated with development of microhemorrhages. Additional safety data would be helpful to inform risk-benefit considerations in this population.

7.3. Integrated Assessment of Effectiveness

Taken together, the evidence supporting the effectiveness of aducanumab is highly persuasive. In short, this evidence is provided in large part by Study 302, which provides important context for an additional and not insubstantial contribution from Study 103. The results of Study 301 are sufficiently well understood that they do not preclude independent consideration of the results of Study 302 and 103.

In order to consider the evidence provided by Study 302 and Study 301, it was first necessary to assess the impact of early termination of the nearly completed studies on interpretability of the observed efficacy data and associated analyses. Modeling and simulation analyses were used to rigorously evaluate the likely outcomes of the studies had they been run to completion. The results of these analyses indicated that the simulation results were highly consistent with the primary analysis of the observed data, establishing the interpretability of the studies and the appropriateness of the observed data prior to early termination for further consideration. Accordingly, Study 302, analyzed in accordance with the prespecified analysis, and supported by multiple additional analyses, is a strongly positive study.

The effect of the high dose of aducanumab in Study 302 is robust and exceptionally persuasive on several of the instruments used to evaluate efficacy. It provides highly persuasive results on the prespecified primary endpoint intended to establish effectiveness and on the prespecified secondary endpoints and exploratory tertiary endpoint, including particularly persuasive results on secondary endpoints which themselves represent an acceptable approach to establishing effectiveness. Its findings are robust to numerous sensitivity analyses and are strongly supported by highly consistent findings in prespecified subgroups and well-characterized biomarker data. Simulations suggest the probability of observing this pattern of results if aducanumab is no different than placebo is extremely small. Beneficial effects on clinical

measures are further supported by evidence suggesting a dose-response relationship on clinical outcomes and by evidence of a dose- and time-dependent relationship on biomarkers of fundamental Alzheimer's disease pathophysiology, including brain amyloid burden, the primary direct marker of aducanumab's intended mechanistic effect. In short, when considered individually, Study 302 is an exceptionally persuasive study and has many characteristics indicating that it is capable of independently providing substantial evidence of effectiveness.

The results of Study 103 provide additional data addressing the effectiveness of aducanumab. Although designed to primarily assess safety and tolerability rather than effectiveness and uncontrolled for multiplicity, the 10 mg/kg dose arm was able to achieve statistical significance according to the prespecified analysis plan on both of the clinical efficacy outcomes assessed. A supplementary analysis of Study 103 using the same primary analysis method that was used in Studies 301 and 302 provides similar efficacy results for the 10 mg/kg dose arm and is supportive of the prespecified findings. Further, the dose-response relationship for A β reduction provides support for the positive 10 mg/kg efficacy findings and is consistent with the dose-response relationship observed for the efficacy outcome measures. The design of Study 103 was consistent with Study 302 in several aspects, including choice of clinical and biomarker outcome assessments. Clinical effects in the 10 mg/kg dose arm in Study 103 and the high dose arm in Study 302 favored aducanumab and biomarker effects in those arms were similar. In the context of the results of Study 302, the results of Study 103 are appropriately viewed as an additional and supportive contribution to substantial evidence of effectiveness.

With Study 302 capable of providing the primary contribution and Study 103 capable of providing an additional contribution to a demonstration of substantial evidence of effectiveness, it is important to understand Study 301 in depth in order to decide if Study 301 detracts from the persuasiveness of that evidence, with particular attention to the evidence provided by Study 302, given that it shares its design with Study 301. An important initial observation of Study 301 is that primary and secondary endpoints for the low dose had responses that were numerically favorable and similar in magnitude to those in Study 302. The response of the high dose was the notable difference between the studies. Explorations of demographic and baseline characteristics and the incidence of ARIA did not reveal differences that could be responsible for the difference in high dose results. An exploratory analysis of rapid progressors indicated that a small imbalance in the number of rapid progressing patients in the high-dose arm in Study 301 had a disproportionate impact on the estimate of the treatment effect using the primary analysis method. An examination of dosing in Study 301 indicates that patients with higher sustained exposure to the 10 mg/kg high dose in Study 301 had similar responses to patients in Study 302. The results of these exploratory analyses contribute to the overall understanding of Study 301 and together do not meaningfully detract from the persuasiveness of Study 302. Study 301 does not provide evidence of effectiveness for clinical outcomes but does provide important information on the effect of aducanumab on amyloid reduction.

Based on the considerations above, the applicant has provided substantial evidence of effectiveness to support approval. Study 302 provides the primary evidence of effectiveness as a robust and exceptionally persuasive study demonstrating a treatment effect on a clinically meaningful endpoint and reinforced by effects on secondary endpoints, biomarkers, and in relevant subgroups. Study 103 was an adequate and well-controlled study which included design components consistent with Study 302 and demonstrated a persuasive treatment effect on both clinical endpoints, providing additional and supportive evidence of effectiveness. The dose-response relationship for A β reduction provides support for the positive finding in the 10 mg/kg treatment arm and to the dose-related effects observed on clinical outcomes in Studies 103 and 302.

8. Review of Safety

Please see the separate safety reviews by Drs. Branagan and Trummer.

9. Advisory Committee Meeting and Other External Consultations

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

The official summary minutes of the meeting are publicly available². 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

² See Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting, dated January 26, 2021, available at <https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting>

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 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)

The Advisory Committee meeting was one of the first such meetings held by teleconference due to the COVID-19 pandemic. It is likely that an in-person meeting would have allowed the applicant and review team greater opportunity to address questions and concerns raised by committee members. Despite active participation by several patients, caregivers, and patient advocates in the open public hearing session, the patient perspective was not fully explored by the committee. Putting aside anecdotal experience with aducanumab, several consistent messages emerged and are consistent with feedback FDA has received from patient groups in other venues. Patients, caregivers, and patient advocates were clear-eyed that an approved new drug does not imply a cure for the disease and may not be the perfect drug for everyone. On the contrary, most stressed the importance of taking steps to slow the disease. A few speakers also noted the importance of activities of daily living and not becoming a burden to family members. The main theme was the importance of time, including time with preserved cognition. A few speakers also noted that the 4- or 5-years' worth of time it would take to perform another clinical trial represent time of continued progression and lost abilities and lost memories for many.

Responses and rebuttals to the points raised by committee members are contained within in the body of this review. There are a few areas which deserve special attention and are discussed in greater detail below.

Context for the Aducanumab Development Program Given Previous and Ongoing Anti-Amyloid Development Programs

In their commentary (Alexander et al. 2021), three of the panel members note that, "more than 25 negative RCTs have tested the 'amyloid cascade hypothesis,' and thus the observed discordance between study 302 and study 301 is consistent with a type I error." This statement implies that previous studies are interchangeable with the aducanumab studies or, at the very least, are particularly informative for the outcomes of Studies 301 and 302 because they are essentially testing the same thing (i.e., the "amyloid cascade hypothesis"). But consider, for example, an agent which binds to different form of amyloid than aducanumab, was studied at a low dose which did not demonstrate an effect on biomarkers, and was administered to a later disease population in which a significant proportion of the population did not even have brain amyloid. Or consider a molecule targeting the formation of amyloid beta in a population that already has established amyloid plaques and neurofibrillary tangles. Are these examples truly

relevant for the evaluation of aducanumab just because it is convenient to refer to them all as “anti-amyloid” therapies? Informative priors should be based on a careful understanding of pharmacology, disease progression, patient population, and trial design. A more relevant prior for the aducanumab trials is represented by a controlled study in patients with early Alzheimer’s disease of an agent that targets aggregated forms of brain amyloid at dose levels which demonstrate a robust removal of brain amyloid plaque. It turns out that there are two current anti-amyloid agents which fit this description: donanemab and BAN2401 (gantenerumab currently has only open-label experience at doses high enough to substantially remove amyloid plaque in an early Alzheimer’s disease population). The authors of the commentary were either unaware of these examples or chose to exclude them. Although each study has its own limitations, the clinical studies of donanemab and BAN2401 have been associated with treatment effects on clinical endpoints similar in magnitude and character to those observed in Studies 302 and 103.

Type I and Type II Error Considerations

The committee’s discussion was focused on the possibility of a Type I error and included debates and commentary about the appropriate p-value for Study 302 (0.01 vs. 0.02) and the approach to control for Type I error for the secondary endpoints in Study 302. Consideration of the possibility of a Type II error primarily fell to one of the open public hearing speakers who astutely noted the rather pessimistic odds quoted in the statistical review (62% posterior probability of the alternative hypothesis) but still noted, “we’ll take those odds now.” In the context of the favorable results observed in Study 302, Study 103, and the donanemab and BAN2401 studies, it is entirely reasonable to conclude that the results for the high dose in Study 301 (actually, only the Pre-PV4 portion of the study) are in fact consistent with a Type II error. Clinical trial simulations performed by OCP show the probability of observing the overall positive results in the aducanumab program under the null assumption that aducanumab is the same as placebo is extremely low. In the context of an approval decision, the cost of committing a Type II error (i.e., falsely concluding that aducanumab is not effective) in the population is clear. Over the 4 to 5 years needed to conduct another study, an entire new cohort of patients with cognitive impairment due to Alzheimer’s disease will continue to lose cognitive and functional abilities without an opportunity to meaningfully slow their disease.

Rationale and Potential Implications of Exploratory Analyses of Studies 301 and 302

Several committee members viewed the exploratory analyses of Studies 301 and 302 as accepting Study 302 as the truth and searching for explanations for the negative results of the high dose in Study 301. For example, one committee member explained his vote by noting that it was not possible to, “transform that [Study 301] into a positive study using post hoc analysis.” This review has noted the risks involved in performing post hoc analyses and has never suggested that these analyses were intended to salvage Study 301. More importantly, the results of these planned analyses very well could have *undermined* the positive results of Study 302. For example, if an apparent effect of functional unblinding on the results of Study 302 had

been evident, this would have significantly diminished the persuasiveness of Study 302. If there had been a small imbalance in the number of highly influential subjects (e.g., rapid progressors) in the high dose of Study 302, and if removal of these few subjects changed the treatment effect estimate, surely this would have raised serious concerns about the reliability of the overall positive results. Serious doubts would also have been raised if an exposure-response relationship in Study 301 had not been found, or if subjects in that study who received sustained dosing with 10 mg/kg did not appear to have outcomes similar to the high-dose arm in Study 302. Ultimately, these types of results were not observed. In contrast, the results of these analyses were more consistent with the presence of a Type II error.

Role of Study 103

Most committee members appeared to embrace the suggestion in Appendix II of the Advisory Committee Briefing Document that Study 103 was given more weight than Study 301 or was presented as a replacement for that study. The opinion of this review, however, is that despite not being designed as a registration trial, data from Study 103 are important and are most appropriately viewed as supportive evidence of effectiveness. The observation that sensitivity analyses may have changed the p-value from $p=0.04$ to $p=0.09$ is not as critical as the fact that the treatment effect remained consistent or the finding of a dose-response relationship.

The Advisory Committee also suggested that if the results of this study had been negative that Studies 301 and 302 would never have been performed. They may not be aware that historically, a positive Phase 2 trial (or Phase 1b as Study 103 has been characterized) has not been a prerequisite for sponsors to decide to proceed to Phase 3 trials in Alzheimer's disease. In fact, the mere *existence* of a Phase 2 trial has often not been a prerequisite for sponsors to decide to proceed with Phase 3 trials in Alzheimer's disease drug development.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been proposed, but the labeling has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Please see the separate safety reviews by Drs. Branagan and Trummer for considerations regarding a REMS.

12. Postmarketing Requirements and Commitments

Post-marketing requirements and/or commitments are still under discussion at the time of this review.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 103, 301, and 302

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: <u>>4500</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>16</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>16</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

KEVIN M KRUDYS
06/07/2021 09:41:02 AM

Clinical Review (ARIA)
 Brian Trummer, MD, PhD
 BLA761178
 Aduhelm/aducanumab

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761178
Priority or Standard	Priority
Submit Date(s)	July 7, 2020
Received Date(s)	July 7, 2020
PDUFA Goal Date	June 7, 2021
Division/Office	DN1
Reviewer Name(s)	Brian Trummer, MD, PhD
Review Completion Date	June 6, 2021
Established/Proper Name	Aducanumab
(Proposed) Trade Name	Aduhelm
Applicant	Biogen
Dosage Form(s)	Injection, intravenous
Applicant Proposed Dosing Regimen(s)	10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks
Applicant Proposed Indication(s)/Population(s)	Patients with Alzheimer's disease
Recommendation on Regulatory Action	This review of ARIA does not result in findings that would preclude approval if efficacy is demonstrated.
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of Alzheimer's disease

Executive Summary

Treatment with monoclonal antibodies targeting A β , including aducanumab, can result in Amyloid Related Imaging Abnormalities (ARIA), that are categorized as vasogenic edema (ARIA-E) and hemosiderin deposition (ARIA-H), which consists of cerebral microhemorrhage, superficial siderosis, and cerebral hemorrhage. ARIA was identified as an adverse event of special interest in the aducanumab development program. Because 10 mg/kg is the proposed maintenance dose of aducanumab, the analyses in this review will largely focus on that dose. In the placebo-controlled portion of studies 301 and 302, any occurrence of ARIA (ARIA-E and/or ARIA-H) was observed in 41% of patients who received aducanumab 10 mg/kg and in 10% of patients who received placebo. Clinical symptoms occurred in 24% of patients who had an observation of ARIA in the 10 mg/kg aducanumab treatment arm and 5% of patients who had an observation of ARIA on placebo. ARIA-E (with or without co-occurrence of ARIA-H) was observed in 35% of the 10 mg/kg aducanumab treated group, compared to 3% in patients on placebo. Isolated ARIA-E (without co-occurrence of ARIA-H) was observed in 13% of the 10 mg/kg aducanumab treated group, compared to 2% in placebo. Subjects who experienced both ARIA-E and ARIA-H concurrently were more common in the 10 mg/kg aducanumab treated group (21%) than in the placebo group (1%). Isolated ARIA-H patients (without co-occurrence of ARIA-E) was relatively balanced and experienced by 6% of patients in the 10 mg/kg aducanumab group, compared to 7% of patients on placebo.

Serious adverse events (SAEs) of ARIA in the placebo-controlled portion of studies 301 and 302 occurred in 2% (17/1105) of patients in the aducanumab 10 mg/kg group, compared with 0.2% (2/1087) of patients on placebo; SAEs occurred in 0.4% of patients with ARIA in the 10 mg/kg group. The most common treatment emergent adverse events in 10 mg/kg aducanumab treated patients with ARIA (and with an incidence greater than on placebo) were headache (12%), confusion/delirium/altered mental status/disorientation (4%), dizziness/vertigo (4%), visual disturbance (2%), nausea (2%), fatigue (1%), and gait disturbance (1%).

The majority of cases of serious ARIA occurred between the 2nd and 11th doses. ARIA findings on MRI generally lasted 12 to 20 weeks, but 2% of cases had not resolved by the end of the study. Cases of symptomatic serious ARIA were too few to fully characterize the extent, duration, outcomes, or clinical significance. In the placebo-controlled portion of studies 301 and 302, for patients treated with 10 mg/kg aducanumab, ARIA-E occurred more frequently in ApoE ϵ 4 carriers compared to noncarriers (42% vs 20%). ApoE ϵ 4 carriers also had an increased frequency of ARIA-E and ARIA-H microhemorrhage, and ARIA-E and ARIA-H superficial siderosis. Males treated with 10 mg/kg aducanumab had ARIA-H superficial siderosis more frequently than females (19% in males, 11% in females). The incidence of ARIA-E was slightly less in patients aged 81-85 (31%) relative to those aged 51-80 (35%). Additionally, in those patients treated with 10 mg/kg aducanumab, there was increasing incidence of ARIA-H microhemorrhages by decade (13% of those aged 51-60, 19% of those aged 61-70, 20% of those aged 71-80, and 26% of those aged 81-85).

The consideration of benefit of treatment with aducanumab should be made with a consideration of the risk of ARIA. While the majority of ARIA is asymptomatic and a purely radiological finding, symptomatic ARIA, including serious ARIA, occurred even with the trials' exclusion criteria and scheduled MRI monitoring and dose suspension parameters in place. Appropriate labeling, including a Warning, and

guidance to monitor and mitigate the risk, will be needed to mitigate the risk. Based on my ARIA analysis, there are different ways to approach scheduled MRI monitoring. A conservative approach would recommend conducting scheduled MRI monitoring before the 4th, 6th, 8th, 10th, and 12th infusions. The rationale for this stems from data from serious ARIA cases and finding that the majority of serious ARIA occurred after administering between the 2nd and 11th doses. If there is a safety benefit to MRI monitoring and holding aducanumab in cases of asymptomatic moderate and severe ARIA, these time points could be appropriate. However, a problem with this approach is that we cannot quantify the safety benefit MRI monitoring and holding aducanumab dosing based on MRI findings. There were too few instances where patients received aducanumab that differed from protocol. A liberal approach would be to recommend no scheduled MRI monitoring at all. However, a problem with this approach is that it is difficult to quantify the risk removing MRI monitoring would pose. After careful reflection, I would recommend MRI monitoring prior to the 7th and 12th infusions, with the following rationale. First, MRI monitoring prior to the 7th infusion would occur during the titration period and prior to the administration of the first 10 mg/kg aducanumab dose. Second, this schedule of MRIs would align with two of the MRI assessment time points from the trials, allowing the potential for a direct comparison with post-marketing findings. For example, based on data from the trials, 95/1105 (8.6%) of patients assigned to the 10 mg/kg group experienced their first new ARIA-H microhemorrhage from baseline prior to the 7th infusion, and 167/1105 (15.1%) of patients assigned to the 10 mg/kg group experienced their first new ARIA-H microhemorrhage from baseline prior to the 12th infusion. If there were an impact of not having an MRI prior to the 5th infusion, a difference in the rate of ARIA-H microhemorrhage could be detectable. Third, conducting a scheduled MRI prior to the 12th infusion would allow for better capture of later first ARIA events, particularly in cases of ApoE ϵ 4 carriers as indicated in Table 14. Given limited data, I believe this would be the best approach to scheduled MRI monitoring.

Enhanced pharmacovigilance should be requested for ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 cm, to 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. This should also include evaluation of patient characteristics, including APO ϵ 4 genotype, if available. Information collected should be used to optimizing monitoring and minimizing risk. It should be noted that the protocols for studies 301 and 302 excluded patients on an antiplatelet or anticoagulation medication other than aspirin $\leq$ 325 mg, those with history of bleeding disorder, blood clotting disorder, abnormal coagulation profile, hypertension, prior cortical or lacunar infarct, seizure within 10 years of screening. The sponsor has also proposed a voluntary educational program for prescribers and radiologists on the risks of ARIA.

The following sections describe the findings of the ARIA evaluation.

Introduction to Amyloid Related Imaging Abnormalities (ARIA)

Monoclonal antibody therapy against amyloid-beta (A β) causes Amyloid Related Imaging Abnormalities (ARIA) [1]. There are two types of ARIA: vasogenic edema (ARIA-E), and hemosiderin deposition (ARIA-H), which consists of cerebral microhemorrhage, superficial siderosis, and cerebral hemorrhage. Pathologically, anti-A β antibodies may accelerate the vascular deposition of A β and bind accessible

vascular A β , thereby disrupting vessel integrity, resulting in ARIA-E and ARIA-H [2]. ARIA-E encompasses MRI alterations with increased intensity on FLAIR thought to represent edema in the gray and white matter as well as effusion or extravasated fluid in the sulcal space [3]. ARIA-E has been noted to rarely occur spontaneously [1]. Contributing factors for ARIA-E and ARIA-H may include anti-A β antibody type (particularly IgG1) and targeting deposited forms of A β over soluble forms [4]. Risk factors for ARIA-E include the dose of the anti-A β antibody and the presence of the APOE ϵ 4 allele [3], [1]. Symptoms of ARIA-E associated with monoclonal antibody therapies against A β have been reported to include headache, confusion, psychiatric, and gastrointestinal symptoms [1]. ARIA was identified as an adverse event of special interest in the aducanumab development program, and studies 301 and 302 were designed to monitor for ARIA.

ARIA Monitoring in Studies 301 and 302

ARIA monitoring in the clinical trials included brain MRIs which were read by central MRI readers experienced in ARIA. All ARIA findings were reported as adverse events with an investigator assessment of the symptomatic status of any ARIA finding, and collection of information on symptoms, if any. Brain MRIs were performed for all participants at protocol-specified timepoints to monitor for the potential occurrence of ARIA. These timepoints for the placebo-controlled portion of Study 302 were at screening, week 14 (Day 99 $\pm$ 3), week 22 (Day 155 $\pm$ 3), week 30 (Day 211 $\pm$ 3), week 42 (Day 295 $\pm$ 3), week 54 (Day 379 $\pm$ 3), week 66 (Day 463 $\pm$ 3), and week 78 (Day 547 $\pm$ 3). This corresponded to before the 5th, 7th, 9th, 12th, 15th, 18th, and after the 20th infusions. Follow-up brain MRIs were performed for all participants in whom ARIA was detected, (except for participants who had only asymptomatic ARIA-H microhemorrhage of mild radiographic severity) every 4 weeks until ARIA resolved (ARIA-E), or stabilized (ARIA-H), per the centrally read MRI. The classification of the radiographic severity of ARIA as follows.

Table 1: Classification of the Radiographic Severity of ARIA by ARIA Type and Radiographic Findings

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	$\leq$ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

This table is from Applicant Table 3 in Summary of Clinical Safety.

ARIA Management

Rules for dose modification or discontinuation were revised with different versions of the study protocol. Throughout all the versions of the protocol for studies 221AD301 and 221AD302, asymptomatic patients with radiographically mild ARIA (both ARIA-E and ARIA-H (microhemorrhage or superficial siderosis)) were to continue dosing at their current dose and schedule. A patient with asymptomatic radiographically moderate or severe ARIA-E was to have the dose suspended and restarted at the next lower dose in version 1 of the protocol; however, later versions of the protocol had the subject suspend dosing and then restart at the same dose. Mild or moderate symptomatic ARIA-E that was of any radiographic severity required suspension of dosing and restarting at the next lower dose in version 1 of the protocol; however, in later versions, subjects were to suspend dosing and restart at the same dose. Severe symptomatic ARIA-E of any radiographic severity initially required permanent discontinuation in Version 1 of the protocol; however, later versions suspended dosing and restarted at the same dose. Patients with ARIA-E with serious clinical symptom severity that was “other medically important event”, and with any radiographic severity of ARIA, required a permanent discontinuation in version 1 of the protocol, but in later versions would suspend dosing and restart at the same dose. Patients who had ARIA-E of any radiographic severity with serious clinical symptoms except “other than medically important event” required permanent discontinuation in all versions of the protocol. Table 2, from the Sponsor’s Summary of Clinical Safety, provides a summary of these protocol version changes to address ARIA-E.

Table 2: Management of ARIA-E by Protocol Version – Studies 301 and 302

Clinical Symptom Severity		Radiographic Severity	Protocol Version		
			V1 (20 Apr 2012)	V3 (21 Jul 2016)	V4 (24 Mar 2017) through V6 (28 Jun 2018)
Asymptomatic		Mild	Continue dosing at current dose and schedule		
		Moderate or Severe	Suspend dosing and restart at next LOWER dose	Suspend dosing and restart at SAME dose	
Symptoms Present	Mild or Moderate	Any	Permanently discontinue		
	Severe				
	Serious				
	“Other medically important event”		Permanently discontinue		Permanently discontinue
Serious, except “other than medically important event”			Permanently discontinue		Permanently discontinue

Note: During Protocol V1 (20 Apr 2012), ARIA were counted over 12-week periods. From Protocol V2 (26 May 2016) through Protocol V5 (18 Sep 2017), if a second ARIA event (either ARIA-E or ARIA-H) requires dose suspension, restart at next **lower** dose. If a third ARIA event requires dose suspension, permanently discontinue drug. Beginning with Protocol V6 (28 Jun 2018), a third episode of ARIA that requires dose suspension no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, restart dosing at same dose.

Note: No participants were enrolled under Protocol V2 (26 May 2016).

Table 2 is from the Summary of Clinical Safety Table 61.

A patient with asymptomatic or symptomatic ARIA-H (microhemorrhage and superficial siderosis) of severe radiographic severity was to permanently discontinue study treatment per protocol in all versions of the protocol. Clinically mild or moderate symptomatic ARIA-H (microhemorrhage or superficial siderosis) that was radiographically mild or moderate required suspension of dosing and in version 1 of the protocol would restart at the next lower dose, while in later versions of the protocol required suspending dosing and then restarting at the same dose. The same applied for asymptomatic

ARIA-H with moderate radiographic severity. Clinically severe and clinically serious “other medically important event” with ARIA of mild or moderate radiographic severity initially required permanent discontinuation in version 1 of the protocol, but in later versions of the protocol called for suspension of dosing and resuming at the same dose. Finally, clinically serious except for “other than medically important event” required permanent discontinuation in all versions of the protocol. While version 1 of the protocol treated recurrent ARIA as the initial episode, version 3-5 of the protocol required resuming at a next lower dose after a second ARIA episode, or discontinuing treatment after a third ARIA episode, and version 6 of the protocol had patients who had their treatment suspended after a 2nd or 3rd ARIA episode continue at the same dose after suspension. Additionally, the protocol required patients with radiographically severe ARIA-H, whether symptomatic or asymptomatic (with ≥ 10 new incident microhemorrhages or > 2 superficial siderosis areas), to permanently discontinue, and later versions of the protocol added to this requirement patients with macro-hemorrhage (defined as hemorrhages > 1 cm) to permanently discontinue from treatment. Serious ARIA-E of any radiographic severity and serious ARIA-H microhemorrhage and superficial siderosis of mild or moderate radiographic severity initially required permanent discontinuation in version 1 of the protocol, but later versions of the protocol allowed for the suspension of dosing and restarting at the same dose if the serious event was an “other medically important event”. Tables 3, from the Sponsor’s Summary of Clinical Safety, provides a summary of these protocol version changes to address ARIA-H.

Table 3: Management of ARIA-H Microhemorrhage and Superficial Siderosis by Protocol Version – Studies 301 and 302

Clinical Symptom Severity		Radiographic Severity	Protocol Version	
			V1 (20 Apr 2012)	V3 (21 Jul 2016) through V6 (28 Jun 2018)
Asymptomatic		Mild	Continue dosing at current dose and schedule	
		Moderate	Suspend dosing and restart at next LOWER dose	Suspend dosing and restart at SAME dose
Symptoms Present	Mild or Moderate	Mild or Moderate		
	Severe	Mild or Moderate	Permanently discontinue	Permanently discontinue
	Serious “Other medically important event”			
	Serious, except “other than medically important event”			
Asymptomatic or Symptoms present		Severe	Permanently discontinue	

Note: During Protocol V1 (20 Apr 2012), ARIA were counted over 12-week periods. From Protocol V3 (21 Jul 2016) through Protocol V5 (18 Sep 2017), if a second ARIA event (either ARIA-E or ARIA-H) requires dose suspension, restart at next **lower** dose. If a third ARIA event requires dose suspension, permanently discontinue drug. Beginning with Protocol V6 (28 Jun 2018), a third episode of ARIA that requires dose suspension no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, restart dosing at same dose.

Note: No participants were enrolled under Protocol V2 (26 May 2016).

Note: Radiographic severity for ARIA-H microhemorrhages counted as follows: ≤ 4 = mild; 5 to 9 = moderate; ≥ 10 = severe. Radiographic severity for ARIA-H superficial siderosis counted as follows: 1 = mild; 2 = moderate; > 2 = severe.

Table 3 is from the Summary of Clinical Safety, Table 62.

Analyses of ARIA

Frequency of ARIA

Table 4 presents the incidence of ARIA in the placebo-controlled portion of Studies 301 and 302.

Table 4: Patients experiencing ARIA by Type and Combination in the Placebo-Controlled Portion of Studies 301 and 302

Patients Experiencing the Following Preferred Term	3 mg/kg	6 mg/kg	10 mg/kg	All Aducanumab	Placebo
	(N = 760)	(N = 333)	(N =1105)	(N =2198)	(N =1087)
Any occurrence of ARIA (-E and/or -H)	274 (36.1%)	75 (22.5%)	454 (41.1%)	803 (36.6%)	111 (10.2%)
ARIA-E	223 (29.3%)	58 (17.4%)	387 (35.0%)	668 (30.5%)	29 (2.7%)
Isolated ARIA-E	81 (10.7%)	33 (9.9%)	142 (12.9%)	256 (11.7%)	17 (1.6%)
Isolated ARIA-H	51 (6.7%)	17 (5.1%)	67 (6.1%)	135 (6.2%)	82 (7.5%)
Concurrent ARIA-E and ARIA-H	135 (17.8%)	22 (6.6%)	233 (21.1%)	390 (17.8%)	12 (1.1%)
ARIA-H	193 (25.4%)	42 (12.6%)	312 (28.2%)	547 (25.0%)	94 (8.6%)
ARIA-H microhemorrhage	141 (18.6%)	35 (10.5%)	212 (19.2%)	388 (17.7%)	71 (6.5%)
ARIA-H macrohemorrhage	1 (0.1%)	0 (0.0%)	6 (0.5%)	7 (0.3%)	4 (0.4%)
ARIA-H superficial siderosis	91 (12.0%)	12 (3.6%)	162 (14.7%)	265 (12.1%)	24 (2.2%)
Isolated ARIA-H Microhemorrhage	36 (4.7%)	16 (4.8%)	53 (4.8%)	105 (4.8%)	65 (6.0%)
Isolated ARIA-H Macrohemorrhage	0 (0.0%)	0 (0.0%)	2 (0.2%)	2 (0.1%)	2 (0.2%)

Patients Experiencing the Following Preferred Term	3 mg/kg	6 mg/kg	10 mg/kg	All Aducanumab	Placebo
	(N = 760)	(N = 333)	(N =1105)	(N =2198)	(N =1087)
Isolated ARIA-H Superficial siderosis	13 (1.7%)	1 (0.3%)	12 (1.1%)	26 (1.2%)	13 (1.2%)

Overall, the incidence of ARIA was increased in the 10 mg/kg aducanumab treated group relative to the placebo group (41.1% vs 10.2%). ARIA-E, as well as concurrent ARIA-E and ARIA-H, occurred more frequently in aducanumab-treated patients than in patients on placebo. Of note, ARIA was also observed in the absence of aducanumab treatment, which is consistent with literature reports. Most patients on placebo who experienced ARIA had isolated ARIA-H. There was no imbalance in isolated ARIA-H between aducanumab treatment and placebo. There was no imbalance in macrohemorrhage, defined as greater than 1 cm, between aducanumab and placebo. Of note, the presence of cerebral microhemorrhages is a common incidental finding on MRI of elderly individuals, and one publication has shown a trend with reduction in cerebral blood flow [5].

Severity of ARIA

As described earlier, the assessment of ARIA severity was based on radiographic findings.

Of the patients who experienced ARIA in the 10 mg/kg aducanumab treated group in the placebo-controlled part of Studies 301 and 302, 15.0% of patients experienced mild ARIA, 17.9% suffered moderate ARIA, and 8.1% of patients experienced severe ARIA. 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 Sponsor reported that severity of ARIA-E was moderate in 58%. The difference from Agency analysis was because of a single patient who had a mild episode in the placebo-controlled trial and moderate in the long-term extension, as noted in the response to an information request dated May 27, 2021. The difference is not meaningful.

A full accounting of ARIA subtype severity is presented in the table below.

Table 5: Treatment Emergent ARIA Events, by Severity, in the Placebo-Controlled Portion of Studies 301 and 302

Patients Experiencing the Following Preferred Term	3 mg/kg	6 mg/kg	10 mg/kg	All Aducanumab	Placebo
	(N = 760)	(N = 333)	(N =1105)	(N =2198)	(N =1087)
Patients with ARIA Events, Maximum Severity					
Mild	103 (13.6%)	42 (12.6%)	166 (15.0%)	311 (14.1%)	97 (8.9%)
Moderate	120 (15.8%)	26 (7.8%)	198 (17.9%)	344 (15.7%)	11 (1.0%)
Severe	51 (6.7%)	7 (2.1%)	90 (8.1%)	148 (6.7%)	3 (0.3%)
Total	274 (36.1%)	75 (22.5%)	454 (41.1%)	803 (36.5%)	111 (10.2%)

Patients Experiencing the Following Preferred Term	3 mg/kg	6 mg/kg	10 mg/kg	All Aducanumab	Placebo
	(N = 760)	(N = 333)	(N =1105)	(N =2198)	(N =1087)
Patients with ARIA-E Events, Maximum Severity					
Mild	67 (8.8%)	27 (8.1%)	116 (10.5%)	210 (9.6%)	21 (1.9%)
Moderate	135 (17.8%)	27 (8.1%)	222 (20.1%)	384 (17.5%)	8 (0.7%)
Severe	21 (2.8%)	4 (1.2%)	49 (4.4%)	74 (3.4%)	0 (0.0%)
Total	223 (29.3%)	58 (17.4%)	387 (35.0%)	668 (30.4%)	29 (2.7%)
Patients with ARIA-H Microhemorrhage Events, Maximum Severity					
Mild	103 (13.6%)	31 (9.3%)	154 (13.9%)	288 (13.1%)	68 (6.3%)
Moderate	11 (1.4%)	2 (0.6%)	29 (2.6%)	42 (1.9%)	3 (0.3%)
Severe	27 (3.6%)	2 (0.6%)	29 (2.6%)	58 (2.6%)	0 (0.0%)
Total	141 (18.6%)	35 (10.5%)	212 (19.2%)	388 (17.7%)	71 (6.5%)
Patients with ARIA-H Superficial Siderosis Events, Maximum Severity					
Mild	50 (6.6%)	8 (2.4%)	79 (7.1%)	137 (6.2%)	22 (2.0%)
Moderate	25 (3.3%)	3 (0.9%)	47 (4.3%)	75 (3.4%)	0 (0.0%)
Severe	16 (2.1%)	1 (0.3%)	36 (3.3%)	53 (2.4%)	2 (0.2%)
Total	91 (12.0%)	12 (3.6%)	162 (14.7%)	265 (12.1%)	24 (2.2%)
Patients with ARIA-H Macrohemorrhage Events, Maximum Severity					
Mild	1 (0.1%)	0 (0.0%)	4 (0.4%)	5 (0.2%)	3 (0.3%)
Moderate	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Total	1 (0.1%)	0 (0.0%)	6 (0.5%)	7 (0.3%)	4 (0.4%)

Overall, this table indicates that severe ARIA was relatively infrequent in those treated with 10 mg/kg aducanumab in the placebo-controlled portion of studies 301 and 302.

Deaths

Nine deaths have occurred in patients who experienced ARIA; however, none have been determined to be due to ARIA. A summary of these are presented in narrative form in Appendix D.

Serious Adverse Events, Discontinuations and Treatment Emergent Adverse Events

The table below shows the frequency of SAEs, discontinuations, and TEAEs attributed to ARIA overall, ARIA-E, and ARIA-H by subtypes in the placebo-controlled portion of studies 301 and 302.

Table 6: Serious Adverse Events, Discontinuations and Treatment Emergent Adverse Events in the Placebo Controlled Portions of Studies 301 and 302

		Aducanumab 10 mg/kg (N=1105) n (%)	Placebo (N=1087) n (%)
ARIA overall	SAEs	17 (1.5%)	2 (0.2%)
	Discontinuations	79 (7.1%)	6 (0.6%)
	TEAEs	454 (41.1%)	111 (10.2%)
ARIA-E	SAEs	15 (1.4%)	1 (0.1%)
	Discontinuations	17 (1.5%)	1 (0.1%)
	TEAEs	387 (35.0%)	29 (2.7%)
ARIA H (microhemorrhage)	SAEs	4 (0.4%)	0 (0.0%)
	Discontinuations	27 (2.4%)	0 (0.0%)
	TEAEs	212 (19.2%)	71 (6.5%)
ARIA-H (superficial siderosis)	SAEs	5 (0.5%)	0 (0.0%)
	Discontinuations	33 (3.0%)	2 (0.2%)
	TEAEs	162 (14.7%)	24 (2.2%)
ARIA-H (cerebral hemorrhage)	SAEs	1 (0.1%)	1 (0.1%)
	Discontinuations	5 (0.5%)	4 (0.4%)
	TEAEs	6 (0.5%)	4 (0.4%)

As shown in Table 6, ARIA was reported as a serious adverse reaction in 1.5% of patients in the aducanumab 10 mg/kg group, compared with 0.2% in patients on placebo. Among patients with ARIA, SAEs occurred in 2/454 (0.4%) of aducanumab 10mg/kg-treated patients and in no patients on placebo.

To demonstrate the overlap of multiple types of ARIA in the same subject, I analyzed Study 302, and found all 8 patients with serious adverse reactions with ARIA experienced ARIA-E. Three of the patients also had ARIA-H superficial siderosis, 2 also had ARIA-H microhemorrhage, and 1 also had an ARIA-H cerebral hemorrhage. Serious adverse events that were reported include: confusion, disorientation, delusional thoughts, seizure, agitation, gait disturbance, right hand weakness, decreased coordination, ataxia, visual disturbances, headache, nausea, and falls. One subject in study 302 (b) (6) died, but the death was not related to ARIA.

Participants with Serious ARIA Events in Studies 301 and 302

There were 29 instances of serious ARIA events in studies 301 and 302, including 23 in the placebo-controlled period and 6 in the long-term extension periods of both studies. Except for one patient who died (b) (6), all other serious ARIA events resolved radiographically, though in some cases, the symptoms initially associated with the ARIA event did not resolve by the end of the study. Serious ARIA generally occurred between the 2nd and the 11th dose, with most events between the 3rd and 8th dose of aducanumab.

Of the 29 serious ARIA cases, 26 were symptomatic, with 13/26 having symptoms prior to finding of radiographic ARIA, 4/26 having symptoms concurrent with finding of radiographic ARIA, and 9/26 patients who developed symptoms after finding of radiographic ARIA. Symptoms arising with ARIA (if they resolved) typically resolved prior to the resolution of the radiographic finding of ARIA. Approach to treatment of ARIA varied, with 15/29 treated with steroids, 1/29 treated with plasmapheresis, and 13/29 who received no specific treatment for ARIA.

There were common symptoms shared among the cases of serious ARIA. Most frequent among these was a sudden onset of confusion, experienced by 11 patients, and described in narratives as an acute worsening of confusion. In cases where the confusion resolved, duration of the event was between 12 and 116 days; there were cases where confusion did not resolve during the study. Specific descriptions of such events include a subject not being oriented to time, able to remember names of grandchildren, shop, or use the dishwasher, or another subject who could not dress oneself and forgot meals, or another who could not operate a dryer or a fourth who could not operate a cell phone. These examples illustrate the acute onset and character of confusional manifestations of symptomatic serious ARIA. However, these symptoms can also occur in the setting of worsening of AD, which can make it challenging to determine if confusion is resolved in some patients.

Visual disturbances were noted in 8 patients with serious ARIA events. Six patients had resolution of their visual impairment, but two patients (b) (6) had visual disturbances that did not resolve during the study despite treatment with dexamethasone.

- Subject (b) (6) had symptomatic ARIA-H macrohemorrhage with a right occipital hematoma and resulting left visual field defect. This case was confounded by a reported cavernoma that was retrospectively seen in the region of the subsequent ARIA-H.
- Subject (b) (6) had an event of symptomatic ARIA-H superficial siderosis in the left occipital region with homonymous peripheral visual defects and visual field defect when looking down, and was unable to recognize various objects on a table in front of him; the visual field defect did not resolve.

Overall, in all but one subject who developed visual impairment, the patients had ARIA in the occipital regions. Findings included visual field defects including homonymous hemianopia, seeing black and white spots, flashes of light moving from left to right, seeing smooth surfaces appearing rough, seeing a “Christmas light” in the visual field, and left gaze preference.

Serious ARIA events also manifested as focal weakness in 4 patients.

- Subject (b) (6) experienced left sided weakness with no movement of the left upper extremity, and 3/5 strength of the left lower extremity, and was having paresthesias in the left lower extremity. Her MRI scan showed moderate vasogenic edema in the left parietal, right frontal, right occipital, and right parietal regions. Six days after symptom onset, she underwent plasmapheresis, and 6 days later could move her left leg and squeeze with her left hand; 23 days after plasmapheresis, her hemiparesis was reported as resolved. The duration of the subject’s hemiplegia was 26 days (or 29 days if one considers the reported 3 days of symptoms prior to her Emergency Department presentation).

- Subject (b) (6) experienced 13 days of gait instability and 33 days of right-sided hemiplegia, with a corresponding MRI showing ARIA-E. She was treated with dexamethasone. Her ARIA-E took 258 days to resolve.
- Additional narratives of serious ARIA mentioning motor weakness include subject (b) (6), who had left sided weakness, and did not undergo treatment with steroids or plasmapheresis, and subject (b) (6), who had 10 days of right leg weakness and ARIA-E and ARIA-H microhemorrhages.

Other common presentations of serious symptomatic ARIA include the following:

- Headache was experienced by 10 patients, with durations ranging from 2 to 63 days in the cases with noted dates of symptom resolution.
- Gait difficulty and wide-based gait was reported in 7 patients
- Potentially related symptoms of balance difficulty, experienced by 4 patients; dizziness, experienced by 3 patients; and fall, experienced by 3 patients
- Nausea was experienced by 3 patients, and emesis was experienced by 2 patients (with one subject experiencing both).
- Seizures were reported in 3 patients.
- Additional findings included: 2 patients with ataxia, 2 patients with elevated blood pressure, 2 patients with fatigue, and 2 with word finding difficulties.

ApoE ϵ 4 carrier status may have implications for the occurrence of ARIA. Cases of serious ARIA events in the placebo-controlled portion of studies 301 and 302 had the following genetic breakdown: 8/23 (34.8%) were noncarriers for ApoE ϵ 4, 7/23 (30.4%) were heterozygous for ApoE ϵ 4, and 8/23 (34.8%) were homozygous for ApoE ϵ 4. In comparison, in the all aducanumab treated population of the placebo-controlled portion of studies 301 and 302, 692/2193 (31.6%) were noncarriers for ApoE ϵ 4, 1121/2193 (51.1%) were heterozygous for ApoE ϵ 4, and 380/2193 (17.3%) were homozygous for ApoE ϵ 4. Since there were fewer ApoE ϵ 4 homozygotes enrolled in the study overall, the number of homozygous ApoE ϵ 4 appears higher than would be anticipated on initial impression. However, I note the numbers of serious ARIA cases are small in the combined placebo-controlled portion of studies 301 and 302, and noncarrier serious ARIA events occurred in proportion with the overall aducanumab treated population. Still, if a larger subject pool were available, it would be helpful to genotype subjects experiencing serious ARIA to determine if ApoE ϵ 4 homozygous status is a risk for serious ARIA, or if this finding of an imbalance was the result of chance, given low numbers involved.

Discontinuations in the Placebo Controlled Period of Studies 301 and 302

Most discontinuations were due to protocol-specified discontinuation criteria that included severe ARIA-H microhemorrhage and severe ARIA-H superficial siderosis to be discontinued per protocol. The protocol stated that "Subjects who develop ≥ 10 new incident microhemorrhages (severe), regardless of symptom severity, during the study will permanently discontinue treatment but remain in study." Additionally, the protocol stated that "Subjects who develop >2 focal areas of hemosiderosis (superficial siderosis) [severe] occurring at any time during the study must permanently discontinue treatment but remain in study." The protocol required that "Subjects who develop any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of symptom severity during the study, will

permanently discontinue treatment, but remain in study.” Discontinuations for ARIA-E also had set criteria per protocol, which stated that “Subjects who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except “other medically important event”) clinical symptoms at any time during the study will permanently discontinue treatment but remain in study.” A summary of treatment emergent ARIA events that led to treatment discontinuation in the placebo-controlled portion of Study 302 is presented in Table 7.

Table 7: Treatment Emergent ARIA Events Leading to Treatment Discontinuation in the Placebo-Controlled Portion of Study 302

Treatment Emergent ARIA Events Lead Treatment Discontinued (Study 302, PC)

Preferred Term	3 mg/kg (N = 368)	6 mg/kg (N = 175)	10 mg/kg (N = 547)	All Aducanumab (N = 1090)	Placebo (N = 548)
Subjects with ARIA events	22 (6.0%)	4 (2.3%)	38 (6.9%)	64 (5.9%)	1 (0.2%)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	10 (2.7%)	1 (0.6%)	16 (2.9%)	27 (2.5%)	0 (0.0%)
Superficial siderosis of central nervous system	7 (1.9%)	1 (0.6%)	16 (2.9%)	24 (2.2%)	0 (0.0%)
Amyloid related imaging abnormality-oedema/effusion	5 (1.4%)	2 (1.1%)	5 (0.9%)	12 (1.1%)	1 (0.2%)
Cerebral haemorrhage	1 (0.3%)	0 (0.0%)	3 (0.5%)	4 (0.4%)	0 (0.0%)

Safety population and TRTEMFL = Y; POOLTR3 is used to define the treatment group. 28 patients in 6 mg/kg were moved to 10 mg/kg and 1 patient in 3 mg/kg was moved to placebo group.
 [tearia2disc.rtf] [tearia2disc.sas] 15SEP2020, 18:06

I have reviewed the 38 patients who had drug discontinued and were flagged for ARIA adverse events in the 10 mg/kg treated group in the placebo-controlled portion of study 302. There were 14 who had severe ARIA-H superficial siderosis, 12 had severe ARIA-H microhemorrhage, 3 had a cerebral hemorrhage (1 of which also had severe ARIA-H superficial siderosis) and 3 had symptomatic severe ARIA-E (one of which also had severe ARIA-H superficial siderosis). These 30/38 patients were discontinued in a way consistent with protocol. Eight additional patients did not fit radiographic criteria for discontinuation of drug based on their ARIA status. Specifically, 4 patients had ARIA-H microhemorrhages, and 2 patients had superficial siderosis that were not radiographically severe and did not require discontinuation based on MRI criteria. Two patients had moderate ARIA-E that did not require discontinuation. On reviewing these 8 cases, it appears some discontinuations were due to the subject withdrawing consent. I did not note any components of these cases that would impact labeling.

A brief review of the discontinuation table for the placebo-controlled portion of studies 301 and 302 appears to generally consistent with the discontinuations reported for Study 302.

Treatment Emergent Adverse Events Associated with ARIA

Symptomatic ARIA occurred in 24% of patients who had an observation of ARIA treated with 10 mg/kg aducanumab in the placebo-controlled portions of studies 301 and 302, and 5% of patients treated with

10 mg/kg aducanumab had serious symptomatic ARIA (see discussion under “Participants with Serious ARIA Events in Studies 301 and 302”).

MRI Severity and Symptom Severity

Table 8, which was provided by the Sponsor in response to an information request, illustrates that most cases of ARIA are asymptomatic. Mild and moderate ARIA events on MRI have a similar incidence and severity of symptoms. Severe ARIA events on MRI are more likely to be symptomatic; however, the incidence of severe symptoms remains low.

Table 8: Summary of MRI Severity of ARIA and Symptom Severity

	Placebo (N=1087) n (%)	BIIB037 10 mg/kg (N=1105) n (%)
Number of ARIA events mild on MRI (a)	126 (100)	484 (100)
Asymptomatic	123 (98)	405 (84)
Symptomatic	3 (2)	79 (16)
Mild (b)	2 (2)	60 (12)
Moderate (b)	1 (<1)	12 (2)
Severe (b)	0	1 (<1)
Missing	0	6 (1)
Number of ARIA events moderate on MRI (a)	14 (100)	407 (100)
Asymptomatic	11 (79)	342 (84)
Symptomatic	3 (21)	65 (16)
Mild (b)	1 (7)	42 (10)
Moderate (b)	1 (7)	16 (4)
Severe (b)	1 (7)	3 (<1)
Missing	0	4 (<1)
Number of ARIA events severe on MRI (a)	5 (100)	124 (100)
Asymptomatic	5 (100)	90 (73)
Symptomatic	0	34 (27)
Mild (b)	0	14 (11)
Moderate (b)	0	13 (10)
Severe (b)	0	4 (3)
Missing	0	3 (2)

Overall Symptomatic ARIA

Treatment emergent adverse events in patients with ARIA in the 10 mg/kg aducanumab group or placebo group and occurring with an incidence of at least 1% are shown in the table below. Among those patients, headache was the most common symptom associated with ARIA.

Table 9: Treatment Emergent Adverse Events in those who Experienced any form of ARIA in the Placebo-Controlled Portion of Studies 301 and 302

Preferred Term	10 mg/kg aducanumab that experienced ARIA N=454 N (%)	Placebo that experienced ARIA N=111 N (%)
Total Patients with ARIA with any Adverse Events	106 (23.3%)	5 (4.5%)
Headache	53 (11.7%)	3 (2.7%)
Confusion/delirium/altered mental status/disorientation	20 (4.4%)	1 (0.9%)
Dizziness/Vertigo	16 (3.5%)	0 (0%)
Visual Disturbance	11 (2.4%)	0 (0%)
Nausea	9 (2.0%)	0 (0%)
Fatigue	6 (1.3%)	0 (0%)
Gait Disturbance	5 (1.1%)	0 (0%)

Regarding the most common symptom in patients treated with aducanumab 10 mg/kg who had ARIA, the sponsor reported headache (13%) and other frequent symptoms of confusion/delirium/altered mental status/disorientation (5%), dizziness/vertigo (4%), visual disturbance (2%), and nausea (2%). The Sponsor derived those events from a dataset that included terms considered related to ARIA by the investigator that may not have temporally overlapped with a symptomatic ARIA event, using AE record with a variable AERELARI = 'RELATED', as noted in the response to an information request dated May 27, 2021. The Sponsor's approach is acceptable and the differences not meaningful.

Isolated ARIA-E was symptomatic in 25% of patients on aducanumab 10 mg/kg who had isolated ARIA-E vs 12% of patients on placebo who had isolated ARIA-E. Isolated ARIA-H was symptomatic in 8% of patients on aducanumab 10 mg/kg who had isolated ARIA-H vs 2% of patients on placebo who had isolated ARIA-H. ARIA-E with ARIA-H was symptomatic in 27% of patients on aducanumab 10 mg/kg who had ARIA-E and ARIA-H vs 8% of patients on placebo who had ARIA-E and ARIA-H. Adverse reactions were in these subsets were similar to those seen with ARIA overall. Headache was the most common adverse reaction in these subsets of ARIA. Given the symptom similarity between subtypes, and the inability to distinguish subtypes by symptom, it is appropriate to describe symptoms of ARIA overall in labeling.

Unresolved Symptomatic ARIA

Table 10 describes unresolved symptoms associated with ARIA in patients treated with any dose of aducanumab in the placebo-controlled and open-label portions of Studies 301 and 302.

Table 10: Unresolved Symptoms Associated with ARIA in those Treated with Any Dose of Aducanumab in the Placebo-Controlled and Open-Label Portions of Studies 301 and 302

Preferred Term	Aducanumab treated patient events that occurred and did not resolve during the placebo-controlled or open label studies N=68 events	Aducanumab treated patient events that occurred and resolved during the placebo controlled or open label studies N=361 events
Confusion/Delirium/Altered Mental Status/Disorientation/Coma	14	45
Headache	12	142
Dizziness/Vertigo	7	23
Aphasia	4	3
Gait disturbance	3	5
Seizure	3	3
Executive dysfunction	2	0
Fatigue	2	11
Tinnitus	2	0
Agitation	1	2
Amnesia	1	0
Anxiety	1	0
Blood pressure fluctuation	1	0
Cerebellar ataxia	1	0
Cognitive disorder	1	4
Dementia Alzheimer's type	1	0
Dyspraxia	1	0
Facial paralysis	1	0
Gaze palsy	1	0
Hallucination	1	0
Hypertension	1	0
Irritability	1	1
Nausea	1	15
Parosmia	1	1
Psychomotor hyperactivity	1	0
Tension headache	1	2
Visual Disturbance	1	17
Visual field defect	1	5

*Note, only event preferred terms for the 68 events that did not resolve are provided in this table, with corresponding numbers of events of that term that did resolve. There are additional event terms that had events that all resolve that are not presented in this table.

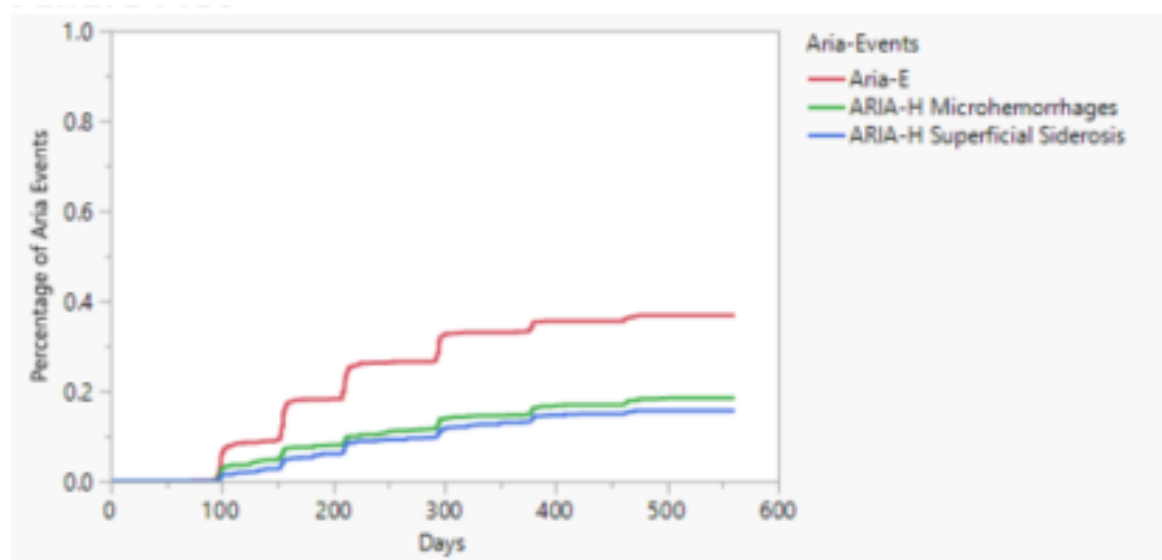
Table 10 shows that 15.9% of ARIA related symptoms that occurred during the placebo-controlled or open-label period did not resolve. On reviewing the preferred terms for each of these symptoms, many

of them overlap with the clinical manifestations of Alzheimer's disease. This makes it difficult to distinguish an ARIA-related unresolved symptom from the progression of Alzheimer's disease. There are notable exceptions, however, specifically the visual disturbance and visual field defect events noted at the bottom of Table 10 (b) (6). These occurred in subjects who received placebo during the placebo-controlled portion of the study and then received aducanumab in the open label period. The offending ARIA with symptoms occurred after the 7th dose for subject (b) (6), and after the 5th dose for subject (b) (6). Subject (b) (6), had a right parietal cortical infarct while receiving placebo during the placebo-controlled period, and after 5th dose of aducanumab in the long-term extension period, had an ARIA-H macrohemorrhage 24 x 21 mm right occipital hematoma.

Timing of ARIA Events:

The timing of ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis for those treated with 10 mg/kg aducanumab in the placebo-controlled portion of studies 301 and 302 is presented in Figure 1.

Figure 1: Incidence of First ARIA Events over time in those treated with 10 mg/kg aducanumab in the Placebo Controlled Portion of Studies 301 and 302



As seen in Figure 1, the risk of first instance of ARIA is highest, with a steeper slope, in the first half of the placebo-controlled portion of the trial. Table 11 shows the timing of a subject's first instance of ARIA-E relative to aducanumab infusion for the 10 mg/kg aducanumab group in the placebo-controlled portions of studies 301 and 302.

Table 11: First instance of ARIA-E in the 10 mg/kg Aducanumab Group in the Placebo-Controlled Portion of Studies 301 and 302, by Infusion Number

Aducanumab infusion #	# of Patients Experiencing First ARIA-E	Percent	Cumulative Frequency	Cumulative Percent	# of the 29 Serious ARIA cases
2	1	0.26	1	0.26	1
3	4	1.03	5	1.29	2
4	88	22.74	93	24.03	11
5	12	3.10	105	27.13	4
6	93	24.03	198	51.16	6
7	5	1.29	203	52.45	2
8	81	20.93	284	73.39	1
9	1	0.26	285	73.64	0
10	8	2.07	293	75.71	1
11	54	13.95	347	89.66	1
12	3	0.78	350	90.44	0
13	2	0.52	352	90.96	0
14	16	4.13	368	95.09	0
16	1	0.26	369	95.35	0
17	8	2.07	377	97.42	0
19	1	0.26	378	97.67	0
20	9	2.33	387	100.00	0

Of note, scheduled MRIs were conducted at screening, week 14 (Day 99 ± 3) (before 5th infusion), week 22 (Day 155 ± 3) (before 7th infusion), week 30 (Day 211 ± 3) (before 9th infusion), week 42 (Day 295 ± 3) (before 12th infusion), week 54 (Day 379 ± 3) (before 15th infusion), week 66 (Day 463 ± 3) (before 18th infusion), and week 78 (Day 547 ± 3) (before 21st infusion). This MRI schedule can help explain why the corresponding cases of ARIA-E are increased after the 4th, 6th, 8th, 11th, 14th, 17th, and 20th infusions. This applies to the subsequent analysis tables for ARIA-H microhemorrhage and ARIA-H superficial siderosis. Another point to note is that 73.39% of first instances of ARIA-E are experienced before the 9th infusion, and 89.66% first instance of ARIA-E is experienced before the 12th infusion. Similar results were observed for ARIA-H microhemorrhage and ARIA-H superficial siderosis, with the percentage of patients who experienced the first instance of ARIA for each type generally peaking between the 4th and the 12th infusion of aducanumab (data not shown in this review). Recall that earlier in this review, I noted that

serious ARIA generally occurred between the 2nd and the 11th dose, with most events between the 3rd and 8th dose of aducanumab.

Radiographic Duration of first ARIA Event

The mean duration of the patients' first radiographic ARIA events in each category of ARIA in days is shown in the table below for patients in whom these first ARIA events resolved during the study. There were too few hemorrhages greater than 1 cm in the aducanumab 10 mg/kg and placebo groups to allow for meaningful comparison of duration.

Table 12: Duration of first episode of radiographic events (days)

	ARIA-E		ARIA-H microhemorrhage		ARIA-H superficial siderosis	
	10 mg/kg	placebo	10 mg/kg	placebo	10 mg/kg	placebo
Mean	n=387 66 days	n=29 56 days	n=212 49 days	n=71 71 days	n=162 29 days	n=24 40 days
SD	42 days	39 days	32 days	37 days	20 days	27 days
Range	5-395 days	26-166 days	3-178 days	13-225 days	9-137 days	15-93 days

Radiographic recovery from a first episode of ARIA-E occurred in 59% of cases by 12 weeks, 80% of cases by 16 weeks, and 90% of cases by 20 weeks and 99% of cases overall. Radiographic recovery from all episodes of ARIA-E occurred in 60% of cases by 12 weeks, 79% of cases by 16 weeks, 90% of cases by 20 weeks, and 98% of cases overall. The Sponsor reported that resolution occurred in 68% of ARIA-E events by 12 weeks, 91% by 20 weeks, and 98% overall after detection. The numbers differ from the Agency's analysis because of differences in rounding of numbers. I counted resolution by 12 weeks literally while the sponsor rounded and counted "an ARIA-E event that was documented as resolved on a scan performed 12 weeks and 2 days after detection would be counted as having resolved within 12 weeks," as noted in the response to an information request dated May 27, 2021. Ten percent (113/1105) of all patients who received aducanumab 10 mg/kg had more than one episode of ARIA-E (May 25, 2021, applicant response to labeling document, appendix 2, page 5).

Impact of ApoE ε4 Allele Status on Frequency of ARIA Type and Timing of First Instance of ARIA

Next, I examined the impact of ApoE ε4 status on the rates of ARIA. The most compelling findings are presented in Tables 13 and 14, with supporting data in Figure 2.

Table 13: Incidence of ARIA types in the Placebo-Controlled Portion of Studies 301 and 302 by ApoE ε4 status

	ARIA-E		ARIA-H Microhemorrhage		ARIA-H Superficial Siderosis	
Laboratory ApoE ε4 status	10 mg/kg aducanumab N=1103	Placebo N=1083	10 mg/kg aducanumab N=1103	Placebo N=1083	10 mg/kg aducanumab N=1103	Placebo N=1083
Homozygote (n=377)	117/182 (64.3%)	6/195 (3.1%)	75/182 (41.2%)	19/195 (9.7%)	60/182 (33.0%)	6/195 (3.1%)
Heterozygote (n=1108)	200/564 (35.5%)	10/544 (1.8%)	93/564 (16.5%)	36/544 (6.6%)	81/564 (14.4%)	8/544 (1.5%)
Noncarrier (n=701)	70/357 (19.6%)	13/344 (3.8%)	44/357 (12.3%)	15/344 (4.4%)	21/357 (5.9%)	10/344 (2.9%)

*Of note, a small number of patients did not have genotype available: 4 patients in placebo and 2 patients in the 10 mg/kg aducanumab group. They are not included in this table.

As can be seen in Table 13, for patients allocated to the treatment arm of 10 mg/kg aducanumab, the risk for ARIA-E, ARIA-H microhemorrhages, and ARIA-H superficial siderosis is higher in ApoE ε4 carriers relative to noncarriers. In general terms, in the treatment arm of 10 mg/kg aducanumab, there is roughly a doubling of risk of ARIA when going from noncarrier to heterozygote ApoE ε4 carrier, and another doubling of risk going from heterozygote ApoE ε4 carrier to ApoE ε4 homozygote carrier. Similar findings were observed when evaluating patients with ARIA-H microhemorrhage or superficial siderosis with ARIA-E (data not shown in this review).

Next, I examined the impact of ApoE4 genotype on the incidence of first episode of ARIA. The data from this analysis is presented in Figure 2, 3, and 4. As shown in the figure below, the steep component of the curve for experiencing ARIA-E also is of longer duration for the ApoE ε4 homozygotes.

Figure 2: Incidence of ARIA-E in the Placebo-Controlled Portions of Studies 301 and 302 in ApoE ε4 Noncarriers

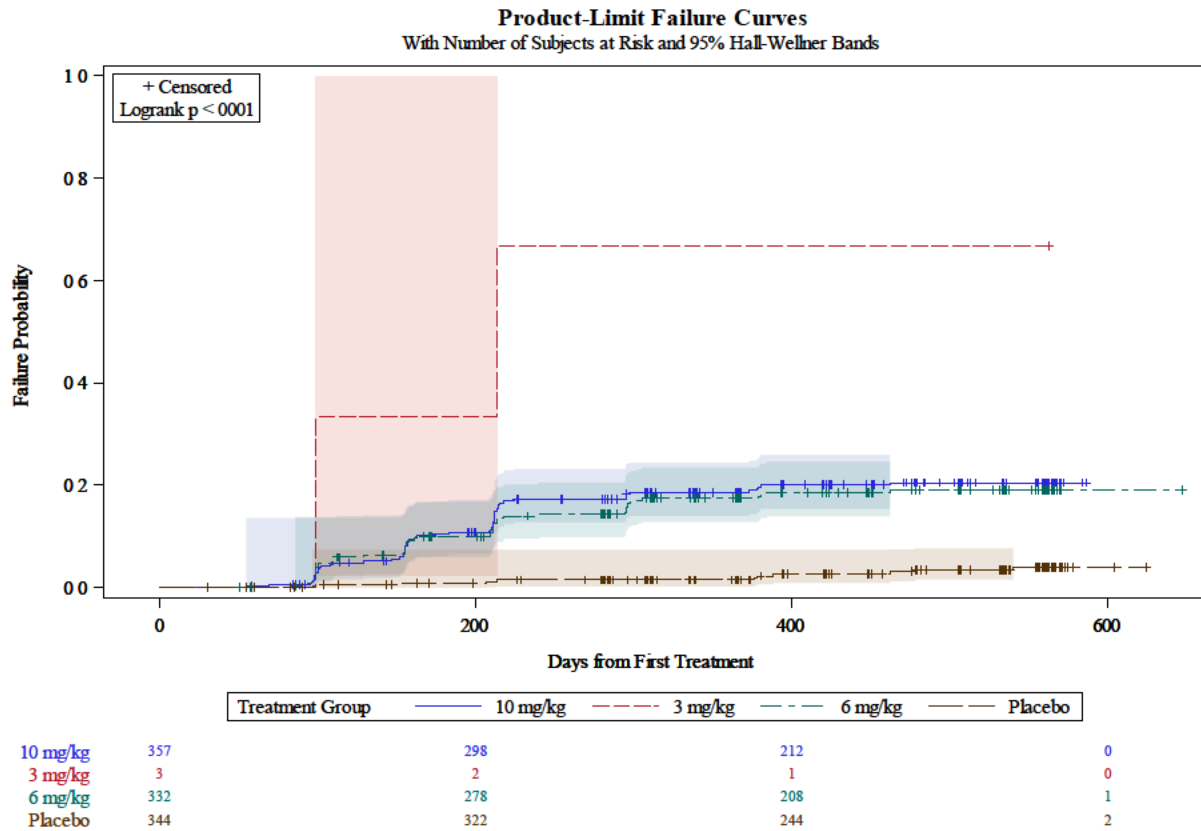


Figure 3: Incidence of ARIA-E in the Placebo-Controlled Portions of Studies 301 and 302 in ApoE ϵ 4 Heterozygotes

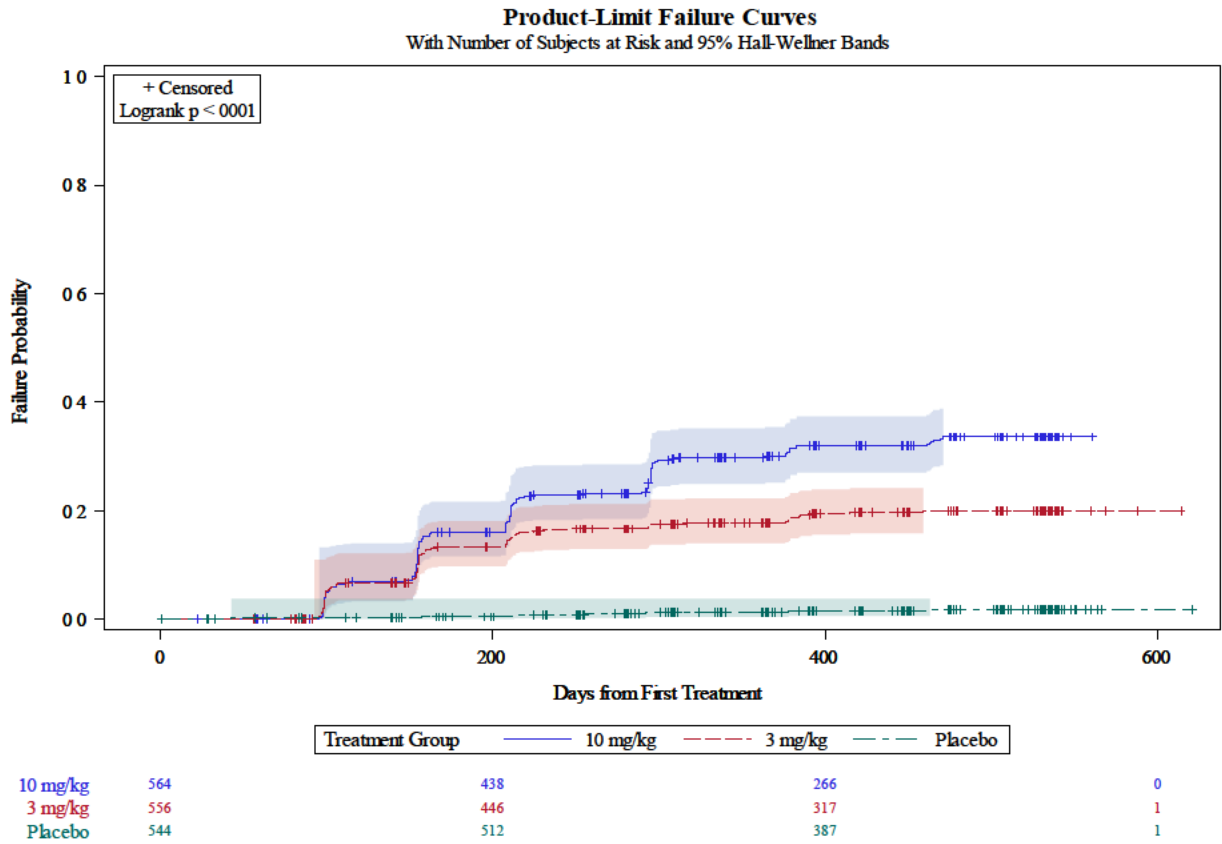
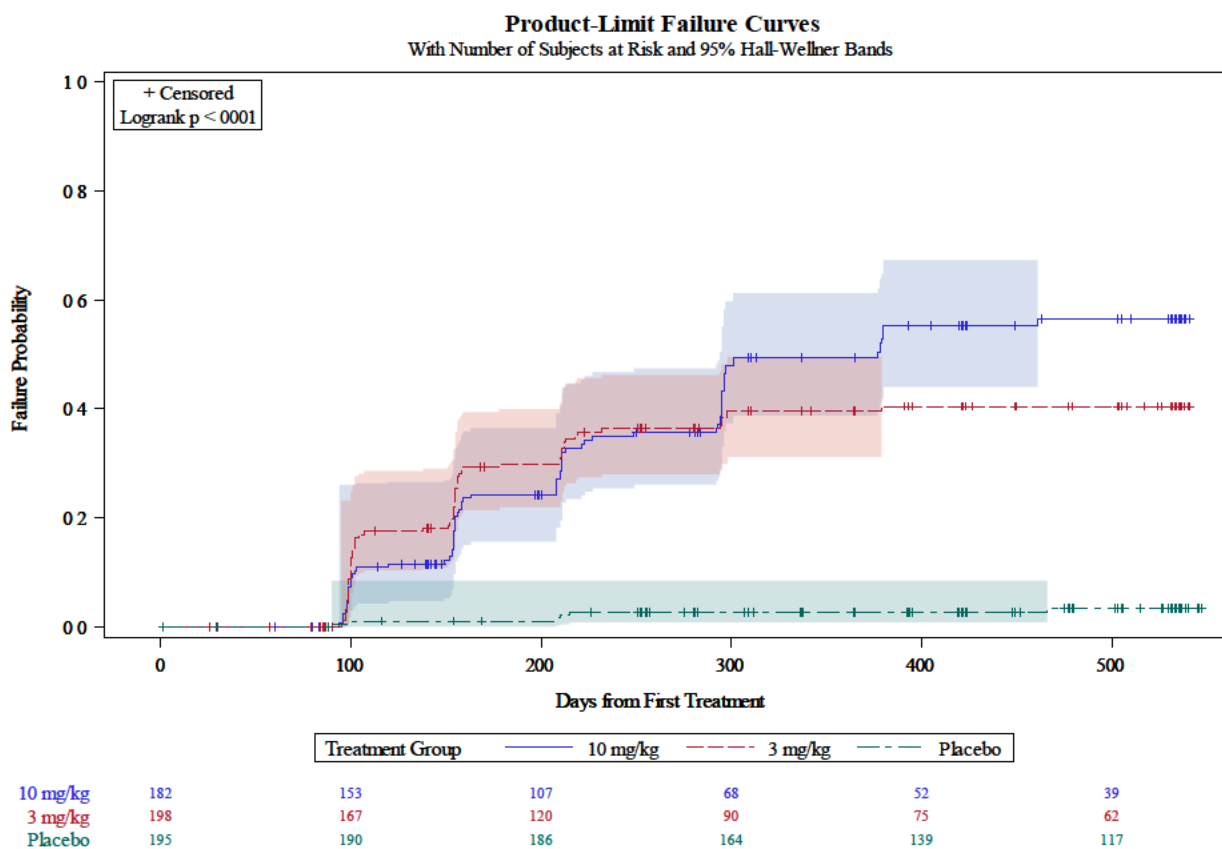


Figure 4: Incidence of ARIA-E in the Placebo-Controlled Portions of Studies 301 and 302 in ApoE ε4 Homozygotes



(b) (4)

Given that there was a case of serious ARIA in an ApoE ε4 homozygote after the 11th infusion, I investigated the incidence of ARIA events by ApoE ε4 status prior to the 9th infusion (Day 224) and prior to the 12th infusion (Day 308).

Table 14: Incidence of ARIA type by ApoE ε4 Status at 9th Infusion and 12th Infusion in those treated with 10 mg/kg aducanumab in the placebo-controlled portion of Study 302

	ApoE ε4 noncarrier		ApoE ε4 heterozygote		ApoE ε4 homozygote	
	Before 9 th	Before 12 th	Before 9 th	Before 12 th	Before 9 th	Before 12 th
ARIA-E	61/357 (17.1%)	65/357 (18.2%)	139/564 (24.64%)	176/564 (31.2%)	84/182 (46.2%)	106/182 (58.2%)
ARIA-H	25/357 (7.0%)	30/357 (8.4%)	54/564 (9.6%)	73/564 (12.9%)	52/182 (28.6%)	64/182 (35.2%)
Microhemorrhage						

	ApoE ε4 noncarrier		ApoE ε4 heterozygote		ApoE ε4 homozygote	
	Before 9 th	Before 12 th	Before 9 th	Before 12 th	Before 9 th	Before 12 th
ARIA-H Superficial Siderosis	17/357 (4.8%)	19/357 (5.3%)	45/564 (8.0%)	61/564 (10.8%)	43/182 (23.6%)	53/128 (41.4%)

As seen in Table 14, extending the time for MRI monitoring results in increased capture of ARIA events in noncarriers, heterozygote, and homozygotes, as would be expected. There are two interesting findings present in the above table. First, it appears that there may be a different risk for the different forms of ARIA based on the number of ApoE ε4 alleles. Second, the increase in yield by extending the MRI imaging out to before the 12th infusion is most profoundly seen in the ApoE ε4 carriers.

Additional Baseline Characteristics and ARIA

Given the frequency of ARIA in the aducanumab treated population, I set out to compare baseline characteristics of patients in the placebo-controlled portion of studies 301 and 302 treated with 10 mg/kg with those treated with placebo to identify if any increased the risk of ARIA. An exploration of risk factors included presence or absence of microhemorrhages on the baseline MRI, presence or absence of select concurrent anti-thrombotic medications (predominantly aspirin), age, and sex.

Presence or Absence of Microhemorrhages on Baseline MRI

Analysis of the presence or absence of microhemorrhages on baseline MRI in the placebo-controlled portion of those in the treatment arm of 10 mg/kg aducanumab relative to placebo revealed that those with baseline microhemorrhages had an increased risk for ARIA-E and ARIA-H microhemorrhages, but not ARIA-H superficial siderosis. The risk for ARIA-H microhemorrhage was also increased in those treated with placebo who had started out with microhemorrhage at baseline.

Table 15: Incidence of ARIA types in the Placebo-Controlled Portion of Studies 301 and 302 by Presence or Absence of Microhemorrhage on Baseline MRI

Baseline Microhemorrhage	ARIA-E		ARIA-H Microhemorrhage		ARIA-H Superficial Siderosis	
	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087
Yes (n=297)	65/138 (47.1%)	6/159 (3.8%)	41/138 (29.7%)	24/159 (15.1%)	24/138 (17.4%)	7/159 (4.4%)
No (n=1874)	322/957 (33.6%)	23/917 (2.5%)	171/957 (17.9%)	47/917 (5.1%)	138/957 (14.4%)	17/917 (1.9%)

However, statistical analysis of the presence or absence of microhemorrhages on baseline MRI in the placebo-controlled portion of studies 301 and 302 of those treated with 10 mg/kg aducanumab relative to placebo revealed hazard ratios with confidence intervals that overlapped.

Presence or Absence of Concomitant Aspirin-Containing Medications and Non-Aspirin Anticoagulants

I investigated whether concomitant use of aspirin, aspirin-containing medications, and non-aspirin anticoagulants (referred to in the BLA as anti-thrombotic medications) had an impact on the incidence of ARIA. It is important to note that these results are primarily driven by patients on concomitant aspirin ≤ 325 mg because the protocol excluded “use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).” However, in a June 2, 2021, response to an information request, the applicant confirmed that there were 95 instances of concomitant use of a non-aspirin antiplatelet or anticoagulant medication in 77 patients. These medications included apixaban, clopidogrel, rivaroxaban, enoxaparin, and heparin, among others. The median duration of use was 19 days (range 1-881 days). Among the indications were venous thrombosis, atrial fibrillation, pulmonary embolism, and prophylaxis.

Table 16: Incidence of ARIA types in the Placebo-Controlled Portion of Studies 301 and 302 by Concomitant Anti-Thrombotic Medication Status*

Anti-thrombotic medication during the study*	ARIA-E		ARIA-H Microhemorrhage		ARIA-H Superficial Siderosis	
	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087
Yes (n=830)	148/430 (34.4%)	11/400 (2.8%)	86/430 (20.0%)	39/400 (9.8%)	62/430 (14.4%)	9/400 (2.3%)
No (n=1341)	239/665 (35.9%)	18/676 (2.7%)	126/665 (18.9%)	32/676 (4.7%)	100/665 (15.0%)	15/676 (2.2%)

*The term “anti-thrombotic” includes aspirin, other antiplatelet drugs, and anticoagulants.

Approximately 83% of patients taking anti-thrombotic medication received aspirin while approximately 17% of patients taking anti-thrombotic medication received other antiplatelet medication or anticoagulant medication.

Concomitant anti-thrombotic medication (primarily aspirin ≤ 325 mg daily) did not increase the risk for ARIA in the treatment arm of 10 mg/kg aducanumab. The protocols also excluded patients with a history of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at screening. In studies 301 and 032, fewer than 2% of patients on aducanumab 10 mg/kg had a history consistent with an underlying bleeding or clotting disorder, according the June 1, 2021 response to an information request. Therefore, whether the use aducanumab in patients predisposed to bleeding increases the risk of hemorrhage caused by aducanumab is not known.

The Impact of Age and Sex on Incidence of ARIA

The incidence of ARIA is overall balanced between the sexes except for ARIA-H superficial siderosis, which was more common in males treated with 10 mg/kg aducanumab relative to females. The incidence of ARIA in the 10 mg/kg aducanumab treatment arm is generally well balanced among the different age groups, except for a slightly lower incidence of ARIA-E in the oldest age group aged 81-85, although the number of patients in that age group was limited relative to younger patients. Additionally, in those patients treated with 10 mg/kg aducanumab, there was an increased incidence of ARIA-H microhemorrhage with increased age. The impact of these demographic factors is shown in the tables below.

Table 17: Incidence of ARIA types in the Placebo-Controlled Portion of Studies 301 and 302 by Sex

Sex	ARIA-E		ARIA-H Microhemorrhage		ARIA-H Superficial Siderosis	
	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087
Female (n=1162)	198/577 (34.3%)	13/575 (2.3%)	118/577 (20.5%)	36/575 (6.3%)	62/577 (10.7%)	10/575 (1.7%)
Male (n=1040)	189/528 (35.8%)	16/512 (3.1%)	94/528 (17.8%)	35/512 (6.8%)	100/528 (18.9%)	14/512 (2.7%)

Table 18: Incidence of ARIA types in the Placebo-Controlled Portion of Studies 301 and 302 by Age Groups

	ARIA-E		ARIA-H Microhemorrhage		ARIA-H Superficial Siderosis	
Age	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087	10 mg/kg aducanumab N=1105	Placebo N=1087
51-60 (n=270)	49/139 (35.3%)	3/131 (2.3%)	18/139 (12.9%)	7/131 (5.3%)	17/139 (12.2%)	1/131 (0.8%)
61-70 (n=758)	134/363 (36.9%)	15/395 (3.8%)	67/363 (18.5%)	26/395 (6.6%)	55/363 (15.2%)	7/395 (1.8%)
71-80 (n=1012)	181/529 (34.2%)	11/483 (2.3%)	108/529 (20.4%)	30/483 (6.2%)	81/529 (15.3%)	15/483 (3.1%)
81-85 (n=152)	23/74 (31.1%)	0/78 (0.0%)	19/74 (25.7%)	8/78 (10.3%)	9/74 (12.2%)	1/78 (1.3%)

Sponsor's Proposal for MRI Monitoring



Conclusions on ARIA and aducanumab

MRI Monitoring:

During the trials, the Sponsor conducted scheduled MRIs before the 5th, 7th, 9th, 12th, 15th, 18th, and after the 20th infusions. Decisions to hold treatment were made based on the results of MRI monitoring. The question is whether detecting isolated radiographic changes in the absence of clinically meaningful

symptoms provides a safety benefit. Referring to Tables 2 and 3, it is important to note that for any ARIA other than asymptomatic radiographic mild ARIA, the dose of aducanumab was held per protocol. It is difficult to quantify the safety benefit of MRI monitoring and holding aducanumab dosing. The sponsor noted 44 cases where participants with moderate or severe ARIA-E were dosed with aducanumab at least once after ARIA was identified. There were 2 cases of these 44 where patients received aducanumab after having moderate ARIA-E and subsequently developed ARIA-H hemorrhage greater than 1 cm. On reviewing the datasets, I found these to be patients (b) (6). Patient (b) (6) had moderate ARIA-E on Day 155, had his dose of aducanumab reduced from 3 mg/kg to 1 mg/kg for his 7th dose, and subsequently developed a cerebral hematoma 5 x 3 x 5 cm in the right frontal lobe, with apathy. Patient (b) (6) had moderate ARIA-E after receiving his 11th dose of aducanumab, and had a mild asymptomatic cerebral hemorrhage after receiving his 12th dose of aducanumab, which, in greatest dimension, was 15 mm right parietal and 12 mm left frontal. Considering that there were 7 patients in all aducanumab treatment arms and 4 patients in placebo that experienced ARIA-H macrohemorrhage, it is interesting that two of them received aducanumab in the setting of moderate ARIA-E. Whether they would have experienced ARIA-H cerebral hemorrhage >1cm if the dose was held is unknown. There were two of the 44 cases who had serious symptomatic ARIA in the long-term extension period of the trials. There was a case with seizure and hemianopsia that I find to be patient (b) (6). This patient had moderate ARIA-E on Day 660, received a 6th dose of aducanumab on Day 702, and on Day 717 had severe ARIA-E and >10 microhemorrhages, with hemianopia on Day 717, and seizure on Day 730, which both resolved. There was also a serious symptomatic ARIA case with unresolved visual impairment. Based on the symptoms and reviewing the narrative, I find this to be case (b) (6). On Day 750, the patient had an MRI with asymptomatic moderate ARIA-E, subsequently received his 7th dose at 10 mg/kg aducanumab on day 757 and developed symptomatic severe ARIA-E and severe ARIA-H superficial siderosis with visual deficit that did not resolve. Overall, the number of cases where patients were dosed with aducanumab in the setting of moderate or severe ARIA-E is small (n= 44), and it is difficult to make a strong conclusion from this data set. However, there is some indication that there could be benefit from MRI monitoring from a safety perspective.

Based on my ARIA analysis, there are different ways to approach scheduled MRI monitoring. A conservative approach would recommend conducting scheduled MRI monitoring before the 4th, 6th, 8th, 10th, and 12th infusions. The rationale for this stems from data from serious ARIA cases and a finding that the majority of serious ARIA occurred after administering between the 2nd and 11th doses, with the majority between the 3rd and 8th dose of aducanumab as illustrated in Table 11. If there is a safety benefit to MRI monitoring and holding aducanumab in cases of asymptomatic moderate and severe ARIA, these time points could be appropriate. However, a problem with this approach is that we cannot quantify the safety benefit MRI monitoring and holding aducanumab dosing based on MRI findings. There were too few instances where patients received aducanumab that differed from protocol rules for holding dose. Additionally, one must consider the patient burden of administering this number of MRIs in an Alzheimer patient population. A liberal approach would be to recommend no scheduled MRI monitoring. However, a problem with this approach is that it is difficult to quantify the risk that removing the extensive MRI monitoring that was done during the trials would pose.

After careful reflection, I would recommend MRI monitoring prior to the 7th and 12th infusions with the following rationale. First, MRI monitoring prior to the 7th infusion would occur during the titration period and prior to the administration of the first 10 mg/kg aducanumab dose. Second, this schedule of MRIs would align directly with two of the MRI assessment time points from the trials, allowing the potential for a comparison with post-marketing findings. For example, based on data from the trials, 95/1105 (8.6%) of patients assigned to the 10 mg/kg group experienced their first new ARIA-H microhemorrhage from baseline prior to the 7th infusion, and 167/1105 (15.1%) of patients assigned to the 10 mg/kg group experienced their first new ARIA-H microhemorrhage from baseline prior to the 12th infusion. One potential way to quantify the impact of reduced MRI monitoring frequency from the clinical trial would be to monitor for a difference in the rate of ARIA-H microhemorrhage in 301 and 302 compared to the frequency (or incidence) in the postmarketing period. This measure or other measures would be best if the scheduled monitoring points aligned with points in the trial. Third, conducting a scheduled MRI prior to the 12th infusion would allow for better capture of later first ARIA events, particularly in cases of ApoE ϵ 4 carriers as, per Table 14, while 46.2% of ApoE E4 homozygote carriers would experience their first ARIA-E prior to the 9th infusion, expanding this to prior to the 12th infusion would result in the detection of 58.2% of ApoE ϵ 4 patients having a first ARIA-E. It is important to note that (b) (4) the optimal schedule for MRI monitoring has not been determined. As the sponsor notes in the revised proposed labeling, there are no systematic data on continuing dosing with aducanumab following detection of radiographically moderate or severe ARIA. In addition, the optimal MRI monitoring schedule has not been identified. Given limited data, I conclude scheduled MRI monitoring prior to the 7th and 12th infusions would be appropriate.

Potential Post-Market Monitoring Considerations if Approved:

Whether patients who have more than 2 superficial siderosis or 10 or more microhemorrhages during treatment should continue to be treated has not been tested in the aducanumab studies. While the protocol discontinued patients who had this number of episodes of superficial siderosis or microhemorrhages, the sponsor states in its proposed label (b) (4) .” Additionally, during the trials, patients with macro-hemorrhage (> 1 cm) were required to permanently discontinue treatment. There is no such requirement in the current proposed label. If aducanumab were to be approved, I would recommend specifically monitoring the outcomes of patients who continue treatment with more than 2 superficial siderosis, 10 or more microhemorrhages, or macro-hemorrhage. We do not have data from the trials on patients with 5 to 9 brain microhemorrhages at baseline as exclusion criteria excluded those with greater than 4 microhemorrhages from entering the trial. Therefore, if aducanumab were to be approved, I recommend specifically monitoring the outcomes of patients who had 5-9 brain microhemorrhages in their baseline MRI.

Postmarketing enhanced pharmacovigilance should be requested for ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 cm, to 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. This should also include evaluation of patient characteristics, including APO ϵ 4 genotype if available. Information collected should be used to optimizing monitoring and minimizing risk.

Clinical Review (ARIA)
Brian Trummer, MD, PhD
BLA761178
Aduhelm/aducanumab

Educational Program on ARIA:

The Sponsor proposed a communication plan Risk Evaluation and Mitigation Strategy to mitigate the risk of ARIA. The Agency has determined that there is not a need for a REMS. The applicant has proposed a voluntary education plan for radiologists and providers on the risk of ARIA.

Warning for ARIA:

I recommend that the label include the warning for ARIA. The warning should describe the symptoms that have been observed with ARIA, including visual disturbances, with mention that some adverse events may not resolve. However, I do not believe a boxed warning would be necessary at this time. It should be noted that this data arose from the controlled setting of a clinical trial. If approved, a reassessment of risk in clinical practice, for example in the absence of concomitant medication exclusion criteria and other clinical trial infrastructure, could be warranted based on the data at that time.

Appendix A:
Cases of Serious ARIA in Studies 301 and 302

There was a total of 29 cases of serious ARIA in the placebo-controlled and long-term extension periods of Study 301 and 302. First, I will present 4 cases as exemplars of certain symptomatic presentations in the setting of serious ARIA, followed by groupings of serious ARIA cases by symptom with an additional 7 cases that involved visual disturbances, 2 cases that involved impact on motor strength, and present the remaining 16 cases of serious ARIA for completion.

An Example of Headache and Confusional State Manifestations of Serious ARIA

Given that the most frequent symptoms of serious ARIA included confusional state and headache, I have selected a case example that presents both in a contextual state.

Participant ID: (b) (6)

Subject (b) (6) was a 72-year-old female with mild cognitive impairment (MCI) due to Alzheimer's Disease diagnosed in (b) (6), with a homozygous ApoE ε4 carrier status who developed symptomatic ARIA-E 15 days after the 4th dose of aducanumab that had been given every 4 weeks (2 doses of 1 mg/kg and 2 doses of 3 mg/kg). Concomitant medications included donepezil. On Day 99, she experienced symptomatic severe ARIA-E as determined by MRI with mild headache and noted feeling ill/fatigue for a couple of days. Her headache was treated with paracetamol and was considered resolved on Day 111. Prior to the event, the patient had been able to independently walk and go shopping. Beginning on Day 107, she had severe episodic memory and word finding difficulties with normal neurological status and a worsening of memory impairment described as not being oriented to time, unable to remember names of her grandchildren, worsening of ability to perform activities of daily living (including shopping or using the dishwasher) and requiring continuous supervision that lasted 3 months. On Day 126, the subject experienced symptomatic ARIA-H microhemorrhage, with 2 new microhemorrhages and worsened severe ARIA-E seen on MRI, with significantly impaired memory reported. The edema, mainly in the right hemisphere, had progressed in size, and the ventricle and sulci were compressed. The subject began treatment with betamethasone sodium phosphate 0.5 mg PO TID (tapered on Day 139 and discontinued on Day 140). Study treatment was permanently discontinued as a result of the SAE of symptomatic ARIA-E. On Day 138, ARIA-H-microhemorrhages and hemosiderin deposits worsened in severity with > 10 new microhemorrhages found in the setting of severe stable vasogenic edema per MRI. On Day 140, the participant was discharged home with some improvement in memory and daily function. On Day 146, the subject had improvement in memory and daily function but not to baseline. ARIA-H was reported as resolved/stabilized on Day 166. Her ARIA-E was reported as resolved on Day 195. MRI scan on this day showed complete resolution of vasogenic edema, severe >10 microhemorrhages (stable), no superficial siderosis, and no macrohemorrhage. Memory impairment was reported as resolved on Day 196.

Reviewer comment:

This patient developed symptomatic ARIA-E with headache and memory loss interfering with activities of daily living beginning 15 days after the 4th dose of aducanumab, with ARIA-H developing in the same locations 37 days later. ARIA-E and ARIA-H/memory impaired resolved approximately 2 and 3 months later, respectively. This case demonstrates that patients can have prolonged cognitive symptoms as she went from independently shopping to requiring supervision for 3 months.

An Example of Visual Manifestations of Serious ARIA

Given the fact that visual manifestations occurred in instances of serious ARIA, I have selected a case example that presents this in a clinical context.

Participant ID: (b) (6)

This was a 69-year-old male with mild cognitive impairment due to Alzheimer's Disease and homozygous for ApoE ϵ 4. On Day 660, 15 days after his 4th dose of aducanumab in the long-term extension period, with last dose at 3 mg/kg, and previously on placebo during the placebo-controlled period subject experienced ARIA-E and ARIA-H microhemorrhages. He was also taking acetylsalicylic acid. His MRI scan showed moderate new vasogenic edema in the right parietal region and 2 new microhemorrhages in the right parietal region. On Day 669, his EEG showed almost continuous focal slowing over the right hemisphere indicative of a structural or functional lesion. His aducanumab continued to be uptitrated based on the reported dosing dates. On Day 717, 15 days after his 6th dose of aducanumab in the long-term extension period, with his last dose at 6 mg/kg, the events of amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits and amyloid related imaging abnormality-edema/effusion worsened in severity in the right parietal, right temporal, and right occipital regions, with nine new microhemorrhage were seen. On Day 717, the participant had nonserious events of hemianopsia and confusion. On Day 730, subject presented to the Emergency Department reporting seeing a "Christmas light" in the left visual field and was confused with a left gaze preference and was admitted to the neurological intensive care unit. His MRI scan that day showed severe vasogenic edema in the left occipital, right frontal, right occipital, right parietal, and right temporal regions which had increased in size since the previous MRI scan, >10 microhemorrhages in the right frontal, right parietal, and right temporal regions, 7 of which were new since the previous MRI scan. He was treated with levetiracetam for seizure and mannitol and dexamethasone for ARIA-E. On Day 740, the participant was discharged from the hospital to an extended care facility. His hemianopia resolved on Day 758, while his confusional state remained unresolved for the remainder of the study. On Day 758, the event of symptomatic ARIA-H was reported as resolved/stabilized. On Day 789 and Day 821, 3 and 4 new microhemorrhages were seen in the right frontal, right parietal and right temporal regions. The event of symptomatic ARIA-H was reported as resolved/stabilized on Day 854. On Day 1059, the participant experienced asymptomatic ARIA-H (microhemorrhage) 4 of which were new in the right frontal, right parietal, and right temporal regions which resolved on Day 1094 (the day of his final assessment in the study).

Reviewer's comments:

I note that the two instances of ARIA-E and ARIA-H microhemorrhage occurred 15 days after his 4th and 6th dose of aducanumab. The symptoms arising after the 6th dose, including seeing light in his

left visual field with the finding of ARIA-E in the left and right occipital regions. His hemianopia was present for 41 days and resolved. While his treatment was discontinued after his last dose on Day 702, he continued to have instances of new ARIA-H microhemorrhages on Days 730, 789, 821, and 1059.

An Example of Impaired Motor Strength in Cases with Serious ARIA

Given the fact that impairment of motor strength occurred in some instances of serious ARIA, I have selected a case example that presents this in a clinical context.

Participant ID: (b) (6)

This was a 59-year-old white female with mild cognitive impairment due to Alzheimer's Disease who was heterozygous for ApoE ε4. She took placebo during the placebo-controlled period and began the long-term extension period. On Day 652, 7 days after her 4th dose of aducanumab with last dose at 3 mg/kg, she experienced symptomatic ARIA-E and was taken to the Emergency Department with 3 days of left-sided weakness and was admitted to the hospital. Her MRI scan showed moderate vasogenic edema in the left parietal, right frontal, right occipital, and right parietal regions. She was symptomatic with left-sided weakness and diplopia. She initially had no movement of the left upper extremity and 3/5 strength of the left lower extremity and was having some paresthesias to the left lower extremity. Her EEG was consistent with a mild diffuse encephalopathy. On Day 654, her MRI showed expansile asymmetric T2 hyperintense signal involving the periventricular white matter extending to involve the subcortical U fibers. Central read of the same brain MRI showed moderate vasogenic edema in the right frontal, right parietal, right occipital, and left parietal and occipital lobes, which was increased in size compared to previous MRI. On Day 655 plasmapheresis was performed. On Day 661, the participant could move her left leg and squeeze with her left hand. On Day 665, the participant was showing some gross movement of her left arm and was discharged to rehabilitation on Day 666. Her hemiparesis was reported as resolved on Day 678. On Day 686, the participant experienced asymptomatic ARIA-H (microhemorrhage) with 2 new microhemorrhages in the right frontal region. This ARIA-H microhemorrhage was reported resolved on Day 722. Her diplopia resolved on Day 739 and her ARIA-E resolved on Day 771.

Reviewer Comment:

This case is unique in that it is the first that I see that used plasmapheresis after subject experienced symptomatic ARIA-E with left sided hemiplegia, which lasted 26 days and ARIA-E that resolved in 119 days. Since plasmapheresis is typically used to remove harmful antibodies across various disorders, it is plausible that plasmapheresis may have been helpful in this case. Future work evaluating plasmapheresis in cases of serious symptomatic ARIA could be useful.

An Example of a Complicated Medical Course and Death in a case with Serious ARIA

Subject (b) (6)

This was an 80-year-old female with mild cognitive impairment due to Alzheimer's Disease, and a past medical history significant for breast cancer, hysterectomy, mastectomy, and dyslipidemia. She

had her 5th dose aducanumab on Day 113. On Day 130, subject was found on the floor with her last known normal state on Day 127 and presented to the hospital with confusion, disorientation, behavior changes, delirious ideas, and a slowdown of her psychomotor skills. Her head CT scan showed what was thought to be an ischemic attack in the right sylvian area and no hemorrhage. On Day 134, 21 days after her 5th dose of aducanumab, she experienced symptomatic ARIA-E and symptomatic ARIA-H (superficial siderosis) and I have reviewed the relevant MRIs myself. She was started on IV methylprednisolone 80 mg for 3 days with discontinuation of study treatment. She experienced symptomatic ARIA-E with episodes of confusion, with disorientation, delusional thoughts, and intermittent inappropriate behavior that resolved on Day 143. On Day 147, she experienced seizure, agitation, gait imbalance, worsening confusion, and 2 falls. The participant received another dose of methylprednisolone 80 mg. On Day 148, electroencephalogram showed slow, moderate anomalies in the right hemisphere, with right temporal-parietal epileptiform discharges spreading to the entire right hemisphere. Treatment medications included levetiracetam and clobazam. The participant's agitation had diminished and an improvement in the temporospatial disorientation was noted. On Day 150, the participant started to return to her normal state. On Day 151, she experienced status epilepticus. Lamotrigine was started, and she was given morphine for pain. On Day 155, she had a pontine lacunar infarct, cortical infarct, left cerebellar infarct and coma. On the same day, the event of ARIA-H (superficial siderosis of central nervous system) was reported as resolved/stabilized. Her MRI scan also showed evidence of new cerebellar ischemic cerebrovascular accident on the left. On Day 157, the participant experienced encephalopathy. On Day 161, an EEG showed trace in favor of metabolic encephalopathy; no epileptic abnormality or crisis was noted. On Day 160, subject was found to have a positive influenza B by PCR lab results and died 11 days later, on Day 171.

Reviewer's comment:

This subject experienced symptomatic ARIA-E and ARIA-H 21 days after her 5th dose of aducanumab. Her ARIA-H consisted of symptomatic ARIA-H (superficial siderosis) and microhemorrhages. Subsequently, she experienced falls, seizure, status epilepticus, coma, and death. I have reviewed this complicated case in detail, looking at medical records, imaging, and laboratory results. On reviewing these MRI images from Day 134, ARIA is clearly visible, but I do not see any midline shift or gross mass effect present that would indicate any danger of increased intracranial pressure. She was treated with methylprednisolone 80 mg for three days and discharged to home on Day 143. I reviewed labs on Day 147 and there was no hyponatremia with a sodium of 136 mmol/L, slight elevated glucose at 7.10 mmol/L, elevated CRP at 22.6 mg/L. When the subject had her repeat MRI on Day 155, the radiologist noted in the FLAIR sequence the areas of hyperintensity in the bilateral temporal cortical-subcortical region were stable, and she had previously been discharged home in that state. I can confirm that the subject does appear to have suffered a relatively small ischemic stroke in the left cerebellum and questionable right pontine stroke on Day 155. There was a notation of attenuated flow in the left vertebral artery, and at the time had a CRP of 91.4 mg/L. She also had a positive influenza B by PCR lab result 11 days before her death.

My overall impression is that the subject did indeed have ARIA, but I conclude this was probably incidental and did not play a role in her death and suspect her positive influenza B status. I saw no compressive or mass effect from the ARIA after reviewing the imaging, and note the patient was initially

discharged to home, and on return to the hospital had repeat imaging with MRI findings characterized as stable. On reviewing the data for the placebo-controlled portion of Study 302 searching the AEDECOD term “seizure”, I found three patients who experienced seizure. One subject was the one discussed here, while the other two patients were on placebo. This balance in seizure frequency in treatment and control reassures me that the ARIA and seizure were likely not related.

7 Additional Cases of ARIA with Visual Symptoms During the Course of the Studies:

Participant ID: [REDACTED] (b) (6)

This was a 70-year-old white male with mild cognitive impairment due to Alzheimer’s Disease who was heterozygous for ApoE ϵ 4 who, on Day 94, 10 days after his 4th (and last) dose of aducanumab with most recent dose of 3 mg/kg experienced head pressure in the occipital region, visual disturbance (characterized as seeing little black and white spots, flashes of light moving from left to right and smooth surfaces appearing rough), balance difficulty, wide-based gait. On Day 97, the visual symptoms increased where he experienced occasional diplopia, a visual sensation of rain or snow falling, multiple spots superimposed on objects, moving images of stationary objects. It was found that on Day 98, 14 days after his 4th dose he experienced symptomatic ARIA-H superficial siderosis in the right occipital and right parietal regions with ARIA-E and the ARIA-H superficial siderosis resolved/stabilized on Day 114, 16 days after onset. On Day 142, subject experienced a second event of symptomatic ARIA-H (superficial siderosis) in the left frontal region, and his study treatment was permanently discontinued as a result of the second event of symptomatic ARIA-H (superficial siderosis) per protocol. On Day 160, he had improved balance and gait since previous examination and visual impairment resolved.

Reviewer comment:

This case provides insight into visual disturbances associated with ARIA-E and ARIA-H. This subject experienced symptomatic ARIA-H superficial siderosis and ARIA-E 14 days after his 4th dose of aducanumab. This resulted in 66 days of visual disturbance (characterized as seeing little black and white spots, flashes of light moving from left to right and smooth surfaces appearing rough with no mention of headache in the narrative), 66 days of balance difficulty, and 66 days of wide-based gait. His ARIA-H superficial siderosis resolved 16 days after onset and ARIA-E resolved 77 days after onset. His treatment was discontinued after experiencing his second superficial siderosis on day 142, 38 days after his 4th dose of aducanumab. Of note, after discontinuation of aducanumab, this subject continued to experience episodes of ARIA-H microhemorrhages (with onset 78, 87, 121, days after last dose) and superficial siderosis (with onset 293 days after last dose).

Participant ID: [REDACTED] (b) (6)

This was a 69-year-old male heterozygote carrier of ApoE ϵ 4 with mild cognitive impairment due to Alzheimer’s disease who received placebo initially, and then started aducanumab in the long-term

extension (LTE) period. On Day 701, he received his 5th dose of aducanumab in the LTE period, most recent dose at 6 mg/kg. Seven days later, on Day 708, he had asymptomatic ARIA-E and asymptomatic ARIA-H with 2 new microhemorrhages. His ARIA-H microhemorrhage resolved on Day 722. He received his 6th dose on Day 729 at 6 mg/kg. On Day 736, the participant experienced another asymptomatic ARIA-H (microhemorrhage) and resolved on Day 750. On Day 750, the participant experienced asymptomatic ARIA-H (superficial siderosis) which resolved/stabilized on Day 764. On Day 757 subject received his 7th dose of aducanumab with most recent dose at 10 mg/kg. On Day 785, the participant experienced worsening symptomatic ARIA-H (superficial siderosis). The participant was symptomatic and was reported with a nonserious treatment emergent adverse event of visual impairment. An increase in difficulties with visual perception, apraxia, and spatial orientation was also reported. MRI scan on this day showed severe vasogenic edema (locations: left parietal, left temporal, right occipital, right parietal, and right temporal regions), which had increased in size compared to his previous MRI scan, 4 stable microhemorrhages in the left parietal and left temporal regions, severe superficial siderosis in the left occipital region that increased in size, left parietal, left temporal, right occipital, and right parietal regions that were all new. He had a new visual field defect when looking down and was unable to recognize various objects on a table in front of him. On Day 786, he was diagnosed with symptomatic ARIA-E with homonymous peripheral visual defects. He received dexamethasone for symptomatic ARIA-E. The event of superficial siderosis of central nervous system was reported as resolved/stabilized on Day 791. High-dose steroid therapy was indicated in the presence of newly occurring clinical symptoms. He was discharged on Day 792. The event of amyloid related imaging abnormality-edema/effusion was reported as resolved on Day 834. His visual impairment remained unresolved for the remainder of the participant's participation in the study.

Reviewer's Comment:

This is a case of symptomatic ARIA that resulted in visual impairment with homonymous peripheral visual defects that did not resolve. Of note, this involved both severe ARIA-E and severe ARIA-H superficial siderosis that included manifestations in the occipital regions. This subject was hospitalized and treated with dexamethasone; however, his visual deficits did not resolve during the study.

Participant ID: (b) (6)

This was a 75-year-old white female with mild Alzheimer's disease homozygous for ApoE ε4 who was assigned to receive placebo during the placebo-controlled period of Study 302 and started aducanumab during the long-term extension period. While on placebo, on Day 295, she experienced 1 new ARIA-H microhemorrhage and was asymptomatic and a right parietal cortical infarct with both reported as stabilized on Day 309. Later, she received aducanumab during the long-term extension period. On Day 647, she received her 4th dose of aducanumab, with most recent dose at 3 mg/kg. On Day 661, she experienced asymptomatic ARIA-H (microhemorrhage) and asymptomatic ARIA-E. She received her 5th and final dose on Day 674 with most recent dose at 3 mg/kg. On Day 689, she was hospitalized for symptomatic ARIA-H (macrohemorrhage) with a right occipital hematoma. She was symptomatic with a left visual field defect and subarachnoid hemorrhage. On Day 689 she also had a nonserious adverse event of ARIA-E. She was disoriented in time and partially in space and had less

fluent language. Intraparenchymal hemorrhage in the right occipital lobe retrospectively seemed related to a small subjacent cavernoma. She was given dexamethasone 4 mg IV single dose on Day 691 for symptomatic ARIA-H (right occipital hematoma). She was discharged on Day 694. On Day 703, the nonserious event of subarachnoid hemorrhage and symptomatic ARIA-H macrohemorrhage right occipital (cerebral hematoma) was reported as resolved/stabilized. Her ARIA-E was reported resolved on Day 744. Her visual field defect remained unresolved for the remainder of the study. The size of the hemorrhage in greatest dimensions was 31 mm.

Reviewer's comment:

This case demonstrates a left visual field deficit arising from an ARIA-H macrohemorrhage in the right occipital region. Of note, this subject had a right parietal cortical infarct prior to starting aducanumab and was noted to have a small subjacent cavernoma that complicates interpretation of the role aducanumab played in the presentation of this right occipital hematoma. Her clinical course included hospitalization and treatment with dexamethasone 4mg IV single dose. Her left visual field deficit remained unresolved during the study.

Participant ID: (b) (6)

This was a 70-year-old white male with mild cognitive impairment due to Alzheimer's Disease who was homozygous for ApoE ε4 whose concomitant medications included acetylsalicylic acid. On Day 1, subject experienced an intermittent sensation of strong smell. On Day 81 he experienced headaches, with a previous 6-week history of occipital headache, nausea, visual disturbance and 2-week history of increased difficulty reading. On Day 95, the subject experienced intermittent visual changes. On Day 100, 21 days after his 4th dose of aducanumab with last dose at 3 mg/kg, he experienced symptomatic ARIA-E and symptomatic ARIA-H microhemorrhage in the left parietal region. On Day 115, subject had symptomatic ARIA-H (superficial siderosis) and ARIA-H (microhemorrhage) and moderate ARIA-E. His visual impairment and parosmia were reported as resolved on Day 119. His ARIA-H was reported as resolved/stabilized on Day 128. On Day 152, his ARIA-H superficial siderosis worsened in the left occipital cortex. The event of serious ARIA-E and ARIA-H superficial siderosis were reported as resolved on Day 173. Study treatment was interrupted as a result of the events of visual impairment, ARIA-E, and ARIA-H (microhemorrhage) and was restarted on Day 194 at the same dose. On Day 196, he experienced intermittent anxiety, intermittent lightheadedness, intermittent nausea, and intermittent sensation of a strong smell. On Day 218, 24 days after receiving his 5th dose of aducanumab with most recent dose at 3 mg/kg, he experienced symptomatic ARIA-H (microhemorrhage). MRI scan showed 8 microhemorrhages (locations: left parietal, left temporal, and right temporal), 2 of which were new and stable moderate superficial siderosis (locations: left frontal and left occipital cortex). The participant's symptoms included anxiety, dizziness, nausea, and parosmia which persisted for the remainder of the study. He continued to receive study treatment at 3 mg/kg on Day 225 in error per the narrative as per protocol study treatment should have been suspended at that time due to his ARIA. On Day 240, 15 days after his 6th dose at 3 mg/kg administered in error, the participant experienced new regions of symptomatic ARIA-H (superficial siderosis) and symptomatic ARIA-E. His symptomatic ARIA-H (superficial siderosis) resolved on Day 253. His ARIA-E resolved on Day 304. Study treatment was permanently discontinued as a result of the event of symptomatic ARIA-H (superficial siderosis).

Reviewer's comments:

This case details negative consequences of continuing dosing when protocol stated aducanumab should not have been administered. Subject had symptomatic ARIA-E as well as two locations of ARIA-H superficial siderosis yet received a dose of aducanumab in error, when it should have been suspended. Subsequent worsening of his ARIA-H superficial siderosis occurred.

Participant ID: [REDACTED] (b) (6)

This was a 62-year-old white female with mild cognitive impairment due to Alzheimer's Disease who was a noncarrier of ApoE ϵ 4 who 13 days after her 3rd dose of aducanumab (with last dose at 3 mg/kg) on Day 56, experienced headache, nausea, confusion, fatigue, loss of balance, intermittent tachycardia, and dizziness on day 59, and on Day 69 experienced ARIA-E. Her MRI scan showed severe new vasogenic edema in the left occipital, left parietal, left temporal, nonhippocampal, right occipital, and right parietal regions as well as 1 microhemorrhage (stable). The participant was symptomatic with onset of visual disturbance and ataxia, as well as with ongoing headache, nausea confusion, dizziness, fatigue, intermittent tachycardia, and loss of balance. On Day 118, the nonserious events of headache and nausea were reported as resolved. On Day 120, the participant experienced symptomatic ARIA-H (microhemorrhage) with increase in ARIA-E from prior scan with 9 microhemorrhages, 8 of which were new in the left occipital cortex. The participant was symptomatic with ongoing nonserious events of confusion, dizziness, fatigue, intermittent tachycardia, loss of balance, visual disturbance, and ataxia. On Day 137, the participant experienced a fall and contusion on forehead. On Day 141, her confusional state, dizziness, fatigue, tachycardia, and visual impairment were reported as resolved without any medication. Her MRI scan on Day 141, 85 days after last aducanumab dose, showed decreased ARIA-E and >10 microhemorrhages with 3 new in the left frontal region. On Day 149, her contusion resolved and on Day 167, her balance disorder and ataxia resolved. ARIA-E resolved on Day 310 with a finding of 2 additional microhemorrhages. Study treatment was permanently discontinued as a result of the event of ARIA-E. On Day 434, the event of ARIA-H was reported as resolved/stabilized.

Reviewer comment:

This subject experienced symptoms 3 days after her 3rd dose of aducanumab, and was later found on MRI to have ARIA-E. Her ARIA-E lasted 241 days, and ARIA-H microhemorrhages occurred over 314 days. Her symptoms included headache, nausea, confusion, fatigue, loss of balance, intermittent tachycardia, and dizziness that resolved in 82 days. She also experienced visual disturbance and ataxia that resolved in 72 days and 80 days respectively. Finally, the subject suffered 2 falls. [REDACTED] (b) (4)

[REDACTED]
[REDACTED] However, the symptomatic nature of the presentation, coupled with an unscheduled MRI led to its detection and suspension of aducanumab treatment. This demonstrates the importance of educating the medical community of ARIA-E and associated symptoms that require awareness.

Participant [REDACTED] (b) (6)

This was a 66-year-old white female with mild cognitive impairment due to Alzheimer's Disease with an ApoE ϵ 4 carrier status that was homozygous. The subject received her 4th dose, most recent

dose at 3 mg/kg, and 8 days later, on Day 99, experienced asymptomatic ARIA-H microhemorrhage. Her concomitant medications included acetylsalicylic acid. MRI scan showed 1 new microhemorrhage. The event of asymptomatic ARIA-H (microhemorrhages) was reported as resolved/stabilized on Day 133. Subject received her 5th dose of aducanumab at 3 mg/kg and 20 days later, on Day 133, experienced symptomatic ARIA-E and ARIA-H superficial siderosis. MRI showed severe vasogenic edema in the following regions: left frontal, left occipital, left parietal, left temporal, right frontal, right occipital, right parietal, and right temporal regions. The patient was also noted at that time to have 1 microhemorrhage (stable), mild new superficial siderosis in the right frontal region. On Day 131, the participant reported feeling unwell and experienced headache, nausea, vomiting, dizziness, and tenderness under her left eye. On Day 133, subject experienced symptomatic ARIA-E with confusion, right upper quadrant peripheral vision deficit and reported she was unable to locate her silverware drawer in the kitchen and was experiencing difficulty operating her cellphone and presented to the ER with complaints of right visual field deficit. Study treatment was permanently discontinued as a result of the event of symptomatic ARIA-E. On Day 134, the narrative reports that she was started on clopidogrel bisulfate for symptomatic ARIA-H (superficial siderosis) and was found on Day 135 to have a new microhemorrhage on MRI and mild superficial siderosis that increased in size in her right frontal region. On Day 143, the participant experienced headache and had resolution of her right upper quadrant peripheral vision deficit. The headache was resolved on Day 144, and headache returned on day 149. On Day 151, ARIA-H microhemorrhage stabilized, but had worsening of her symptomatic ARIA-H superficial siderosis new in the left frontal and increased in size in the right frontal region with headache and right eye pain, both of which resolved the next day, with stabilization of the superficial siderosis 45 days later. On Day 289, subject experienced headache, nausea, and vomiting and on Day 295 experienced symptomatic ARIA-H superficial siderosis of severe intensity in the right parietal region and asymptomatic ARIA-H microhemorrhage which both resolved/stabilized on Day 324.

Reviewer's comments:

This subject had an instance of ARIA-H microhemorrhage after her 4th dose of aducanumab and continued dosing and 20 days after her 5th dose, experienced symptomatic ARIA-E with confusion, right upper peripheral visual field deficit, and difficulty locating her silverware drawer and operate her cell phone. She was discontinued from treatment for the symptomatic ARIA-E with one day of confusion and a vision deficit that resolved in 10 days. She was on acetylsalicylic acid and, per the narrative, started on clopidogrel for symptomatic ARIA-H and subsequently experienced episodes of new or worsening superficial siderosis that was symptomatic with right eye pain and headaches. This case would discourage the use of clopidogrel for symptomatic ARIA-H.

Participant ID: (b) (6)

This was a 67-year-old white female with mild cognitive impairment due to Alzheimer's disease who, 12 days after her 4th dose of aducanumab, with most recent at 3 mg/kg, experienced

asymptomatic ARIA-H (microhemorrhage) and initially asymptomatic ARIA-E on Day 99. MRI scan on the same day showed severe new vasogenic edema (locations: left frontal, left parietal, and left temporal, nonhippocampal), >10 new microhemorrhages (locations: left parietal and left temporal). Study treatment was permanently discontinued. The events of ARIA-H (microhemorrhage) and ARIA-E were reported as resolved/stabilized on Day 114. On the same day, 27 days after her 4th dose of aducanumab, her asymptomatic ARIA-E became symptomatic. She experienced the onset of confusional state, gait disturbance, and headache. MRI scan at event showed severe vasogenic edema in the left frontal, left parietal, and left temporal, which had increased in size compared to previous MRI scan; and >10 microhemorrhages (stable) in the left frontal, left parietal, and left temporal regions. On Day 119, she was hospitalized. The participant reported that her balance was off, she forgot how to turn on the dryer as well as the code to open her phone, and had difficulty with word finding and walking, dragging her right leg. She noted that her headache was located in the base of her neck and the occiput and rated it as 5/10 in severity. She denied nausea and vomiting and admitted to some sensitivity to lights. Examination on admission was significant for short-term memory difficulties, transcortical sensory aphasia, right homonymous hemianopia, right-sided hypertonia, and right leg weakness. MRI scan showed severe vasogenic edema in the left frontal; left parietal; and left temporal, nonhippocampal, which had increased in size since the previous MRI scan; and >10 microhemorrhages (stable) in the left frontal, left parietal, and left temporal. There was greater edema in the motor area. Subject started paracetamol for ARIA-E headache and methylprednisolone 1 g QD IV for 5 days was administered for symptomatic ARIA-E. On Day 123, neurological examination showed Glasgow Coma Scale score at 15, difficulty with calculations and multistep commands, 2/3 short-term recall, mild apraxia with complex hand gestures, and increased (3+) reflexes on the right. MRI scan on the same day showed severe vasogenic edema in the left frontal, left parietal, and left temporal, which had decreased in size since previous MRI scan and >10 microhemorrhages (stable). There was also improvement in focal edema in the left supra-insular white matter and mild persistent midline shift. The participant had received inpatient rehabilitation. On the same day, the participant was discharged from the hospital. On Day 126, the events of confusional state, gait disturbance, and headache were reported as resolved. On Day 127, the subject was started on oral steroid taper. On Day 129, the participant presented with improvement of symptoms. Physical examination showed no field cut, no drift of right arm, and no dragging of right foot. On Day 156, the participant had significantly improved without any leg weakness, cognitive decline, headache, and field cut by history and examination. The event of ARIA-E was reported as resolved on Day 186 with an MRI scan that showed complete resolution of vasogenic edema, >10 microhemorrhages (stable), no superficial siderosis, and no macrohemorrhage.

Reviewer's comments:

This 64-year-old female experienced severe ARIA-E and ARIA-H (>10 microhemorrhages), 12 days after her 4th dose of aducanumab with most recent dose at 3 mg/kg. Of note, this is a case example of how her aducanumab was permanently discontinued per protocol after the 4th dose given the >10 microhemorrhages. This case also illustrates how initially asymptomatic ARIA-E and ARIA-H can become symptomatic 15 days after identified on MRI, in this case with onset of confusional state, gait

disturbance, and headache. A visual field cut was also found later on exam. A final point from this case is how the subject's symptoms improved prior to the radiographical resolution of her ARIA-E, which was documented as resolved 30 days after symptoms resolved.

Narratives Describing Impaired Motor Strength in Cases with Serious ARIA

Participant ID: (b) (6)

This was a 74-year-old white male with mild cognitive impairment due to Alzheimer's Disease and noncarrier for ApoE ϵ 4 who on Day 55, 26 days after receiving his 2nd dose of aducanumab with most recent dose at 1 mg/kg, experienced symptomatic ARIA-E. He presented with left-sided numbness of the arm and leg and weakness. His MRI scan that day showed moderate vasogenic edema (locations: left temporal, right occipital, right parietal, and right temporal regions). Study treatment was interrupted as a result of the event of symptomatic ARIA-E. His concomitant medications included acetylsalicylic acid. He was discharged from the hospital the next day on Day 56. On Day 61, he experienced a headache and 2 further episodes of left-sided tingling and numbness. Treatment included ibuprofen, oxycodone, oxycodone hydrochloride/paracetamol, and paracetamol. On Day 81, his symptomatic ARIA-E worsened in severity with new onset of ARIA-H superficial siderosis in the left frontal and left parietal regions. His MRI scan showed severe vasogenic edema and moderate superficial siderosis. On Day 98 his headache resolved. His ARIA-H superficial siderosis resolved on Day 109. His ARIA-E resolved on Day 165. His left-sided numbness was reported as resolved on Day 179. His treatment was discontinued with his 2nd dose being his last dose.

Reviewer's comment:

This subject experienced symptomatic ARIA-E that was initially thought to be a transient ischemic attack with onset of left-sided numbness and weakness and subsequently developed ARIA-H superficial siderosis. The duration of ARIA-E was 110 days, and ARIA-H superficial siderosis resolved in 28 days. In this case, the patient's left-sided numbness resolved two weeks after the resolution of his ARIA-E. (b) (4)

the subject experienced serious ARIA after his 2nd infusion.

Participant ID: (b) (6)

This was a 67-year-old female with mild cognitive impairment due to Alzheimer's Disease homozygous for ApoE ϵ 4 who received placebo during the placebo-controlled period of the trial and started aducanumab during the long-term extension period. On Day 659, 13 days after receiving her 4th dose of aducanumab, with last dose at 3 mg/kg, she experienced asymptomatic ARIA-E with an MRI scan showing severe new vasogenic edema in the left parietal, left temporal, right frontal, right occipital, right parietal and right temporal regions. Study treatment was interrupted as a result of the event and was restarted at the same dose (3 mg/kg) on Day 785. The participant continued up-titration per protocol. On Day 974, her MRI scan showed complete resolution of vasogenic edema. On Day 1081, 16 days after her 11th dose with most recent dose at 6 mg/kg, the participant experienced another asymptomatic ARIA-E. Her MRI scan showed moderate new vasogenic edema in the left frontal, left

parietal, left temporal, right frontal, right occipital, right parietal, right temporal regions. On Day 1088, her ARIA-E became symptomatic and she experienced gait instability and right-sided hemiplegia requiring hospitalization and treated with dexamethasone which started on Day 1090 at 3 mg every 6 hours. On Day 1091, a CT scan of the head without contrast showed diffuse edematous change in the left frontal and parietal lobes exerting mass effect upon the left lateral ventricle. On Day 1095, her dose was increased to 9 mg QID, and reduced to 4 mg TID on Day 1096. On Day 1101 her gait disturbance was considered resolved and her dose of dexamethasone was reduced to 2 mg BID. On Day 1109, her dose was reduced to 2 mg daily, which ended on Day 1113. On Day 1121 her hemiplegia was resolved. On an unspecified date, she developed dysphagia, unsteady gait, confusion, and compulsiveness. She went to the Emergency Department on Day 1125 and on Day 1128, her ARIA-E was found to have worsened with severe vasogenic edema in the left frontal, left parietal, right frontal, right occipital, and right parietal regions and she was symptomatic with lower extremity muscle weakness. She was readmitted to the hospital on Day 1129 and started on dexamethasone at 0.75 mg TID. She was discharged on Day 1138. On Day 1139, the participant was started on dexamethasone (starting from 4 mg TID with a taper until Day 1210) for ARIA-E. On Day 1163, she experienced asymptomatic ARIA-H (superficial siderosis) in the left frontal and right frontal regions and mild vasogenic edema in the right occipital region. On Day 1193, her confusional state and aphasia were considered resolved. On Day 1217, her superficial siderosis worsened in severity with a new episode in the right parietal region with increased ARIA-E in the right frontal and right occipital regions that had increased in size. On Day 1249, the participant experienced asymptomatic ARIA-H (microhemorrhage) with >10 microhemorrhages, ARIA-H (superficial siderosis that was new in the left frontal region) and moderate vasogenic edema (locations: right frontal, right occipital cortex, right parietal regions). She was restarted on dexamethasone at 2 mg QID on Day 1252. Her ARIA-H (superficial siderosis) and ARIA-H microhemorrhages resolved on Day 1265. Her ARIA-E was reported as resolved on Day 1339, 258 days after onset.

Reviewer's Comments:

This subject experienced an episode of ARIA-E 13 days after her 4th dose of aducanumab. Her dose was held and then restarted at the same dose. She had a second instance of ARIA-E after her 11th dose which was initially asymptomatic but became symptomatic 7 days into its course with gait instability and right sided hemiplegia with these symptoms persisting 33 days. On reviewing patient narratives, this duration of symptoms is in line with other serious cases of ARIA. She was treated with dexamethasone and at the same time, her ARIA-E was noted to radiographically worsen with subsequent development of ARIA-H superficial siderosis and microhemorrhages. The duration of her second ARIA-E was significantly longer than others.

16 Additional Narratives of Cases of Serious ARIA Not Previously Mentioned in this Review:

Participant ID: (b) (6)

This was a 64-year-old white male with mild cognitive impairment due to Alzheimer's Disease with a past medical history of hypertension treated with enalapril for at least 10 years and headache treated with ibuprofen as needed for at least 7 years. He took placebo during the controlled period, during which time the narrative noted a possible TIA. He started aducanumab during the long-term

extension period, receiving his 4th dose on Day 645, at 3 mg/kg. 4 days after his 4th dose of aducanumab he experienced ARIA-H microhemorrhage and ARIA-E. 29 days later he experienced ARIA-H superficial siderosis and 36 days later experienced seizure. His concomitant medications included acetylsalicylic acid and ciprofloxacin. In retrospect, he had increase in headache frequency on Day 584 and had difficulty reading noted on Day 615. On Day 646, 1 day after receiving his 4th dose of aducanumab, he was found to have mild unstable blood pressure and on Day 648, he experienced a thunderclap headache in the occipital region with a blood pressure measured in the Emergency Department of 220/120 mmHg and a CT concerning for posterior reversible encephalopathy syndrome(PRES), for which he was admitted to the intensive care unit. On Day 649, the participant experienced symptomatic ARIA-H (microhemorrhage) and symptomatic ARIA-E. His MRI scan showed severe vasogenic edema in the left frontal, left parietal, left temporal, right frontal, right occipital, right parietal, and right temporal regions; >10 microhemorrhages, all of which were new compared to the previous MRI scan. He was discharged from the hospital on Day 650. On Day 674, he was found to additionally have symptomatic ARIA-H (superficial siderosis) in the left frontal, left temporal, right frontal, and right temporal regions. On Day 676, his aphasia worsened to moderate severity. On Day 681, EEG showed frequent bilateral temporal epileptiform discharges (left more than right) and nearly continuous left temporal focal slowing. This was reported as partial seizures and he was started on levetiracetam and a 5-day course of methylprednisolone 1000 mg QD. On Day 694, he completed a 5-day course of steroids with significant improvement in word finding difficulties, memory and reading comprehension. His ARIA-H microhemorrhages and superficial siderosis of central nervous system were reported as resolved/stabilized on Day 687. On Day 696, he was hospitalized for acute pancreatitis which resolved on Day 697 and he was discharged. His ARIA-E was reported as resolved on Day 871. His headache, blood pressure fluctuation, aphasia, and partial seizures remained unresolved for the remainder of the study. Study treatment was permanently discontinued as a result of the events of amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits and amyloid related imaging abnormality-edema/effusion.

Reviewer's comments:

This subject experienced symptomatic ARIA-E and ARIA-H microhemorrhages with thunderclap headache after his 4th dose of aducanumab. While he was reported to have bilateral temporal epileptiform discharges, left more than right, characterized as partial seizures, it is not clear that this would be associated with his ARIA. His treatment was stopped due to the >10 microhemorrhages per protocol. I do not suspect his acute pancreatitis to be related to ARIA.

Participant ID: (b) (6)

This was a 77-year-old white female with mild Alzheimer's Disease, noncarrier for ApoE ε4 who, on Day 211, 14 days after receiving her 8th dose of aducanumab at 10 mg/kg, experienced asymptomatic ARIA-H (superficial siderosis) and asymptomatic ARIA-E. Her MRI scan showed moderate vasogenic edema in the left frontal, left parietal, left temporal, right occipital, and right parietal regions, and severe superficial siderosis in the left frontal, left occipital cortex, and right occipital cortex regions. Her concomitant medications included acetylsalicylic acid. Her superficial siderosis was reported as resolved/stabilized on Day 248. Her ARIA-E was reported completely resolved on Day 289. Study treatment was permanently discontinued as a result of the event of severe superficial siderosis of central nervous system.

Reviewer's comment:

After receiving her 8th dose of aducanumab, this subject suffered ARIA-E and severe superficial siderosis in multiple brain hemispheres and was discontinued from study treatment per protocol.

Participant ID: (b) (6)

This was a 69-year-old white male with mild cognitive impairment due to Alzheimer's Disease with noncarrier ApoE ε4 carrier status who received his 4th dose of aducanumab on Day 91 with the most recent dose at 3 mg/kg. On Day 110, he experienced a confusional state. On Day 113, he was seen in the hospital due to a transient loss of consciousness. On Day 114, the participant presented with an episode of syncope with secondary cranial trauma. On Day 115, his loss of consciousness was reported as resolved and participant was discharged from the hospital. On Day 121, the participant experienced symptomatic ARIA-E with an MRI scan that showed mild vasogenic edema in the right temporal region. Study treatment dosing was interrupted as a result of the event of mild symptomatic ARIA-E. On Day 149, the participant experienced worsening symptomatic ARIA-E located in the right temporal region that increased in size as well as asymptomatic ARIA-H (superficial siderosis) located in the right temporal region. The event of asymptomatic ARIA-H (superficial siderosis) was reported as resolved/stabilized on Day 168. On Day 196, he experienced moderate asymptomatic ARIA-H (superficial siderosis) in the right occipital and right temporal regions. On Day 210, the event of asymptomatic ARIA-H (superficial siderosis) worsened in severity with a new instance located in the left frontal region and persistence in the right occipital cortex and right temporal regions. His symptomatic ARIA-E, ARIA-H superficial siderosis, and confusional state resolved on Day 226. The participant withdrew from the study due to withdrawn consent, and final assessment was on Day 226.

Reviewer Comments:

This subject experienced symptomatic ARIA-E 30 days after his 4th dose of aducanumab. This case illustrates symptoms that can present prior to MRI identification of ARIA-E, which include, in his case, a confusional state, a loss of consciousness, and an episode of syncope with head trauma. He subsequently had two instances of ARIA-H superficial siderosis. While his confusional state preceded the identification of his ARIA, his confusion resolved in 116 days, and his ARIA-E resolved in 105 days and ARIA-H episodes resolved in 19 days and 30 days.

Participant ID: (b) (6)

This was a 72-year-old white male with mild cognitive impairment due to Alzheimer's Disease and a heterozygous ApoE ε4 carrier whose concomitant medications included acetylsalicylic acid. On Day 155, 14 days after receiving his 6th dose of aducanumab with last dose of 6 mg/kg, he experienced asymptomatic ARIA-E. His MRI scan showed severe vasogenic edema located in the hippocampus, left frontal, left occipital, left parietal, left temporal, right frontal, right occipital, right parietal, and right temporal regions. Study treatment was interrupted as a result of the event. On Day 186, he experienced asymptomatic ARIA-H microhemorrhage with a single microhemorrhage in the left temporal region, 45 days after his 6th dose of aducanumab, and this ARIA-H microhemorrhage resolved on Day 212. His ARIA-E resolved on Day 275. Study treatment was restarted on Day 281 at the same dose (6 mg/kg). On Day 365, he received his 10th and last dose of aducanumab, with this dose at 10 mg/kg. On Day 377, he experienced brief acute confusion in the morning lasting for 1 to 2 hours and characterized by inability

to recognize his primary caretaker. On Day 378, the participant experienced an SAE of symptomatic ARIA-E and asymptomatic ARIA-H (superficial siderosis) and acute mental status change. His MRI scan showed new severe vasogenic edema in the same regions as before, and the same stable microhemorrhage in the left temporal region, but new severe superficial siderosis located in the left occipital, left parietal, right occipital, and right parietal regions. He received oral prednisone 10 mg QD for the ARIA-E and study treatment was permanently discontinued as a result of the SAE of symptomatic ARIA-E. On Day 380, he was admitted to the intensive care unit in the setting of worsening confusion. On Day 389 he was noted to be improved and stable and was discharged to rehabilitation. On Day 409, he experienced an SAE of pulmonary embolism and deep vein thrombosis and benign lung neoplasm and began treatment with heparin, and warfarin. On Day 497 he experienced an SAE of pneumonia which was reported as resolved on Day 507. His ARIA-E and superficial siderosis of central nervous system were reported as resolved/stabilized on Day 514, but he now had new asymptomatic ARIA-H with >10 new microhemorrhages in the left frontal, left parietal, left temporal, right frontal, right occipital, right parietal, and right temporal regions. The SAE of pulmonary embolism and the nonserious events of acute mental status changes, deep vein thrombosis, and benign lung neoplasm remained unresolved for the remainder of the study. The event of symptomatic ARIA-E led to the participant's subsequent withdrawal from the study. The participant's final assessment was on Day 514.

Reviewer's comment:

This subject's study treatment was interrupted as a result of MRI finding of severe ARIA-E found 14 days after his 6th dose of aducanumab. His ARIA-E lasted 120 days, and he had one ARIA-H microhemorrhage during this period. He was asymptomatic, and treatment resumed 6 days after his ARIA-E resolved. Twelve days after he received his 10th dose, he became acutely confused, did not recognize his primary caregiver, and had another instance of ARIA-E with ARIA-H superficial siderosis.

Participant ID: (b) (6)

This was an 80-year-old female, with a history of hypertension and concomitant medications including hydrochlorothiazide and valsartan, with mild cognitive impairment due to Alzheimer's Disease who was homozygous for ApoE ε4. On Day 142, she received her 6th dose of aducanumab at 3 mg/kg. Her concomitant medications included acetylsalicylic acid. On Day 156, she experienced dizziness, headache, and gait difficulty. On Day 157, she experienced ARIA-H (microhemorrhage) and vomiting which resolved on the same day after treatment with metoclopramide. The participant's symptoms were thought to be due to ARIA-H and she was taken to the Emergency Department, where her systolic blood pressure was noted to be 190 mmHg, and she was found to be confused and have incoherent speech. Her MRI scan showed 2 new microhemorrhages. On Day 158, she had hypertensive encephalopathy and her dizziness and headache were considered resolved. She was started on intravenous steroid and labetalol hydrochloride for hypertension. On Day 159, her symptomatic ARIA-H (microhemorrhage) worsened in severity. Her MRI scan showed 10 microhemorrhages, 8 of which were new since the previous scan. Study treatment was permanently discontinued as a result of the severe symptomatic ARIA-H. On Day 164 she was treated with prednisolone for hypertensive encephalopathy and was discharged from the hospital on Day 164. On Day 178, she was found to have moderate ARIA-E in the right frontal and right parietal regions 36 days after her 6th dose. Her ARIA-E and confusion resolved on Day 232. She continued in the study until withdrawing from the study due to withdrawal of consent with final assessment on Day 232.

Reviewer's comment:

This subject experienced ARIA-H (microhemorrhage) 15 days after her 6th dose of aducanumab with last dose at 3 mg/kg. She was admitted to the hospital for the ARIA-H and had a systolic blood pressure of 190 mmHg, which was temporally associated with an increase in the number of microhemorrhages, and she was treated with prednisolone. She suffered ARIA-E 36 days after the 6th dose and was found to have 10 microhemorrhages. Symptoms during her ARIA episodes included dizziness, headache, gait difficulty, confusion, vomiting and incoherent speech. Her treatment was discontinued due to the symptomatic ARIA-H (microhemorrhages).

Participant ID: (b) (6)

This was a 72-year-old female with mild cognitive impairment due to Alzheimer's Disease and homozygous for ApoE ε4. Her concomitant medications included acetylsalicylic acid. She received her 8th dose of aducanumab, with most recent dose at 6 mg/kg, on Day 195. On Day 223, (and notably 16 days after rectal bleeding from a reported intestinal perforation post resection of an intestinal polyp) she experienced asymptomatic ARIA-E, 28 days after her 8th dose of aducanumab with most recent dose at 6 mg/kg. Her MRI scan showed mild vasogenic edema in the right occipital region, and 2 stable microhemorrhages. Her ARIA-E resolved on Day 249. On Day 293, 14 days after receiving her 11th dose of aducanumab with most recent dose of 10 mg/kg, she experienced asymptomatic ARIA-E and asymptomatic ARIA-H. Her MRI scan showed moderate vasogenic edema and 4 new microhemorrhages. On Day 320, 41 days after her 11th dose of aducanumab, the events of ARIA-H (microhemorrhage) and ARIA-E worsened in severity with increased size of ARIA-E and worsening of ARIA-H microhemorrhages, 8 of which were new, making a total >10. Her caregiver noted that the participant was confused and with concentration difficulties. Due to the increase of ARIA-E with the in the left parietal and occipital regions, the participant was admitted to the hospital on Day 322 to receive treatment with corticoids. Treatment medications included dexamethasone and methylprednisolone and she was discharged on Day 328. The event of asymptomatic ARIA-H resolved/stabilized on Day 349. The event of symptomatic ARIA-E was reported as resolved on Day 537. Study treatment was permanently discontinued. On Day 537, the participant experienced peripheral vertigo which remained unresolved for the remainder of the participant's participation in the study.

Reviewer comment:

This subject experienced ARIA-E after her 8th dose of aducanumab and ARIA-E and ARIA-H microhemorrhages after her 11th dose. Symptoms of confusion and concentration difficulties were noted, and she was admitted to the hospital and treated with steroids. I do not believe her prior intestinal perforation was related to ARIA or aducanumab, however, may have lowered a clinical threshold for hospital admission for the ARIA. This case demonstrates that serious ARIA can occur after the 11th infusion of aducanumab (b) (4)

I also note that this subject was homozygous for ApoE ε4 and note that my prior analysis indicates that the window for ARIA has a longer duration in the homozygote population.

Participant ID: (b) (6)

This was a 70-year-old female with mild Alzheimer's Disease and was a heterozygous ApoE ϵ 4 carrier. Her baseline MRI showed 2 microhemorrhages. On Day 85 the subject received her 4th dose of aducanumab, with most recent dose of 3 mg/kg. On Day 91, the participant experienced cognitive impairment and was confused and was unable to recognize her longtime nurse. On Day 93, the participant experienced symptomatic ARIA-H (microhemorrhage) and symptomatic ARIA-E. Her MRI scan showed severe vasogenic edema and 9 microhemorrhages, 7 of which were new. On Day 95, the participant had mild balance disorders which resolved on Day 97, and her cognitive disorder resolved on Day 98. She was discharged from hospital on Day 99. On Day 112, she had loss of autonomy (difficulties in dressing herself and choosing clothes) and forgetting meals in context of confusion. On Day 113, she was admitted to the hospital and the event of symptomatic ARIA-H worsened in severity with MRI scan showing severe vasogenic edema in the same regions which had increased in size and >10 new microhemorrhages. On Day 114, she received IV methylprednisolone 80 mg QD for ARIA. Her EEG on Day 116 showed presence of slow right parietal-temporal waves with no paroxysmal signs and she started oral corticosteroids. On Day 121, methylprednisolone was continued orally at tapered doses (from 20 mg QID to 20 mg BID). She was discharged from the hospital on Day 130, and ARIA-H resolved on Day 144. On Day 219, she received oral prednisone 60mg QD for ARIA-E. Her ARIA-E resolved on Day 269. Her final assessment was on Day 549.

Reviewer's comments:

This subject experienced symptomatic ARIA-H and symptomatic ARIA-E 8 days after her 4th dose of aducanumab at 3 mg/kg. Symptoms included confusion, difficulty dressing herself, balance disorder. It is notable that her ARIA worsened, and she was treated with steroids.

Participant ID: (b) (6)

This was a 73-year-old white male with mild cognitive impairment due to Alzheimer's disease and noncarrier of ApoE ϵ 4. On Day 85, he received his 4th dose of aducanumab with most recent dose at 3 mg/kg. On Day 93, he experienced symptomatic ARIA-E with drowsiness. His MRI scan showed severe vasogenic edema located in the left frontal, right frontal, and right parietal regions. On Day 98, he received dexamethasone for ARIA-E. On Day 103 he was hospitalized for clinical observation and discharged on Day 107, when his drowsiness was resolved. His ARIA-E was reported resolved on Day 121. Study treatment was permanently discontinued as a result of the event with his 4th dose being his last dose. He continued in the study until the Sponsor terminated the study. His final assessment was on Day 413.

Reviewer's comment:

Subject experienced ARIA-E 8 days after his 4th dose of aducanumab, and it lasted 28 days. Symptoms appear to be limited to drowsiness and he was hospitalized and treated with dexamethasone. This is a case where study treatment was discontinued after symptomatic ARIA-E with no recurrences of ARIA-E or ARIA-H.

Participant ID: (b) (6)

This was a 70-year-old white female with mild cognitive impairment due to Alzheimer's disease and homozygous for ApoE ϵ 4. On Day 154, 13 days after receiving her 6th dose of aducanumab with most recent dose of 3 mg/kg, she experienced ARIA-E. Her MRI scan showed mild new vasogenic edema in the right temporal region. On Day 164 she experienced confusion and paranoia. She received her 7th dose of aducanumab on Day 169, with most recent dose of 3 mg/kg, and 6 days later, Day 175, had a 15-minute seizure during which she hit her head and had post ictal confusion. She had no prior history of seizures and it resolved on Day 175. Study treatment was permanently discontinued as a result of the event of seizure. On Day 176 ARIA-E was classified as symptomatic ARIA-E, and her MRI scan on this day showed moderate vasogenic edema in the right temporal region which had increased compared to the previous scan. She was discharged on Day 177. On Day 182 she had increased confusion and paranoia. On Day 185, she experienced asymptomatic ARIA-H (superficial siderosis) that was moderate and located in the left temporal and right temporal regions. This ARIA-H superficial siderosis was reported as resolved/stabilized on Day 202. On Day 231, she experienced 3 new ARIA-H microhemorrhages. Her ARIA-E and ARIA-H microhemorrhages were reported as resolved on Day 259. On Day 380, she experienced 1 new asymptomatic ARIA-H (microhemorrhage) 211 days after her 7th dose of aducanumab that stabilized/resolved on Day 469. Her final assessment in the study was on Day 674.

Reviewer's comment:

This subject experienced ARIA-E 13 days after her 6th dose of aducanumab. Of note in this subject, she suffered a seizure with no prior seizure history 6 days after her 7th dose which was administered prior to the resolution of her mild ARIA-E. Symptoms of confusion and paranoia (and the seizure) were concurrent with her ARIA-E in the temporal regions. Although the treatment was stopped due to the ARIA-E and seizure, she subsequently developed ARIA-H superficial siderosis and instances of ARIA-H microhemorrhages.

Participant (b) (6)

This is a 62-year-old female with mild cognitive impairment due to Alzheimer's Disease. After 46 days from her 7th dose of aducanumab, most recent at 3 mg/kg, on Day 214, the participant was hospitalized due to serious adverse events of asymptomatic ARIA-H (microhemorrhage) and asymptomatic ARIA-E. MRI scan showed moderate vasogenic edema in the right frontal region with >10 new microhemorrhages. The participant was asymptomatic, and neurological examination was unremarkable. EEG was unremarkable. Study treatment was permanently discontinued as a result of the event of asymptomatic ARIA-H, with the final dose received on Day 168. On Day 231, the events of asymptomatic ARIA-H and asymptomatic ARIA-E were reported as resolved/stabilized, though that day the patient experienced a reported falling tilt, hypertension, headache, and nightmares. On Day 241, the event of falling tilt was considered resolved. On Day 242, MRI scan showed improving, mild, ARIA-E, and 1 new microhemorrhage. On Day 245, the events of headache and nightmare were reported as resolved and on Day 261, ARIA-H was reported as resolved/stabilized with ARIA-E resolved on Day 275.

Reviewer's comment:

This 62-year-old female experienced severe asymptomatic ARIA-H microhemorrhages with >10 new microhemorrhages and ARIA-E 46 days after her 7th dose of aducanumab at 3mg/kg. She

experienced fall, hypertension, headache, and nightmares. With the exception of hypertension, these adverse events resolved, and she was discontinued from the study due to the severe ARIA-H with >10 microhemorrhages.

Participant ID: (b) (6)

This was a 70-year-old male with mild cognitive impairment due to Alzheimer's disease who was noted to have increased forgetfulness on Day 119 and 16 days after his 6th dose of aducanumab, with most recent dose at 3 mg/kg, experienced symptomatic ARIA-E on Day 157. MRI scan showed moderate vasogenic edema in the right parietal region. Study treatment was interrupted per protocol as a result of the event of symptomatic ARIA-E. On Day 158, his neurologic examination was normal except for mild difficulty with tandem gait. The subject did recall a very mild transient 1-day headache after the previous infusion. The event of ARIA-E was reported as resolved on Day 212. Study treatment was restarted, and the participant received a reduced of 1 mg/kg on Day 224. On Day 253, the participant received another study treatment dose of 1 mg/kg before continuing with the assigned 3 mg/kg per protocol on Day 283. On Day 545, 12 days after his 18th dose of aducanumab, with most recent at 3 mg/kg, the participant experienced asymptomatic ARIA-E and asymptomatic ARIA-H (superficial siderosis) in the right frontal region. ARIA-E and ARIA-H superficial siderosis both resolved on Day 578. On Day 656, the participant experienced another asymptomatic ARIA-E after 18 doses in the placebo-controlled period with last dose at 3 mg/kg and 4 doses in the long-term extension period at 3 mg/kg. MRI scan showed mild new vasogenic edema in the left occipital cortex. This ARIA-E resolved on Day 710. On Day 1043, after 18 doses of aducanumab in the placebo-controlled period and 17 doses of aducanumab in the long-term extension period with most recent dose at 3 mg/kg, the subject experienced moderate ARIA-E in the right parietal region which was asymptomatic and resolved on Day 1080.

Reviewer's comment

This 70-year-old male experienced symptomatic ARIA-E 16 days after his 6th dose of aducanumab with most recent dose at 3 mg/kg noting transient 1-day headache after infusion, and mild difficulty with tandem gait. Subject was reported to have increased forgetfulness on Day 119, prior to this event. It is notable that this subject experienced four ARIA-E events, at Day 157 which was symptomatic with associated increased forgetfulness and difficulty with tandem gait, at Day 545 (with ARIA-H superficial siderosis) which was asymptomatic and resolved at Day 578, at Day 656 which was asymptomatic and resolved on Day 710, and on Day 1043 which was asymptomatic and resolved on Day 1080.

Participant ID: (b) (6)

This was a 70-year-old white female with mild cognitive impairment due to Alzheimer's Disease who was homozygous for ApoE ε4 who on Day 109, 24 days after receiving her 4th dose of aducanumab, and most recent dose of 3 mg/kg experienced asymptomatic ARIA. Study treatment was interrupted.

On Day 137, 52 days after her 4th and last dose of aducanumab, her ARIA-H (microhemorrhage) and ARIA-E worsened in severity. MRI scan on this day showed severe vasogenic edema in the left parietal, left temporal, right occipital, right parietal, and right temporal regions; 5 microhemorrhages in the left temporal region, 2 of which were new since the previous MRI scan; severe superficial siderosis in the left occipital, left parietal, and left temporal regions (all new). The participant remained asymptomatic. While the events were ongoing, the participant also began treatment with methylprednisolone on Day 148 which continued to Day 151. On Day 148, her ARIA-E worsened and on Day 155, her ARIA-H (microhemorrhage) worsened in severity with 11 new microhemorrhages in the left temporal and right parietal regions, while her severe superficial siderosis was reported as resolved/stabilized. Study treatment was permanently discontinued. The event of asymptomatic ARIA-H (microhemorrhage) was reported as resolved/stabilized on Day 166. ARIA-E showed complete resolution on Day 193.

Reviewer's Comment:

This subject experienced asymptomatic ARIA-H microhemorrhage 24 days after her 4th dose of aducanumab, had her treatment interrupted and 52 days after her 4th dose had ARIA-E, new ARIA-H microhemorrhages and new ARIA-H superficial siderosis, all of which were asymptomatic. She was permanently discontinued from treatment after the episodes of superficial siderosis and 11 new microhemorrhages per protocol guidelines. Superficial siderosis was reported as resolved/stabilized 18 days after onset, microhemorrhages were reported resolved 29 days after onset and ARIA-E was reported resolved 56 days after onset.

Participant ID: (b) (6)

This was an 82-year-old male with mild cognitive impairment due to Alzheimer's Disease and a heterozygous ApoE ϵ 4 carrier who, on Day 140, 14 days after receiving his 6th dose of aducanumab, and most recent dose of 6 mg/kg, experienced ARIA-E. On Day 154, he experienced asymptomatic ARIA-H (microhemorrhage) and symptomatic ARIA-E. His MRI scan showed severe new vasogenic edema in the right occipital cortex, right parietal, and right temporal regions, and 3 new microhemorrhages in the right temporal region. On Day 161, his neurological examination showed decreased sensation of vibration from the knee down, slight, and mild imbalance, and slightly wide-based gait. On Day 162, the participant experienced nonserious AE of minor head trauma. On Day 170 he had worsening of a tremor in the left hand and bilateral hand fasciculations with mild increase in memory and problem-solving difficulty. On Day 182, the memory impairment was reported as resolved and ARIA-H was also reported as resolved/stabilized. The ARIA-E was reported as resolved on Day 239. Study treatment was interrupted as a result of the event of ARIA-E and was restarted on Day 253 at the same dose (6 mg/kg). On Day 280, 27 days after receiving his 7th dose of aducanumab, he experienced decreased coordination and cerebellar ataxia on left finger nose finger, gait disturbance, decreased upward gaze. On Day 284, the participant experienced symptomatic ARIA-E. His MRI scan showed mild new vasogenic edema in the right frontal region and 3 stable microhemorrhages in the right temporal region. The

participant was symptomatic with ongoing cerebellar ataxia, gait disturbance, and gaze palsy. While his ARIA-E was reported as resolved on Day 318, his cerebellar ataxia, gait disturbance, hand fasciculations, and gaze palsy remained unresolved for the remainder of his participation in the study.

Reviewer's Comment:

This subject experienced ARIA-E 14 days after his 6th dose of aducanumab with symptoms of increased memory problems that resolved 28 days later. His aducanumab was held, and restarted 127 days later, 14 days after the ARIA-E was reported resolved. Of note, 27 days after receiving his restarted dose of aducanumab (at the same 6 mg/kg dose), he again experienced symptomatic ARIA-E and while the ARIA-E resolved in 34 days, his symptoms of cerebellar ataxia, gait disturbance and gaze palsy persisted.

Participant ID: (b) (6)

This was a 70-year-old male with mild cognitive impairment due to Alzheimer's Disease who 60 days after receiving his 3rd dose of aducanumab, with most recent dose received on Day 63 at 3 mg/kg experienced ARIA-H macrohemorrhage. This subject was taking acetylsalicylic acid. On Day 119 he was unable to coordinate movement of his right hand and on Day 120, had a CT scan that showed an intraparenchymal hematoma with a maximum diameter of 1.6 cm in the left frontal subcortical area, at the vertex in pre-rolandic area and was hospitalized. On Day 123, the subject experienced symptomatic ARIA-H (macrohemorrhage), symptomatic ARIA-H (superficial siderosis), and symptomatic ARIA-E. His MRI scan showed new moderate vasogenic edema in the left frontal and left temporal regions, severe new superficial siderosis in the left frontal, left occipital cortex, left parietal, and left temporal regions, and mild new macrohemorrhage in the left frontal region. On Day 131 the subject was discharged with improvement of the strength deficit on the upper right limb. On Day 172, the events of cerebral hemorrhage and ARIA-H (superficial siderosis) were reported as resolved/stabilized. Study treatment was permanently discontinued as a result of these events. On Day 252, ARIA-E was reported to be resolved.

Reviewer's comment:

This subject suffered a macrohemorrhage 60 days after receiving his 3rd dose of aducanumab with last dose at 3 mg/kg. He was also on acetylsalicylic acid. This ARIA-H macrohemorrhage was symptomatic, with additional superficial siderosis and ARIA-E. He had ARIA-E, ARIA-H macrohemorrhage and ARIA-H superficial siderosis in the left hemisphere with accompanying weakness in his right hand which was reported to improve 12 days later. His cerebral hemorrhage and superficial siderosis resolved 49 days after onset, and ARIA-E resolved 129 days later.

Participant ID: (b) (6)

This was a 78-year-old white male with mild cognitive impairment due to Alzheimer's Disease who, on Day 142, 12 days after receiving his 5th dose of aducanumab with most recent dose at 6 mg/kg, experienced asymptomatic ARIA-H (superficial siderosis) and asymptomatic ARIA-E. His MRI scan showed new moderate vasogenic edema in the right temporal region, and 1 stable microhemorrhage and new mild superficial siderosis in the right parietal region. The superficial siderosis resolved/stabilized on Day 167, and ARIA-E resolved on Day 188. Study treatment was interrupted as a result of the events and restarted on Day 231 at the same dose (6 mg/kg) and continued up-titration per protocol. He received his final dose on Day 646.

Reviewer Comment:

This appears to be an instance of asymptomatic ARIA-H superficial siderosis and asymptomatic ARIA-E that occurred 12 days after his 5th dose of aducanumab, with ARIA-H superficial siderosis resolving in 25 days and ARIA-E resolving in 46 days. This is a case where a subject's aducanumab was held for 101 days and resumed at the same dose after experiencing and resolving/stabilizing asymptomatic ARIA-E and asymptomatic ARIA-H (superficial siderosis).

Participant ID: (b) (6)

This was a 67-year-old male with mild cognitive impairment due to Alzheimer's Disease who was a noncarrier for ApoE ϵ 4 who on Day 102, 18 days after receiving his 4th dose of aducanumab, with last dose at 3 mg/kg, experienced asymptomatic ARIA-E and asymptomatic ARIA-H. His MRI scan showed moderate vasogenic edema in the left parietal, right occipital cortex, right parietal, and right temporal, nonhippocampal; 3 microhemorrhages, 1 of which was new. His ARIA-H (microhemorrhage) was reported resolved/stabilized on Day 147. On Day 133, his ARIA-E became symptomatic ARIA-E reporting right lower field blurring. MRI scan showed moderate vasogenic edema in the left parietal, right occipital, and right temporal, regions; 5 microhemorrhages in the left occipital cortex, 2 of which were new compared to previous MRI scan. Study treatment remained interrupted as a result of the event of symptomatic ARIA-E and he was treated with methylprednisolone 1 g QD for 3 days followed by a prednisone taper from 40 mg QD decreasing by 10 mg QD each week for the event of symptomatic ARIA-E. His blurred vision was reported as resolved on Day 147. His symptomatic ARIA-E was reported as resolved on Day 186. Study treatment was restarted on Day 197 and he received his third 3 mg/kg dose. On Day 293, 9 days after his 8th dose of aducanumab with most recent dose at 6 mg/kg, the participant experienced another asymptomatic moderate ARIA-E which resolved on Day 363. On Day 309, the participant had received study treatment at 10 mg/kg, which the Sponsor reports was administered in error. The Sponsor reports that per protocol, the participant should have been suspended from the study treatment at this time. On Day 363, the participant experienced one new asymptomatic ARIA-H (microhemorrhage) 54 days after his 9th dose of aducanumab, with most recent dose at 10 mg/kg which was reported to be resolved/stabilized on Day 385. On Day 462, 15 days after the subject received his 12th dose of aducanumab, with most recent dose at 10 mg/kg, the participant experienced two new asymptomatic ARIA-H microhemorrhages in the left occipital region and

asymptomatic moderate ARIA-E in the right occipital region. His ARIA-H was reported as resolved/stabilized on Day 476. His ARIA-E was reported as resolved on Day 532. Study treatment was permanently discontinued as a result of the event of ARIA-H (microhemorrhage), with the final dose of study treatment (10 mg/kg) received on (b) (6) (Day 447).

Reviewer's comments:

Subject experienced his first ARIA-E and ARIA-H after receiving his 4th dose of aducanumab and ARIA-E resolved in 29 days (in that it became symptomatic then with a right lower field visual disturbance that lasted 14 days and this symptomatic ARIA-E lasted an additional 53 days) and later and ARIA-H resolved 45 days later. He underwent methylprednisolone treatment with steroid taper. 9 days after his 8th dose, he experienced a 70-day episode of asymptomatic ARIA-E. During this episode of ARIA-E, he received a 10 mg/kg dose in error and 59 days later experienced one new ARIA-H microhemorrhage. 15 days after his 12th dose, he again experienced an episode of ARIA-H (stabilizing in 14 days) and ARIA-E (resolving in 70 days). It is unclear why his study treatment was permanently discontinued for ARIA-H microhemorrhage if he experienced a total of 8 microhemorrhages.

There were an additional 2 cases of serious adverse events involving cerebral hemorrhage that could be linked to ARIA.

Participant ID: (b) (6)

This was a 67 year old male, with a history of hypertension, with mild cognitive impairment due to Alzheimer's Disease who on Day 207, 3 days after receiving his 8th dose of placebo in the placebo controlled period, experienced asymptomatic ARIA-H (microhemorrhage) and asymptomatic ARIA-E in the left occipital region with ARIA-H reported as resolved/stabilized on Day 289 and ARIA-E reported as resolved on Day 344. Subject was taking acetylsalicylic acid. After the 2nd dose of aducanumab in the long term extension period, on Day 599, 8 days after the 2nd dose of aducanumab at 1 mg/kg, subject experienced a 3.4-cm intraparenchymal hemorrhage in the left occipital region resulting in the subject driving into a vehicle parked on the side of the road and backing into trash cans, both on the right side. He was hospitalized with right-sided visual deficits, specifically a right homonymous hemianopsia, and was hypertensive up to 190s mmHg. On day 786, subject experienced asymptomatic ARIA-H (microhemorrhage) and asymptomatic ARIA-H (macrohemorrhage) in the left occipital region which did not resolve during the study. His last dose of aducanumab was received on Day 591 and consent was withdrawn with final assessment on Day 891.

Reviewer's comment:

It is notable that this subject experienced ARIA-E and ARIA-H (microhemorrhage) in the left occipital region while on *placebo* 310 days prior to his cerebral hemorrhage in the same region after receiving his second dose of aducanumab in the long-term extension period. It appears that the left occipital cerebral hemorrhage was a manifestation of ARIA-H macrohemorrhage. A significant consequence of this was the subject having an auto accident with another parked vehicle and backing

into trash cans on the right side. This may have been related to aducanumab given the temporal association to the event, however I also note the subject had ARIA-E and ARIA-H (microhemorrhage) in the same brain region earlier while on placebo. Contributing factors to the cerebral hemorrhage include his elevated blood pressure at 190 mmHg and concomitant medication use with acetylsalicylic acid.

Participant ID: (b) (6)

This was a 71-year-old male with mild Alzheimer's disease who experienced on Day 103 asymptomatic ARIA-H with 1 microhemorrhage after receiving 4 doses of aducanumab with most recent dose at 3 mg/kg. He received 2 additional doses at 3 mg/kg. The microhemorrhage resolved on Day 155, but on that day, he had asymptomatic ARIA-E in the right temporal region and mild asymptomatic ARIA-H superficial siderosis in the right frontal region. His 7th dose on Day 169 was decreased to 1 mg/kg and continued in the study. His ARIA-E resolved on Day 205 and ARIA-H superficial siderosis resolved/stabilized on Day 211. On Day 243, he experienced an acute hematoma in the right frontal lobe 5 x 3 x 5 cm which increased in size on Day 250 to 70 x 45 mm. His final assessment was on Day 342 and he withdrew from the study due to the cerebral hematoma.

Reviewer's comment:

It appears likely that the right frontal cerebral hematoma was a manifestation of ARIA-H macrohemorrhage with prior ARIA-H superficial siderosis in the same right frontal region.

Appendix B:

Serious Adverse ARIA Events in Study 103

I searched study 103 for cases flagged for ARIA and that were flagged as serious and reviewed 20 associated narratives. Generally, the narratives were similar those presented above for serious ARIA in studies 301 and 302. Headache and visual disturbances were noted among the serious ARIA cases. Among these were cases of serious adverse events involving cerebral hemorrhage that could be linked to ARIA. Subject (b) (6) was a 81 year old female who had 5 doses of aducanumab at 1 mg/kg, and 5 days later on Day 127 had symptomatic ARIA-E in the left occipital and temporal regions and symptomatic ARIA-H superficial siderosis in the left occipital region and on Day 269 had ARIA-H macrohemorrhage in the left frontal region 21 mm in greatest dimension. She withdrew from the study and final assessment was on Day 365. Subject (b) (6) was a 69 year old male who received placebo in the placebo controlled period and after receiving his 3rd dose of aducanumab, with most recent dose at 3 mg/kg on Day 445, experienced worsening confusion and rapid cognitive and functional decline on Day 456, and on Day 477 had a blood pressure of 159/80, and MRI finding of severe ARIA-E and ARIA-H microhemorrhages ≥ 10 both in the left occipital, right occipital, left parietal, left temporal and right temporal regions and a macrohemorrhage in the left temporal region and had headache and delirium. The ARIA-E and ARIA-H microhemorrhages were reported as resolved on Day 579 and

macrohemorrhage 13 x 17 mm was ongoing at the time the subject withdrew from the study. I conclude that the macrohemorrhage was ARIA related given the location of concurrent ARIA-E and ARIA-H microhemorrhage. The subject's elevated blood pressure and concomitant use of acetylsalicylic acid may have been contributing factors. Subject (b) (6) was a 72-year-old male who received placebo during the placebo-controlled trial and received 3 doses of aducanumab 3 mg/kg in the long-term extension period with last dose received on Day 449. 17 days later, on Day 465, the subject experienced severe symptomatic ARIA-E and cardiac arrest secondary to seizure and became pulseless for 3 minutes. He was given enoxaparin for deep vein thrombosis prophylaxis. On Day 481, he additionally experienced ARIA-H microhemorrhage and ARIA-H macrohemorrhage. Of note, on Day 485, subject was had a blood pressure of 148/94, low platelet levels of 109 and had intake of enoxaparin. The subject withdrew from the study due to symptomatic ARIA-E and final assessment was on Day 581. These three cases demonstrate there is a risk for macrohemorrhage in the setting of ARIA-E, particularly in individuals with other risk factors including elevated blood pressure, abnormal platelet count, and the concurrent use of medications that increase bleeding risk. It also should be noted that 2 of these 3 cases were treated at 3 mg/kg and for Study 103 did not have titration of aducanumab dose.

Appendix C:
Serious Adverse ARIA Event in Study 104

Study 104 Subject (b) (6)

This was an 81-year old female with a history of hypertension and Alzheimer's disease who received a single dose of aducanumab 3 mg/kg. On Day 24, the subject was found to have asymptomatic ARIA-E (mild edema) in the left occipital lobe, asymptomatic ARIA-H (11 x 5 mm macrohemorrhage) in the left occipital lobe, and asymptomatic ARIA-H (superficial siderosis) on MRI. The participant discontinued study treatment and withdrew from the study due to these imaging findings. On Day 38, the participant experienced a TEAE of malaise assessed by the Investigator as mild in intensity. On Day 44, the participant had an episode of vomiting was hospitalized and went into a coma with a CT showing an extensive cerebral hemorrhage in the left occipital lobe, which resolved on Day 169. Subject was placed in a geriatric health care facility on Day 253 was reported to have higher brain dysfunction, including apraxia impaired attention and severe dementia, affected by the cerebral hemorrhage and her daughter reported the subject was almost blind due to the cerebral hemorrhage.

Reviewer's Comment:

I have looked at images from the MRI and CT for this subject and it appears the macrohemorrhage on Day 44 could be due to study treatment based on the temporal association of microhemorrhage 24 days after administration of a single dose of aducanumab at 3 mg/kg. The Investigator classified the relationship to study treatment for cerebral hemorrhage as related. Therefore, the coma, and subsequent higher brain dysfunction, including apraxia, impaired attention, report of being "almost blind" and severe dementia could be related to study treatment. It should be

noted that the protocol for the subsequent protocols in studies 301 and 302 started patients at 1 mg/kg, and titrated upwards. This subject received a single dose of aducanumab at 3 mg/kg.

Appendix D:

Deaths in Patients who experienced episodes of ARIA:

Using data from the Integrated Summary of Safety Table 22 (list of participants who died during studies of Aducanumab) and the provided narratives I identified 9 patients treated with aducanumab who experienced ARIA during the studies and subsequently died. I reviewed these cases, and none of the deaths could be attributed to ARIA.

Subject (b) (6) :

Case discussed in Appendix A.

Subject (b) (6)

This was an 84-year-old male with mild Alzheimer's disease. After he received 14 doses of aducanumab at 1 mg/kg in the placebo-controlled period and 12 doses at 3 mg/kg in the long-term extension period, 19 days later, on Day 702, he experienced possible asymptomatic vasogenic edema in the left occipital region. He was taking concomitant medications including acetylsalicylic acid, and donepezil. His ARIA-E was reported as resolved one month later on Day 751.

The following year, 3 days after subject received his 30th dose in the long-term extension period, on Day 1208, the subject reported increasing weakness and was found on the floor. On day 1210, he was hospitalized due to pancreaticoduodenal artery pseudoaneurysm bleed. During hospitalization, patient was found to have atrial fibrillation, bilateral pleural effusion, blood loss anemia, hemoperitoneum, leukocytosis, mild delirium, and right hemothorax. The subject was started on enoxaparin sodium at 30 mg BID subcutaneous starting on Day 1210 and stopping on Day 1211, and enoxaparin 80 mg BID subcutaneous on Day 1212. On Day 1212, a CT angiography of the chest showed likely hemoperitoneum, and atrial fibrillation was considered resolved this day. On Day 1213, a CT scan of the abdomen showed moderate to severe probable hemorrhage with a superior mesenteric artery branch with possible fusiform aneurysmal dilation as a possible source of the hemorrhage. He underwent an interventional radiology embolization of SMA pancreaticoduodenal branch and was started on medications including heparin on day 1217, which ceased on Day 1217. On Day 1246, subject experienced an acute left intraparenchymal hemorrhage with no recent trauma, falls, hypertension, or intracranial infection. The subject had an 8.2 cm maximal dimension intraparenchymal hematoma in the left occipital area producing a local mass effect and mild 4-mm left to right midline shift with a large left occipital hemorrhage with vasogenic edema. The Sponsor notes laboratory values on Day 1246 of a

platelet count of 380, PT of 10.4, and INR of 1 and on Day 1247 a platelet count of 355, PT of 11.4 and INR of 1.1

(b) (6)

The sponsor speculates that the hemorrhage could be secondary to amyloid angiopathy and that there may have been an arteriovenous malformation or fistula based on an area of low blood flow. The subject died on day 1252.

Reviewer's Comment:

This case is interesting in that the subject had possible asymptomatic ARIA-E on Day 702 in the left occipital region and subsequently, on Day 1246, had an acute left intraparenchymal hemorrhage in the same region. On reviewing the Sponsor's central radiologist report on this case with imaging, I have viewed the potential ARIA-E on Day 702 and concur that this could be present at that time with no evidence of ARIA-H. The subsequent ARIA-H macrohemorrhage is in the same region on Day 1246. On reviewing baseline screening presented by the Sponsor, I concur that the subject had asymmetry of the left PCA relative to the right, and agree with an etiology of a small arterio-venous malformation vs arterio-venous fistula in the left occipital region as a likely etiology of the subject's intracranial hemorrhage and not related to aducanumab.

Subject (b) (6)

This was a 79-year-old male with mild cognitive impairment due to Alzheimer's disease and a medical history that included hypercholesterolemia, hypertension and tobacco use experienced ARIA-H following 11 doses of study drug. On study day 327 (19 days after last dose) the subject developed chest

pain and was admitted 2 days later for an aortic dissection. He underwent surgical repair, but the post-operative course was complicated by labile blood pressure, renal failure, respiratory failure, cardiac arrest, resuscitation, embolic CVA and the patient died.

Reviewer's comment:

This death was due to aortic dissection. ARIA-H microhemorrhage preceded the event, however, is unlikely to have contributed to the subject's death.

Subject (b) (6)

This was a 73-year-old white male with mild cognitive impairment (MCI) due to Alzheimer's disease who experienced asymptomatic ARIA-E 12 days after he received his 4th dose of aducanumab. Twenty-one days after his 5th dose, on Day 128, he experienced asymptomatic ARIA-H (microhemorrhage) with 4 new microhemorrhages and mild ARIA-E which increased compared to prior scan. The ARIA-H (microhemorrhage) was reported as resolved/stabilized on Day 153, but he experienced new asymptomatic ARIA-H (superficial siderosis) and the event of ARIA-E worsened in severity. The events of ARIA-E and ARIA-H (superficial siderosis) were reported as resolved/stabilized on Day 215. Study treatment was restarted at the same dose (6 mg/kg) on Day 224; the participant continued up-titration to 10 mg/kg per protocol following the events. On Day 303, subject received his 9th dose of aducanumab, and 21 days later, on Day 324, the participant experienced asymptomatic ARIA-E and asymptomatic ARIA-H (superficial siderosis). The events of ARIA-E and ARIA-H (superficial siderosis) remained unresolved for the remainder of the participant's participation in the study.

On Day 334, the subject was hospitalized due to cardiac arrest and kidney failure. He was unconscious with neurological symptoms and had severe acidosis, with acute renal failure. On Day 347, the participant died due to anoxic brain damage, renal failure, and cardiac arrest.

Reviewer's Comment:

The subject died from anoxic brain damage from renal failure and cardiac arrest with a history of diabetes and arteriosclerosis. While subject did have an event of ARIA-E and ARIA-H (superficial siderosis in the left parietal) 10 days prior to this event, the history does not support a causal link between the two.

Subject (b) (6)

This was an 81-year-old white male with mild cognitive impairment (MCI) due to Alzheimer's Disease who received his 4th dose of aducanumab and 13 days later, on Day 99, experienced asymptomatic ARIA-H (microhemorrhage) with 3 new microhemorrhages. On Day 115, was found on MRI to have 2 additional new microhemorrhages and new asymptomatic ARIA-E. On Day 138, the ARIA-H (microhemorrhage) resolved/stabilized but had new asymptomatic ARIA-H superficial siderosis and his

ARIA-E showed improvement. The event of asymptomatic ARIA-E and ARIA-H (superficial siderosis) was reported as resolved on Day 166. Study treatment restarted on Day 198 on a reduced dose of 1 mg/kg. After the subject received his 8th dose of aducanumab, with most recent dose at 1 mg/kg, 14 days later, on Day 295, the participant experienced new asymptomatic ARIA-H (superficial siderosis) which resolved on Day 337. After the subject received his 20th dose of aducanumab, (consisting of 16 doses in the placebo-controlled period and 4 doses in the LTE period with 2 doses at 6mg/kg and 2 doses at 10 mg/kg), 13 days later, on Day 659, the participant experienced asymptomatic ARIA-E and asymptomatic ARIA-H (superficial siderosis). The event of superficial siderosis of central nervous system was reported as resolved/stabilized on Day 676. On the same day, 30 days after the 20th dose, the event of asymptomatic ARIA-E worsened in severity from mild to moderate.

On Day 694 subject had 10 days of abdominal pain with hardness in the left lower quadrant noted with a diagnosis of chronic idiopathic constipation and had been on polyethylene glycol for the prior 5 days. On Day 698, the participant died due to Alzheimer's disease. The participant complained of stomach pains, slumped over, and died. No autopsy was performed.

Reviewer's Comment:

Subject's cause of death was Alzheimer's disease. Subject had a history of constipation, right inguinal hernia, umbilical hernia, and had a mass in the left lower quadrant prior to his death with no autopsy conducted. I do not suspect his ARIA-E or ARIA-H as a contributing factor to his death.

Subject (b) (6)

This was a 72-year-old white female with mild Alzheimer's disease who 14 days after her 11th dose of aducanumab on Day 296 experienced asymptomatic ARIA-H (superficial siderosis) in the right frontal region which stabilized on day 379. On day 660, 15 days after receiving her 24th dose of aducanumab, she experienced asymptomatic ARIA-E and ARIA-H (microhemorrhage) with one new microhemorrhage with ARIA-H resolved/stabilized on Day 697 and ARIA-E resolved on Day 743. On Day 697, subject experienced a moderate asymptomatic ARIA-H superficial siderosis which worsened into a severe asymptomatic ARIA H (superficial siderosis) on Day 725 and resolved on Day 771. On Day 1021, the subject complained of abdominal pain and experienced a myocardial infarction.

Reviewer's Comment:

While this subject experienced ARIA-E and ARIA-H while being treated with aducanumab, I do not suspect this contributed to her death due to myocardial infarction.

Subject (b) (6)

This is a 78-year-old white male with mild cognitive impairment due to Alzheimer's disease who experienced asymptomatic ARIA-E 12 days after her 26th dose of aducanumab on Day 714 which resolved on Day 745. No action was taken with study treatment as a result of the event. The participant continued in the study. On Day 794, the participant was hospitalized due to Alzheimer's disease progression as the subject was unable to walk and had difficulty following commands. On Day 801, a brain MRI showed no acute changes and subject was discharged from the hospital on Day 802 with diagnoses that included failure to thrive secondary to progressive AD, worsening encephalopathy, history of irritable bowel syndrome/constipation, and insomnia. On Day 808, the participant died due to the event of dementia Alzheimer's type.

Reviewer's Comments:

While the subject experienced ARIA-E prior to her death, this was reported resolved on day 745 and subject died on Day 808 with an MRI on Day 801 with no acute changes. I do not suspect ARIA-E contributed to subject's death.

Subject (b) (6)

This was an 81-year-old white male with mild cognitive impairment due to Alzheimer's disease who 14 days after receiving her 6th dose of aducanumab experienced asymptomatic ARIA-E on Day 155 which resolved on Day 210. On Day 295, 15 days after receiving the 11th dose, the participant experienced another episode of asymptomatic ARIA-E which resolved on Day 442. On Day 667, the subject was diagnosed with adenocarcinoma in the left lower lung, with a 1.5-cm tumor. On Day 704, the participant experienced pneumonia and on Day 707, the subject experienced left lower lung collapse. On Day 724, while hospitalized, the participant died due to pneumonia.

Reviewer's Comment:

Subject died from pneumonia in the setting of adenocarcinoma of the left lower lung. Patient's prior ARIA-E significantly preceded this event and was unlikely to be a contributing factor to her death.

Subject (b) (6)

This was a 59-year-old white male with mild Alzheimer's disease who experienced asymptomatic ARIA-E 14 days after his 4th dose of aducanumab on Day 97, which resolved on Day 181. Study treatment dosing was interrupted as a result of the event and was restarted at the same dose (3 mg/kg) on Day 197. On Day 295, 14 days after his 8th dose, the participant experienced asymptomatic ARIA-H (microhemorrhage) with two new microhemorrhages and asymptomatic ARIA-E. ARIA-H resolved on Day 350 and ARIA-E resolved on Day 377. On Day 583, the participant was hospitalized due to lung cancer. A chest CT scan showed a primary bronchial neoplasm arising in the right lower lobe,

with an unusual nodal involvement below the diaphragm. Differential diagnosis included lymphoma. On Day 590, the participant was discharged to palliative care at home. On Day 618, the participant died due to the lung neoplasm.

Reviewer's Comment:

This subject died from a lung neoplasm, with incidental ARIA-E and ARIA-H earlier in the study. I do not suspect the ARIA-E or ARIA-H contributed to this patient's death.

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/s/

BRIAN J TRUMMER
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DN1 Review of Clinical Data

BLA (Serial Number)	761178
Sponsor:	Biogen Inc.
Drug:	Aducanumab
Proposed Indication:	To delay clinical decline in patients with Alzheimer's Disease
Date Received / Agency:	07/07/2020
Date Review Completed:	06/06/2021
Reviewer:	Michelle Campbell, PhD

1. Background

This marketing application is for aducanumab (previously BIIB037), a human immunoglobulin gamma 1 (IgG1) anti-amyloid beta (A β) monoclonal antibody targeting aggregated forms of A β . The applicant's proposed indication is to delay clinical decline in patients with Alzheimer's disease.

Alzheimer's disease is a progressive, degenerative brain disorder that affects memory, thinking, and behavior and is the most common cause of dementia. According to a recent report (Alzheimer's Association 2021), an estimated 6.2 million Americans age 65 and older are currently living with Alzheimer's disease dementia. In the absence of interventions to prevent or slow the disease, the number is projected to reach 12.7 million by 2050. The report notes that Alzheimer's disease is the sixth-leading cause of death in the United States and the fifth-leading cause of death for those age 65 and older. 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 Association 2021).

Alzheimer's disease exists on a continuum from pathophysiological changes in the brain which are undetectable to the person affected, to subtle problems with memory and thinking, and ultimately difficulties with memory, language, problem-solving, and other skills that affect an individual's ability to perform everyday activities. The disease process may begin 20 years or more before symptoms arise (Vermunt et al. 2019). Life expectancy varies depending on many factors, but after a diagnosis of Alzheimer's dementia the average survival is 4 to 8 years (Alzheimer's Association 2021). The long duration of the disease contributes to the burden not only of the individuals with the disease, but also their families and caregivers who provide most of the patient care and are at an increased risk for emotional distress and negative mental and physical outcomes.

Patients with Alzheimer's disease and their caregivers have stated that loss of memory and forgetfulness, concentration, communication, impact of moods and emotions, and decreased social engagement are critical areas of the disease which impacts their lives the most. Patients also identified that meaningful treatment outcomes include better

memory function, disease modification, and maintaining independence (DiBenedetti et al. 2020). These concepts are aligned with the Agency's 2018 Early Alzheimer's Disease: Developing Drug for Treatment Guidance for Industry on endpoints for early Alzheimer's disease trials. This review will focus only on the appropriateness of the clinical outcome assessments used by the applicant in its development program. For a complete review of the efficacy data, see Dr. Krudys' s clinical review.

2. Summary of Submission

Study Design

Study 302 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with Alzheimer's disease (stage of disease – MCI or mild dementia). The study was conducted in 181 centers globally. Randomization was stratified by site and by ApoE ϵ 4 carrier status (carrier or non-carrier), and enrollment was monitored such that 80% of the population included patients with a baseline clinical stage of MCI due to Alzheimer's disease. The study included an 8-week screening period, a 78-week placebo-controlled treatment period and a safety follow-up period of 18 weeks after the final dose. For the placebo-controlled period, patients were randomized to aducanumab low dose, aducanumab high dose, or placebo treatment in a 1:1:1 ratio. Patients who completed the placebo-controlled period had the option to enter the 5-year, dose-blind, long-term extension (LTE) period. Patients randomized to placebo during the placebo-controlled period were assigned to aducanumab low dose or aducanumab high dose in the LTE. Patients randomized to aducanumab in the placebo-controlled period continued in the same treatment group for the LTE period.

Diagnostic Criteria

At the time of enrollment, patients 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). Patients were also required to have evidence of brain A β pathology by visual read of a positron emission tomography (PET) scan.

Key Inclusion Criteria

1. Male or female patients age 50 to $\leq$ 85 years
2. At least 6 years of education or work experience
3. Positive amyloid PET scan
4. CDR global score of 0.5
5. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score $\leq$ 85
6. Mini-Mental State Examination (MMSE) score $\geq$ 24

7. Must consent to ApoE genotyping
8. Has one informant/care partner who is able to provide accurate information about the subject's cognitive and functional abilities and should be available for the duration of the study

Key Exclusion Criteria

1. Any uncontrolled medical or neurological condition (other than Alzheimer's disease) that may be a contributing cause of the subject's cognitive impairment
2. Clinically significant unstable psychiatric illness within 6 months prior to screening
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening
4. Brain MRI performed at screening that shows evidence of any of the following: acute or sub-acute hemorrhage, prior microhemorrhage 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
5. Contraindications to having a brain MRI or PET scan
6. History of bleeding disorder
7. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤ 325 mg daily)
8. Uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic heart failure or clinically significant conduction abnormalities
9. Participation in any active immunotherapy study targeting A β , any passive immunotherapy study targeting A β within 12 months of screening or any study with purported disease-modifying effect in AD within 12 months of screening unless documentation of receipt of placebo

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in CDR-SB at Week 78. The CDR-SB is a clinician-reported outcome measure which assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews with the patient and a reliable companion or informant. A qualified rater uses patient/caregiver interview data and clinical judgment to assign scores for each domain ranging from none=0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3. The personal care domain does not include the 0.5 score. Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating

greater disease severity. CDR-SB has been described in the literature (Cederbaum et al. 2013) as a suitable primary endpoint for clinical trials in patients with early Alzheimer's disease due to its ability to assess both cognitive and functional disability. CDR-SB is accepted by FDA as an acceptable primary outcome assessment for studies of Alzheimer's disease intended to demonstrate substantial evidence of effectiveness. It has been widely used as the primary efficacy endpoint in clinical trials for other investigational drugs in this population.

CDR-SB assessments were conducted by an independent and blinded HCP not involved in patient care or management. Given the importance of the reliable informant or companion, the inclusion criteria included a stipulation that the informant should be available for the duration of the study and the use of the same informant for the duration of the study was encouraged. Raters were required to complete qualification and training prior to being eligible to administer the assessment. All sites were asked to maintain the same rater throughout the study to ensure consistency. If a rater administered the CDR-SB to a patient, that rater was not allowed to administer the other neurocognitive assessments to that patient at any point during the study. Selected assessments were reviewed by central raters for consistency. If the central review resulted in feedback to the site rater, the site rater either agreed with the feedback and updated the assessment or provided rationale for not making the update.

Secondary Endpoints

The secondary endpoints were assessed by a second HCP who was independent from the rater responsible for administering the CDR-SB. This rater was also independent from and blinded to study treatment and not part of the patient's care or management. As with CDR-SB, all sites were asked to maintain the same rater throughout the study to ensure consistency.

MMSE

The MMSE is a performance outcome measure which assesses cognitive ability, and consists of 11 tasks evaluating orientation, word recall, attention and calculation, language, and visuospatial functions. The scores from the 11 tests are summed to obtain a total score, which ranges from 0 to 30, with lower scores indicating greater cognitive impairment. It is often used in clinical practice or as a staging instrument for trial inclusion. It is also used as an efficacy assessment in clinical trials.

ADAS-Cog 13

The ADAS-Cog is a clinician-reported outcome cognitive assessment consisting of clinical ratings and cognitive tasks that was originally developed for use in clinical trials of patients with later stages of Alzheimer's disease dementia. ADAS-Cog 13 contained the ADAS-Cog-11 items, which measure disturbances of memory, language, and praxis, plus two additional tasks, delayed word recall and number cancellation, to create the ADAS-Cog 13, for use in an earlier disease population. The ADAS-Cog 13 includes 9 items that test performance (up to 65 points) and 4 clinician-rated items that test language and memory (up to 20 points), for a total score ranging from 0 to 85, with higher scores indicating greater cognitive impairment. The 13 items assess word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, comprehension of spoken language, memory, word-finding, language ability, delayed word recall, and concentration.

ADCS-ADL-MCI

The ADCS-ADL-MCI is an interview-administered questionnaire for patients and their caregivers to respond on activities of daily living. The ADCS-ADL-MCI consists of 17 instrumental items and 1 basic item (getting dressed), intended to reflect activities of daily living. Informants are asked whether the patient attempted each item during the prior 4 weeks and their level of performance. Responses are "Yes," "No," or "Don't Know" with additional sub-ratings depending on the item. The total score ranges from 0 to 53 with lower scores indicating greater impairment. The ADCS-ADL-MCI was adapted from the ADCS-ADL, which was developed for a population with more advanced disease.

Tertiary Endpoint

NPI-10 is an interviewed administer questionnaire for patients and their caregivers. The NPI-10 assesses the presence, frequency, and severity of 10 neuropsychiatric domains: delusions, hallucinations, dysphoria, apathy, euphoria, disinhibition, agitation/aggression, irritability/liability, anxiety, and aberrant motor behavior. The total score ranges from 0 to 120 with higher scores indicating worse symptoms.

Correlations Values of Endpoints

To examine the potential for any redundancy or multicollinearity, the applicant performed both a Spearman rho correlation and a principal components analysis. The correlation matrix showed a range of small to moderate correlation between the clinical outcome assessments used to support the primary and secondary endpoints.

Table 1. Study 302 Correlations at Week 78 between changes from baseline on Primary and Secondary endpoints

Prob > r under H0: Rho=0 Number of Observations				
	CDRSB	MMSE	ADAS-cog	ADCS-ADL-MCI
CDRSB	1.000	-0.557 <.0001 877	0.494 <.0001 866	-0.639 <.0001 862
MMSE	-0.557 <.0001 876	1.000	-0.583 <.0001 869	0.443 <.0001 864
ADAS-cog	0.494 <.0001 866	-0.583 <.0001 869	1.000	-0.397 <.0001 857
ADCS-ADL-MCI	-0.639 <.0001 862	0.443 <.0001 864	-0.397 <.0001 857	1.000 864

From FDA Statistical Review, Table 26, page 102

Using a principal components analysis of the 48 individual items from CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI, baseline and change from baseline data from Study 301 and Study 302 to assess the degree to which the items capture similar or distinct information, the applicant determined that the overlap or shared variance between the items was 5-25%, and concluded that each outcome assessment was independent from one another and captured distinct concepts from the patient.

3. Reviewer's Summary Comments

The clinical outcome assessments used to support the study endpoints are assessments that are adequate and suitable for use in this drug development program. These assessments captured the symptoms and impacts of Alzheimer's disease that are meaningful to patients (Harty et al. 2020). Additionally, these assessments align with the Agency's 2018 *Early Alzheimer's Disease: Developing Drug for Treatment Guidance for Industry* and measures concepts/domains adequately to support study endpoints. There

was an SPA agreement for the endpoints selected and used in this drug development program. For additional details, see Dr. Krudys' s efficacy review.

The correlations values shown in Table 1 do not suggest concern for redundancy or multicollinearity of the outcome assessments or the items included in the outcome assessments used in this drug development program. Correlations values that are 0.85 or over would suggest a concern for the presence of redundant items. The correlations values seen in this drug development program are acceptable. It is expected with the progressive nature of Alzheimer's disease to see some correlation between the clinical outcome assessments. The clinical outcome assessments used in this drug development program do measure distinct concepts. The applicant's principal components analysis also support that distinct, independent domains are being measured using the clinical outcome assessments for this drug development program.

4. Conclusions

Patients with Alzheimer's disease and their caregivers have stated that loss of memory and forgetfulness, concentration, communication, impact of moods and emotions, and decreased social engagement are critical areas of the disease which impact their lives the most. Patients also identified that meaningful treatment outcomes include better memory function, disease modification, and maintaining independence (DiBenedetti et al. 2020). The clinical outcome assessments used in the aducanumab development program were appropriate and adequate to support study endpoints. These clinical outcome assessments capture clinically meaningful aspects of an Alzheimer's patient's life. These clinical outcome assessments capture distinct, independent concepts and domains. There is no concern for redundancy or multicollinearity with the correlation values presented in Table 1. Collectively, the clinical outcome assessments supporting the primary, secondary, and tertiary endpoints capture the broad impact of Alzheimer's disease in a patient's life.

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Clinical Review
 Natalie Branagan, MD
 BLA761178
 Aduhelm/aducanumab

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761178
Priority or Standard	Priority
Submit Date(s)	July 7, 2020
Received Date(s)	July 7, 2020
PDUFA Goal Date	June 7, 2021
Division/Office	DN1
Reviewer Name(s)	Natalie Branagan, MD
Review Completion Date	
Established/Proper Name	Aducanumab
(Proposed) Trade Name	Aduhelm
Applicant	Biogen
Dosage Form(s)	Injection, intravenous
Applicant Proposed Dosing Regimen(s)	10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks
Applicant Proposed Indication(s)/Population(s)	Patients with Alzheimer's disease
Recommendation on Regulatory Action	Excluding safety related to ARIA, if efficacy is demonstrated and the benefits of aducanumab outweigh the risks, then I recommend that approval include appropriate labeling language to address adverse reactions of concerns.
Recommended Indication(s)/Population(s) (if applicable)	(b) (4) Alzheimer's disease

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Glossary

AC	advisory committee
ADU	Aducanumab
AE	adverse event
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

Clinical Review
Natalie Branagan, MD
BLA761178
Aduhelm/aducanumab

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Information

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

1.3. Patient Experience Data

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

2. Therapeutic Context

2.1. Analysis of Condition

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

2.2. Analysis of Current Treatment Options

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3.2. Summary of Presubmission/Submission Regulatory Activity

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology review.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for a table of clinical studies. For a table of key clinical studies for the safety review, see section 8.1.

5.2. Review Strategy

The clinical review of BLA 761178 is divided into a review of clinical efficacy (by Dr. Kevin Krudys), a review of safety of the events of ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system by Dr. Brian Trummer, and this review of clinical safety. Information submitted as part of BLA 761178 and published literature are discussed in this review. I will primarily present analysis conducted by myself and Senior Clinical Analyst Dr. Rui Li. The primary safety review presented here will focus on Study 302 to reflect the safety in the study that is the primary source of evidence of effectiveness. Studies 301 and 103 will provide supportive information.

6. Review of Relevant Individual Trials Used to Support Efficacy

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

7. Integrated Review of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys.

8. Review of Safety

8.1. Safety Review Approach

The safety population was defined as all patients who were randomized and received at least one dose of study drug.

The key studies that were analyzed for the clinical review of safety were comprised of a placebo-controlled period followed by an open-label long-term extension period. The table below contains the key studies analyzed for the clinical review of safety.

Table 1. Studies Supporting Safety by Assigned Treatment

Study	Primary Objective	Type of Study	Dose by Assigned Treatment for Placebo-Controlled Period (Safety population)
221AD103	Evaluate the safety and	Randomized, double-blind,	Placebo (48) Aducanumab 1 mg/kg (31)

Study	Primary Objective	Type of Study	Dose by Assigned Treatment for Placebo-Controlled Period (Safety population)
	tolerability of multiple doses of aducanumab	placebo-controlled with staggered parallel-group study, followed by an optional dose-blind long-term extension period Length of PC period: 52 weeks Length of LTE Period: up to 8 years	Aducanumab 3 mg/kg (32) Aducanumab 6 mg/kg (30) Aducanumab 10 mg/kg (32) Aducanumab titrated from 1 mg/kg to 3 mg/kg to 6 mg/kg to 10 mg/kg (23)
221AD301	Evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional	Randomized, double-blind, placebo-controlled, parallel-group study, followed by a dose-blind, long-term extension period Length of PC period: 76 weeks Length of LTE period: up to 5 years	Placebo (540) Aducanumab 3 mg/kg (391) Aducanumab 6 mg/kg (202) Aducanumab 10 mg/kg (514)
221AD302	Evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional	Randomized, double-blind, placebo-controlled, parallel-group study, followed by a dose-blind, long-term extension period Length of PC period: 76 weeks Length of LTE	Placebo (547) Aducanumab 3 mg/kg (369) Aducanumab 6 mg/kg (203) Aducanumab 10 mg/kg (519)

Study	Primary Objective	Type of Study	Dose by Assigned Treatment for Placebo-Controlled Period (Safety population)
		period: up to 5 years	

PC: placebo-controlled. LTE: long-term extension

I refer to studies by their numeric values for the remainder of this review.

Study 302 is the proposed primary source of evidence of effectiveness; therefore, results are presented for this study individually. The two other studies were chosen for key safety analyses because Study 301 shared an identical protocol with Study 302, and Study 103 was the first study of aducanumab that evaluated the safety and tolerability of multiple doses of aducanumab in subjects with prodromal or mild Alzheimer's disease dementia. The remaining studies had smaller enrollment (populations of less than 100 subjects for Studies 101, 102, 104, or 205). One additional open-label study was ongoing at the time of the Applicant's submission (Study 304). Results from the 90-Day Safety Update of Study 304 are included in this review.

In the Phase 1 study, Study 103, subjects were assigned a fixed dose of their assigned treatment dose. Assigned treatments in Studies 301 and 302 differed from Study 103 in that subjects were titrated to their assigned treatment dose per protocol. Because the aducanumab arms involved titration of aducanumab to the assigned treatment dose, not all subjects reached their assigned dose level. Further titration of the dose could be stopped for reasons including the development of an AE or withdrawal from the study. This review evaluates safety outcomes by assigned treatment arm and by maximum dose received.

Reviewer comment:

Upon further review of the applicant's analyses by assigned treatment group in Studies 301 and 302, I note that for the purposes of analysis the applicant reassigned treatment groups in the placebo-controlled period of the studies, as explained in the paragraph below. For subjects who were ApoE ε4 carriers, the maximum assigned treatment dose was increased from 6 mg/kg to 10 mg/kg in Protocol Version 4 of Studies 301 and 302.

In the applicant's analyses of safety, 72 subjects who were ApoE ε4 carriers were analyzed in the 6 mg/kg assigned treatment arm despite the protocol change (44 subjects in Study 301; 28 subjects in Study 302). In the applicant's analyses of efficacy, these subjects were analyzed in the 10 mg/kg treatment arm.

In order to better reflect the safety outcomes of the population analyzed for efficacy, I reassigned these 72 subjects to the 10 mg/kg treatment arm for my analyses.

Additionally, I note five subjects from the placebo-controlled periods of Study 301 and one subject from Study 302 who were randomized to placebo, inadvertently received one dose of aducanumab during the study, and were assigned to aducanumab arms in the applicant's analyses

(b) (6)

In my analyses for this review, these subjects remained in their respective aducanumab arms.

The reader is referred to the Appendix for a table of adverse events occurring in these subjects in the placebo-controlled period of Studies 301 and 302 and timing with respect to the aducanumab dose [\(see Appendix 13.1\)](#).

I also performed analyses with these 6 subjects analyzed as originally randomized to placebo. In Study 302, this resulted in the reassignment of one subject from the aducanumab 3 mg/kg arm to placebo. Analyses using this method were presented at the Peripheral and Central Nervous System Drugs Advisory Committee meeting, held on November 6, 2020, in the Clinical Overview of Safety for aducanumab for the treatment of Alzheimer's disease for Study 302. I refer to this analysis as "Analysis 2" in this review.

The following table indicates the number of subjects in the reassigned treatment arms for the placebo-controlled periods of Studies 301 and 302 for my analyses.

Table 2. Placebo-Controlled Period for Phase 3 Studies Supporting Safety by Reassigned Treatment Arms^a

Study	Dose (Safety population)
301	Placebo (540) Aducanumab 3 mg/kg (391) Aducanumab 6 mg/kg (158) Aducanumab 10 mg/kg (558)
302	Placebo (547) Aducanumab 3 mg/kg (369) Aducanumab 6 mg/kg (175) Aducanumab 10 mg/kg (547)

^aThis includes 72 subjects assigned to the 6 mg/kg group who are reassigned to the 10 mg/kg group in the placebo-controlled periods of Studies 301 and 302.

For the remainder of this review, treatment arms are based on reassigned treatment arms unless otherwise stated.

The following table shows the maximum dose received by treatment arm for the placebo-controlled periods of Studies 301 and 302.

Table 3. Placebo-Controlled Periods of Study 302 and Pooled Studies 301 and 302 Supporting Safety by Maximum Dose Received

Study	Dose by Maximum Dose Received (Safety population)
302	Placebo (547) Aducanumab 1 mg/kg (13) Aducanumab 3 mg/kg (412) Aducanumab 6 mg/kg (208) Aducanumab 10 mg/kg (458)
301 and 302	Placebo (1087) Aducanumab 1 mg/kg (29) Aducanumab 3 mg/kg (844) Aducanumab 6 mg/kg (403) Aducanumab 10 mg/kg (922)

Safety Pools for Studies 103, 301, and 302

The pools used to analyze safety outcomes for this review are outlined in the following table.

Table 4. Safety Pools by Study by Assigned Treatment

Pools	Description	Studies	Assigned Treatment
Phase 3, placebo-controlled periods	Placebo-controlled Phase 3 Studies	301 302	Aducanumab 3 mg/kg: 760 Aducanumab 6 mg/kg: 333 Aducanumab 10 mg/kg: 1105 Placebo: 1087
Placebo-controlled and long-term extension periods of Study 302	All Aducanumab-treated Study 302	302	Aducanumab < 10 mg/kg: 674 Aducanumab 10 mg/kg: 679
Placebo-controlled and long-term extension periods of pooled Studies 301 and 302	All Aducanumab-treated for pooled Studies 301 and 302	301 302	Aducanumab < 10 mg/kg: 1371 Aducanumab 10 mg/kg: 1386
All Aducanumab-treated	All Aducanumab-treated for 3 key studies	103 301 302	Aducanumab < 10 mg/kg: 1493 Aducanumab 10 mg/kg: 1449

Reviewer comments: The Phase 3 placebo-controlled pool allows for a comparison of adverse events between placebo and aducanumab for the two key Phase 3 studies. The all-aducanumab treated pool for pooled Studies 301 and 302 and pooled Studies 103, 301, and 302 includes

subjects who received aducanumab in the placebo-controlled and long-term extension periods of the studies and allows for detection of safety events occurring in patients treated with aducanumab for up to 8 years in the three pivotal trials. Study 104 was not included in the all-aducanumab treated pool as the study did not demonstrate efficacy. This may have been due to lower exposure levels to aducanumab. The incidence of events related to safety outcomes in Study 104 may not reflect the incidence of outcomes related to safety at efficacious doses of aducanumab; therefore, this study was not included in the pooled data. Additionally, because Study 301 did not demonstrate efficacy, outcomes related to safety from Studies 302 and 103 were evaluated separately from Study 301.

The following table shows the maximum dose received by a subject in Studies 103, 301, and 302 in the combined placebo-controlled period and long-term extension period of the individual studies and pooled studies.

Table 5. Maximum Dose Received in the Placebo-Controlled and Long-Term Extension Periods of Study 302 and the Pooled Studies 103, 301, and 302.

Studies	Maximum Dose Received	
	<10 mg/kg	10 mg/kg
302	822	531
103/301/302	1787	1155

This table was created by the reviewer using ISS ADSLI, POOLC=POOLB; SAFFL=Y; tabulated on PMAXTR2.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The total number of subjects in Phase 1, 2, and 3 studies exposed to at least 1 dose of aducanumab was 3,078. Of note, the exposure at the intended dose of 10 mg/kg was 1,505 total, 959 for 6 months, and 770 for 1 year, meeting ICH guidelines of at least 300 patients for 6 months, and 100 patients for one year for exposure at the clinically relevant dose. The table below indicates number of subjects enrolled across Phase 1, 2 and 3 studies by population type.

Table 6. Safety Population, Size, and Denominators

Safety database for the study drug Individuals exposed to any treatment in this development program for the indication under review N=4231 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Aducanumab (n=3078)	Placebo (n=1153)
Healthy volunteers	28	0

Safety database for the study drug Individuals exposed to any treatment in this development program for the indication under review N=4231 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Aducanumab (n=3078)	Placebo (n=1153)
Controlled trials	2402	1153
Uncontrolled trials (includes new exposures in the long-term extension periods of Studies 103, 301, and 302)	648	N/A

The above data is calculated from data presented in the ISS Tables 1 and 2 submitted by the applicant. Data for Studies 301 and 302 were based on assigned treatment from the applicant's analyses.

The Applicant notes 3,078 subjects who received at least one dose of aducanumab across the clinical program. The total number of subjects who received at least one dose of aducanumab in the placebo-controlled periods of Study 302 was 1091. The table below summarizes my calculations for exposure in subjects at the 10 mg/kg dose in the combined placebo-controlled and long-term extension periods of Studies 301 and 302 at 6, 12, and 18 months.

Table 7. Exposure in the Combined Placebo-Controlled and Long-Term Extension Periods of Studies 301 and 302 at 10 mg/kg Dose.

Study	≥6 months	≥12 months	≥18 months
301	423	270	163
302	411	281	146
Total	834	551	309

This table was created by the reviewer using ISS ADEX, POOLC=A2, EXDOSE=10; grouped on StudyID and USUBJID; where 6-month exposure ≥ 6 doses; 12-month exposure ≥ 12 doses; 18-month exposure ≥ 18 doses.

The applicant reports higher numbers of subjects with 6- and 12-month exposures (1151 subjects at 6 months and 872 subjects at 12 months, ISS page 54). The difference in numbers is in part based on different methods used to estimate exposure. The applicant's calculations include time periods where subjects were being titrated up to their goal dose of 10 mg/kg.

My calculations include time periods after a subject had reached their goal of 10 mg/kg dosing. The table below summarizes exposure in subjects at the 10 mg/kg dose in the placebo-controlled periods of Studies 301 and 302. I note that Study 301 had a slightly lower percentage of subjects assigned to the 10 mg/kg group who had exposure for at least 6 and 12 months compared to Study 302.

Table 8. Exposure for Placebo-Controlled Periods of Studies 301 and 302 at Aducanumab 10 mg/kg Dose.

StudyID	≥ 6 months n (%)	≥ 12 months n (%)
301 (N=558)	319 (57)	151 (27)
302 (N=547)	332 (61)	170 (31)

This table was created by the reviewer using ISS ADEX, POOLC=POOLA1; EXDOSE=10; grouped on StudyID and USUBJID; where 6-month exposure = any subject with ≥ 6 doses; 12-month exposures ≥ 12 doses. The denominator is based on Reassigned Treatment group.

The applicant notes the total number of subjects who received at least one dose of aducanumab 10 mg/kg or higher across the clinical program was 1487. The applicant's calculations are based on assigned treatment status and do not necessarily reflect whether the subject actually received a 10 mg/kg dose. I calculated the number of subjects who received at least one dose of aducanumab 10 mg/kg based on actual treatment received and note that 1,165 subjects received at least one dose of aducanumab 10 mg/kg across the clinical program.

Trial Design in Studies 103, 301, and 302

In Studies 301 and 302, subjects who were A β positive as assessed by PET imaging and who fulfilled clinical criteria for either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia were randomized by ApoE ϵ 4 carrier status to receive 4-week intravenous infusions of placebo or titrated to aducanumab low-dose or aducanumab high-dose treatment groups for a total of 20 doses during the placebo-controlled period. The aducanumab low-dose treatment group was defined as 3 mg/kg for carriers and 6 mg/kg for a noncarriers. The high-dose treatment group was defined as 6 mg/kg for carriers and 10 mg/kg for noncarriers. The maximum dose in the high-dose treatment group for carriers was later updated to 10 mg/kg (Protocol Version 4).

Titration was based on ApoE ϵ 4 carrier status. For ApoE ϵ 4 carriers assigned to the low-dose group, titration included 1 mg/kg for the first two doses, followed by 3 mg/kg thereafter. For ApoE ϵ 4 carriers assigned to the high-dose group in protocol version 4 or higher, titration included 1 mg/kg for the first two doses, 3 mg/kg for the next two doses, 6 mg/kg for the next two doses, and 10 mg/kg thereafter. For ApoE ϵ 4 carriers assigned to the high-dose group between protocol versions 1 through version 3, titration included 1 mg/kg for the first two doses, 3 mg/kg for the next four doses, and 6 mg/kg thereafter. For ApoE ϵ 4 noncarriers assigned to the low-dose group, titration included 1 mg/kg for the first two doses, followed by 3 mg/kg for the next four doses, and 6 mg/kg thereafter. For ApoE ϵ 4 noncarriers assigned to the high-dose group, titration included 1 mg/kg for the first two doses, 3 mg/kg for the next two doses, 6 mg/kg for the next two doses, and 10 mg/kg thereafter.

After completion of the placebo-controlled period, subjects were eligible to enter a dose-blind,

long-term extension period. Subjects who had been assigned to an aducanumab treatment group in the placebo-controlled period continued their original assigned treatment in the long-term extension period and subjects who had been assigned placebo in the placebo-controlled period were randomized to low-dose aducanumab or high-dose aducanumab treatment groups. The duration for the placebo-controlled period was 76 weeks and for the long-term extension period was up to 5 years.

Study 103 was a randomized, double-blinded, placebo-controlled, dose-ranging study where subjects with prodromal or mild Alzheimer's disease were assigned to placebo, fixed dosing of aducanumab of 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg, or titration of aducanumab from 1 mg/kg to 10 mg/kg. Subjects were dosed intravenously every four weeks. After completing the placebo-controlled period, subjects could opt to continue in a dose-blind long-term extension period where they were randomized to receive fixed doses of aducanumab (3 mg/kg, 6 mg/kg, or 10 mg/kg intravenously every four weeks) or titration doses of aducanumab (3 mg/kg to 6 mg/kg or 1 mg/kg to 10 mg/kg). The duration for the placebo-controlled period was 52 weeks and for the long-term extension period was up to 8 years.

Exposure in Studies 103, 301, and 302

The overall number of subjects who received at least one dose of aducanumab in Studies 103, 301, and 302 was 2,942.

90-Day Safety Update

At the time of the 90-Day Safety Update, 120 subjects had been exposed to aducanumab in the open-label Study 304. Most subjects had received either one or two infusions (96.7%). The titration protocol included two doses of aducanumab at 1 mg/kg, two doses at 3 mg/kg, two doses at 6 mg/kg, followed by a maintenance dose of 10 mg/kg.

8.2.2. Relevant Characteristics of the Safety Population

Overall, I note that the applicant's proposed population is patients with Alzheimer's; however, patients with moderate or severe dementia due to Alzheimer's disease were not eligible for enrollment in Studies 103, 301, or 302. Safety outcomes for treatment with aducanumab are not known in patients with moderate or severe dementia.

In Study 302, the aducanumab 10 mg/kg arm had similar baseline demographic characteristics compared to the placebo arm. Baseline demographic characteristics were similar among the aducanumab arms except for carrier status. Given that the study protocol identified the maximum target dose for a subject based on carrier status, the difference in carrier frequency among the aducanumab arms was expected. The below table shows demographics for Study 302 for the safety population.

Table 9. Baseline Demographics by Treatment Group in Study 302

Demographic Parameters	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Sex					
Female	187 (51)	82 (47)	284 (52)	553 (51)	290 (53)
Male	182 (49)	93 (53)	263 (48)	538 (49)	257 (47)
Age (years)					
Mean (SD)	70.6 (7.1)	70.4 (8.2)	70.6 (7.5)	70.6 (7.5)	70.8 (7.4)
Median	71	72	72	72	71
Min, Max	50, 85	50, 85	50, 85	50, 85	50, 85
Age Group (years)					
<=64	66 (18)	41 (23)	113 (21)	220 (20)	103 (19)
65-74	192 (52)	70 (40)	257 (47)	519 (48)	255 (47)
>=75	111 (30)	64 (37)	177 (32)	352 (32)	189 (35)
Race					
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Asian	24 (7)	15 (9)	42 (8)	81 (7)	47 (9)
Black or African American	5 (1)	1 (1)	4 (1)	10 (1)	1 (0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Not Reported	50 (14)	15 (9)	75 (14)	140 (13)	67 (12)
Other	0 (0)	1 (1)	3 (1)	4 (0)	1 (0)
Unknown	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)
White	290 (79)	143 (82)	422 (77)	855 (78)	430 (79)
Ethnicity					
Hispanic or Latino	14 (4)	8 (5)	23 (4)	45 (4)	22 (4)
Not Hispanic or Latino	315 (85)	156 (89)	461 (84)	932 (85)	469 (86)
Not reported	40 (11)	11 (6)	62 (11)	113 (10)	56 (10)
Unknown	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)
Region					
Asia	24 (7)	14 (8)	40 (7)	78 (7)	43 (8)
Europe/Canada/Australia	193 (52)	94 (54)	291 (53)	578 (53)	287 (52)
United States	152 (41)	67 (38)	216 (39)	435 (40)	217 (40)
Body Mass Index (kg/m ²)					
Mean (SD)	25.8 (4.5)	26.1 (4.8)	25.5 (4.6)	25.7 (4.6)	25.7 (4.6)
Median	25.2	25.6	24.7	25	25.1

Demographic Parameters	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Min, Max	16.7, 49.6	17, 47.3	15, 48.2	15, 49.6	16.3, 49.4
ApoE Carrier Status					
Carrier	363 (98)	0 (0)	365 (67)	728 (67)	367 (67)
Non-Carrier	3 (1)	175 (100)	181 (33)	359 (33)	178 (33)
Undetermined	3 (1)	0 (0)	1 (0)	4 (0)	2 (0)
ApoE Gene Allele					
e2/e2	0	0	0	0	1 (0)
e2/e3	0	11 (6)	15 (3)	26 (2)	15 (3)
e2/e4	6 (2)	0	14 (3)	20 (2)	13 (2)
e3/e3	3 (1)	164 (94)	166 (30)	333 (31)	162 (30)
e3/e4	260 (70)	0	274 (50)	534 (49)	262 (48)
e4/e4	97 (26)	0	77 (14)	174 (16)	92 (17)
Undetermined	3 (1)	0	1 (0)	4 (0)	2 (0)
Baseline Alzheimer's Disease Stage					
Mild Dementia due to AD	53 (14)	38 (22)	109 (20)	200 (18)	102 (19)
Mild Cognitive Impairment due to AD	316 (86)	137 (78)	438 (80)	891 (82)	445 (81)
Baseline Alzheimer's Disease Medication Use					
No	175 (47)	87 (50)	262 (48)	524 (48)	266 (49)
Yes	194 (53)	88 (50)	285 (52)	567 (52)	281 (51)
Acetylsalicylic Acid Used as Concomitant Medication					
Yes	131 (36)	63 (36)	178 (33)	372 (34)	164 (30)
Acetylsalicylic Acid containing Concomitant Medication					
Yes	139 (38)	65 (37)	195 (36)	399 (37)	172 (31)
Non-Aspirin Anticoagulant Concomitant Drug					
Yes	23 (6)	15 (9)	31 (6)	69 (6)	37 (7)

This table was created by the reviewer using ISS ADSLI, SAFFL=Y; POOLC=POOLA1; STUDYID=302; tabulated on POOLTR3 Reassigned. AD: Alzheimer's disease.

The 10 mg/kg and placebo treatment groups in the placebo-controlled periods of pooled Studies 301 and 302 had similar demographic characteristics as the 10 mg/kg and placebo treatment groups in the placebo-controlled period of Study 302. The following table shows demographics for pooled Studies 301 and 302 for the safety population.

Table 10. Baseline Demographics by Treatment Group in Pooled Studies 301 and 302

Demographic Parameters	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 (%)
Sex					
Female	395 (52)	159 (48)	577 (52)	1131 (51)	575 (53)
Male	365 (48)	174 (52)	528 (48)	1067 (49)	512 (47)
Age (years)					
Mean (SD)	70.4 (6.7)	70.7 (8.3)	70.3 (7.6)	70.4 (7.4)	70.3 (7.6)
Median	71	72	71	71	71
Min, Max	50, 85	50, 85	50, 85	50, 85	50, 85
Age Group (years)					
<=64	139 (18)	84 (25)	238 (22)	461 (21)	232 (21)
65-74	410 (54)	117 (35)	514 (47)	1041 (47)	498 (46)
>=75	211 (28)	132 (40)	353 (32)	696 (32)	357 (33)
Race					
American Indian or Alaska Native	0	0	0	0	1 (0)
Asian	63 (8)	31 (9)	107 (10)	201 (9)	102 (9)
Black or African American	6 (1)	1 (0)	6 (1)	13 (1)	6 (1)
Native Hawaiian or Other Pacific Islander	1 (0)	0	0	1 (0)	0
Not Reported	101 (13)	39 (12)	147 (13)	287 (13)	135 (12)
Other	2 (0)	3 (1)	6 (1)	11 (1)	4 (0)
Unknown	0	0	1 (0)	1 (0)	0
White	587 (77)	259 (78)	838 (76)	1684 (77)	839 (77)
Ethnicity					
Hispanic or Latino	19 (3)	14 (4)	36 (3)	69 (3)	35 (3)
Not Hispanic or Latino	673 (89)	291 (87)	963 (87)	1927 (88)	954 (88)
Not reported	68 (9)	28 (8)	105 (10)	201 (9)	98 (9)
Unknown	0	0	1 (0)	1 (0)	0
Region					
Asia	60 (8)	29 (9)	100 (9)	189 (9)	95 (9)
Europe/Canada/Australia	357 (47)	167 (50)	535 (48)	1059 (48)	527 (48)
United States	343 (45)	137 (41)	470 (43)	950 (43)	465 (43)
Body Mass Index (kg/m ²)					
Mean (SD)	25.6 (4.4)	25.7 (4.5)	25.4 (4.4)	25.5 (4.4)	25.5 (4.4)
Median	24.9	25.1	24.7	24.9	24.9
Min, Max	16.2, 49.6	17, 47.3	15, 48.2	15, 49.6	15, 49.4
ApoE Carrier Status					
Carrier	754 (99)	1 (0)	746 (68)	1501 (68)	739 (68)

Demographic Parameters	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 (%)
Non-Carrier	3 (0)	332 (100)	357 (32)	692 (31)	344 (32)
Undetermined	3 (0)	0	2 (0)	5 (0)	4 (0)
ApoE Gene Allele					
e2/e2	0	0	0	0	1 (0)
e2/e3	0	20 (6)	30 (3)	50 (2)	26 (2)
e2/e4	20 (3)	0 (0)	25 (2)	45 (2)	25 (2)
e3/e3	3 (0)	312 (94)	327 (30)	642 (29)	317 (29)
e3/e4	536 (71)	1 (0)	539 (49)	1076 (49)	519 (48)
e4/e4	198 (26)	0	182 (16)	380 (17)	195 (18)
Undetermined	3 (0)	0	2 (0)	5 (0)	4 (0)
Baseline Alzheimer's Disease Stage					
Mild Dementia due to AD	122 (16)	77 (23)	223 (20)	422 (19)	202 (19)
Mild Cognitive Impairment due to AD	638 (84)	256 (77)	882 (80)	1776 (81)	885 (81)
Baseline Alzheimer's Disease Medication Use					
No	347 (46)	145 (44)	506 (46)	998 (45)	510 (47)
Yes	413 (54)	188 (56)	599 (54)	1200 (55)	577 (53)
Acetylsalicylic Acid Used as Concomitant Medication					
Yes	279 (37)	129 (39)	368 (33)	776 (35)	350 (32)
Acetylsalicylic Acid containing Concomitant Medication					
Yes	292 (38)	131 (39)	392 (35)	815 (37)	367 (34)
Non-Aspirin Anticoagulant Concomitant Drug					
Yes	43 (6)	27 (8)	77 (7)	147 (7)	87 (8)

This table was created by the reviewer using ISS ADSLI, SAFFL=Y; POOLC=POOLA1; STUDYID=301 and 302; tabulated on POOLTR3 Reassigned. AD: Alzheimer's disease.

The mean age of subjects in pooled Studies 301 and 302 was 70 years. Seventy-nine percent of subjects were 65 years and over, and 32% were 75 years and older.

Subjects in pooled Studies 301 and 302 were also balanced between aducanumab versus placebo and across aducanumab doses for baseline MMSE, baseline measures of cognitive function, symptom duration, diagnosis duration, and number of years of education.

Reviewer comment: Patients with moderate or severe dementia due to Alzheimer's disease were not eligible for enrollment in Studies 103, 301, or 302. Given that patients with moderate and severe dementia were not included in the studies, the safety outcomes from these studies potentially underestimate the impact of adverse events in patients with moderate or severe dementia given the increased likelihood of occurrence of other comorbid conditions with

advanced dementia such as impaired memory, executive function decline, functional decline, problems of gait and movement, malnutrition, neuropsychiatric symptoms, and falls.¹

According to the Alzheimer's Association 2015 Alzheimer's Disease and Facts and Figures, approximately 4% of the population less than age 65 years has Alzheimer's disease, 15% of those 65 to 74 years, 43% of those ages 75 to 84 years, and 38% of those over age 85 years.² Approximately two-thirds of Americans with Alzheimer's are women. In the same report, the Alzheimer's Association notes that in terms of race, studies have shown that African Americans are twice as likely to have Alzheimer's dementia as compared to older whites, and Hispanics about 1.5 times as likely compared to older whites. Between 40 to 65% of people diagnosed with Alzheimer's disease have one or two copies of the ApoE ϵ 4 gene.

The population studied was younger than the average patient with Alzheimer's disease. This is likely due to subjects being eligible for enrollment if they had mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia. The study enrolled a lower percentage of female subjects than that seen in the U.S. general population. In terms of race and ethnicity, Black or African American and Hispanics were underrepresented in the study compared to the U.S. population. The percentage of subjects who were carriers for the ApoE ϵ 4 gene in the 10 mg group appeared representative of the U.S. population.

Taking into consideration the smaller number of subjects per treatment arm, I did not note any significant differences in the baseline demographic characteristics by age, sex, race, or ethnicity in Study 103 compared to Study 302 or pooled Studies 301 and 302.³ Study 103 differed from Study 302 and pooled Studies 301 and 302 in that all subjects were from the United States. Additionally, a higher proportion of subjects in Study 103 were more impaired at baseline from AD (higher proportion with mild dementia rather than mild cognitive impairment). In Study 103, the incidence of mild dementia in the aducanumab 10 mg/kg arm was 59% compared to 20% in Study 302 and pooled Studies 301 and 302.

8.2.3. Adequacy of the Safety Database

The exposure of the safety database overall appears adequate in terms of size and dosing. Studies 301 and 302 meet ICH E1A guidelines for exposure of at least 300 subjects at 6 months and 100 subjects at 12 months at the proposed doses. The clinical program met ICH E1A guidelines for having at least 1500 subjects exposed to aducanumab overall as the number of subjects exposed to at least one dose of aducanumab was 3,078. The database includes 1,165 subjects who received at least one 10 mg/kg-dose. The percentage of female subjects was

¹ Feldman H and Woodward M. The staging and assessment of moderate to severe Alzheimer's disease. AAN 2005 DOI: https://doi.org/10.1212/WNL.65.6_suppl_3.S10

² Alzheimer's Association. 2015 Alzheimer's disease facts and figures. *Alzheimers Dement* 2015 Mar;11(3):332-384. doi: 10.1016/j.jalz.2015.02.003.

³ Evaluated by the reviewer using Study 103 dataset ADSL; SAF01=Y; tabulated by TRT01P.

lower than the percentage of females expected to have Alzheimer's disease in the U.S. population. Subjects were younger compared to the general population of patients with Alzheimer's dementia in the U.S. population. Black or African American and Hispanics were underrepresented. The population in the 10 mg/kg treatment group appears representative of the U.S. population in terms of the frequency of ApoE ϵ 4 gene carrier status.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the datasets was evaluated by the Office of Computational Science Jumpstart team. Overall, the application was well-organized, and information was easy to find.

8.3.2. Categorization of Adverse Events

In Studies 301 and 302, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with the treatment. AEs were recorded regardless of whether they were assessed as related to the study drug. A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death; in view of the Investigator, placed the subject at immediate risk of death; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; resulted in a congenital anomaly/birth defect; medically important event that, in the opinion of the Investigator, may have jeopardized the subject or required intervention to prevent one of the other outcomes listed previously. A treatment emergent adverse event (TEAE) was defined as having an onset date on or after the start of study treatment, or as worsening after the start of study treatment.

In Studies 301 and 302, any AE experienced by the subject between time of first dose of study treatment and the subject's final clinic visit was to be recorded on the case report form, regardless of severity of the event or its relationship to study treatment.

Study 103 had the same definition for AEs and SAEs as Studies 301 and 302. AEs were recorded regardless of whether they were assessed as related to the study drug.

Adverse events were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 22.0 for Studies 103, 301, and 302.

I evaluated the applicant's translation of adverse events from verbatim terms to preferred terms for Studies 103, 301, and 302 and the translations appeared adequate.

8.3.3. Routine Clinical Tests

Vital signs

In the placebo-controlled period of Studies 301 and 302, vital signs were collected at the screening visit, Day 1, and every four weeks starting at Week 4 through Week 94 (or 18 weeks after final dose for subjects who discontinued treatment early). In the long-term extension period, vital signs were collected every four weeks, starting at Week 80 through Week 336, Weeks 338 and 354 (or 18 weeks after final dose for subjects who discontinued treatment early).

In the placebo-controlled period of Study 103, vital signs were collected at the screening visit, Day 1, Weeks 4, 8, 12, 16, 20, 22, 28, 32, 36, 40, 44, 48, 52, and the end of study visit (only if the patient did not enroll in the long-term extension period). In the long-term extension period, vital signs were collected every four weeks, starting at Week 56 through Week 502, and at the end of study visit (or 18 weeks after final dose for subjects who discontinued treatment early).

Laboratory Tests

In the placebo-controlled period of Studies 301 and 302, laboratory tests were collected at the screening visit, Day 1, Week 24, 48, 72, 78, 94 (or 18 weeks after final dose for subjects who discontinued treatment early). In the long-term extension period, laboratory tests were collected at Week 104, 128, 152, 176, 232, 284, 336, and 354 (or 18 weeks after final dose for subjects who discontinued treatment early).

In the placebo-controlled period of Study 103, laboratory tests were collected at the screening visit, Day 1, Week 4, 8, 12, 16, 20, 22, 28, 32, 36, 40, 44, 48, 52, and the end of study visit (or 18 weeks after final dose for subjects who discontinued treatment early). In the long-term extension period, laboratory tests were collected at Week 56, 60, 64, 68, 72, 76, 88, 100, 110, 112, 124, 136, 148, 160, 172, 184, 196, 208, 220, 222, 248, 278, 304, 334, 360, 390, 416, 446, 472, 502, 518 (or 18 weeks after final dose for subjects who discontinued treatment early).

Laboratory testing included hematology, clinical chemistry, and urine analysis. The applicant used the Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on June 14, 2010, to determine grade for laboratory tests.

I reviewed the applicant's criteria for potentially clinically significant laboratory values and the criteria appears acceptable. The following table of potentially clinically significant laboratory abnormalities was submitted by the applicant.

Figure 1. Applicant's Criteria to Determine Potentially Clinically Significant Laboratory Abnormalities.

Clinical Laboratory Outlier Criteria		
Parameter name	PCS Low	PCS High
White blood cells	$<3.0 \times 10^9/L$	$>16 \times 10^9/L$
Lymphocytes	$<0.8 \times 10^9/L$	$>12 \times 10^9/L$
Neutrophils	$<1.5 \times 10^9/L$	$>13.5 \times 10^9/L$
Monocytes	N/A	$>2.5 \times 10^9/L$
Eosinophils	N/A	$>1.6 \times 10^9/L$
Basophils	N/A	$>1.6 \times 10^9/L$
Red blood cells	$\leq 3.5 \times 10^{12}/L$	$\geq 6.4 \times 10^{12}/L$
Hemoglobin - Females	$\leq 95 \text{ g/L}$	$\geq 175 \text{ g/L}$
Hemoglobin - Males	$\leq 115 \text{ g/L}$	$\geq 190 \text{ g/L}$
Hematocrit - Females	$\leq 32\%$	$\geq 54\%$
Hematocrit - Males	$\leq 37\%$	$\geq 60\%$
Platelet count	$\leq 75 \times 10^9/L$	$\geq 700 \times 10^9/L$
<u>BLOOD CHEMISTRY</u>		
Alanine aminotransferase (ALT)	N/A	$>3 \times \text{ULN}$
Aspartate aminotransferase (AST)	N/A	$>3 \times \text{ULN}$
Alkaline phosphatase (ALP)	N/A	$>3 \times \text{ULN}$
Total bilirubin	N/A	$>1.5 \times \text{ULN}$
Blood urea nitrogen (BUN)	N/A	$\geq 10.7 \text{ mmol/L}$
Creatinine	N/A	$\geq 176.8 \text{ umol/L}$
Sodium	$\leq 126 \text{ mmol/L}$	$\geq 156 \text{ mmol/L}$
Potassium	$\leq 3 \text{ mmol/L}$	$\geq 6 \text{ mmol/L}$
Chloride	$\leq 90 \text{ mmol/L}$	$\geq 118 \text{ mmol/L}$
Bicarbonate	$\leq 16 \text{ mmol/L}$	$\geq 35 \text{ mmol/L}$
Glucose	$\leq 2.2 \text{ mmol/L}$	$\geq 9.7 \text{ mmol/L}$
Calcium	$\leq 2 \text{ mmol/L}$	$\geq 3 \text{ mmol/L}$
Phosphorus	$\leq 0.6 \text{ mmol/L}$	$\geq 1.7 \text{ mmol/L}$
Albumin	$\leq 25 \text{ g/L}$	$\geq 625 \text{ g/L}$
Total protein	$\leq 45 \text{ g/L}$	$\geq 100 \text{ g/L}$
<u>URINALYSIS</u>		
Glucose	N/A	$\geq ++++$
Ketones	N/A	$\geq ++++$
Protein	N/A	$\geq ++$
ULN = upper limit of normal		

The above figure was submitted by the applicant in the Statistical Analysis Plan, Version 1, Table 8 of Appendix 16.1.9).

ECGs

In the placebo-controlled period of Studies 301 and 302, a 12-lead ECG was collected at the

screening visit, at Weeks 28, 48, 72, 78, and 98 (or 18 weeks after final dose for subjects who discontinued treatment). In the long-term extension period, a 12-lead ECG was collected at Weeks 104, 128, 152, 176, and 354 (or 18 weeks after final dose for subjects who discontinued treatment early).

In the placebo-controlled period of Study 103, a 12-lead ECG was collected at the screening visit, study Day 1, Weeks 4, 8, 12, 22, 52, and the end of study visit (only if the patient did not enroll in the long-term extension period). In the long-term extension period, a 12-lead ECG was collected at Weeks 56, 60, 64, 68, 88, 110, and every 24 weeks starting at Week 112 through Week 220, then Weeks 222, 248, 278, 304, 334, 360, 390, 416, 446, 472, 502, and at the end of study visit (or 18 weeks after the final dose for subjects who discontinued treatment early).

In a response dated July 24, 2020, to an information request dated July 20, 2020, the applicant noted that quantitative ECG parameters were not recorded in the Phase 3 Studies. The applicant noted quantitative ECG analyses were performed in the Phase 1 bioavailability Study 102. I reviewed qualitative ECG analyses from the Phase 3 studies and quantitative ECG analyses from Study 102 for this review.

8.4. Safety Results

8.4.1. Deaths

In the placebo-controlled periods of Studies 301 and 302, there was not an excess of deaths in the aducanumab-treated group compared to placebo. There were too few deaths during the controlled periods to support conclusions about relative mortality risks by treatment dose. Most subjects had underlying risk factors for events with fatal outcome. I did not identify any deaths that were attributable to treatment with aducanumab.

A total of 31 deaths occurred across the clinical program of which 25 occurred in aducanumab-treated subjects ($25/3,078 = 0.8\%$). All of the deaths in aducanumab-treated subjects occurred in Studies 103, 301, or 302. No deaths occurred in Studies 101, 102, 104, or 205.

Deaths in the Placebo-Controlled Periods of Studies 103, 301, and 302

The incidence of deaths in the controlled portions of Studies 103, 301, and 302 is shown in the table below.

Table 11. Incidence of Deaths in the Placebo-Controlled Periods of Studies 103, 301, and 302.

Study	Aducanumab (%)	Placebo (%)
103	1/148 (0.7)	1/48 (2.1)

Study	Aducanumab (%)	Placebo (%)
301	5/1107 (0.5)	0/540 (0)
302	6/1091 (0.5)	5/547 (0.9)
Total	12/2346 (0.5)	6/1135 (0.5)

Analysis 2 of Study 302, presented at Peripheral and Central Nervous System Drugs Advisory Committee meeting on November 6, 2020, resulted in an increase in the incidence of death in the aducanumab arm from 0.5% to 0.6% (6/1090) with no change in the incidence on placebo (0.9% (5/548)).

In the placebo-controlled period of pooled Studies 301 and 302, the incidence of death in aducanumab-treated subjects was not in excess of the incidence on placebo (0.5% (11/2198) versus 0.5% (5/1087), respectively).

In the aducanumab group of the placebo-controlled periods of Studies 301 and 302, the preferred terms of TEAEs with fatal outcomes were: cardiac arrest (n=3), cerebellar infarction (n=2), cerebrovascular accident, completed suicide, dystonia, lacunar infarction, lung neoplasm malignant, myocardial infarction; pleural mesothelioma; pulmonary embolism, renal failure (each reported in 1 subject). In the placebo group, the preferred terms of TEAEs with fatal outcome were congestive cardiac failure (n=2), death, myocardial infarction, and urosepsis (each reported in 1 subject).

Adverse events in this review were evaluated by individual preferred term and by groupings of closely related preferred terms called MedDRA query groups (MQG). The reader is referred to the [Appendix](#) for a list of MQG in this review and the preferred terms that make up the groupings.

In an analysis of deaths using MQGs of closely related preferred terms, I note a slightly higher incidence of the grouping Acute Coronary Syndrome FDA B in the aducanumab 10 mg/kg arm compared to placebo in pooled Studies 301 and 302 (0.3% versus 0.1%, respectively).

In the placebo-controlled period of Study 103, the preferred term for the event with fatal outcome occurring in the aducanumab-treated subject was cerebrovascular accident. The preferred term for the AE with fatal outcome in the placebo-treated subject was cardiac arrest.

Deaths in Long-Term Extension Periods of Studies 103, 301, and 302

In the long-term extension periods of Studies 301 and 302, there were an additional eight deaths (five in Study 301 and three in Study 302). The incidence of death among the all-aducanumab-treated group for the combined placebo-controlled and long-term extension periods of Studies 301 and 302 for the < 10 mg/kg and 10 mg/kg group was 0.6% (8/1371) and

0.8% (11/1386). The preferred terms for AEs with fatal outcome for the aducanumab-treated group for the long-term extension period were dementia Alzheimer's type (n=3), pneumonia, myocardial infarction, respiratory failure, pneumonia aspiration/pulmonary sepsis, and cholangiocarcinoma.

In the long-term extension period of Study 103, there were five additional deaths. The incidence of death among the all-aducanumab-treated group for the combined placebo-controlled period and long-term extension periods of Study 103 was 3.3% (4/122) for the <10 mg arm and 3.2% (2/63) for the 10 mg/kg arm. The preferred terms for AEs with fatal outcome were dementia Alzheimer's type (n=2), cerebral hemorrhage, myocardial infarction, and coronary artery arteriosclerosis.

The incidence of death among the all-aducanumab-assigned group for the combined placebo-controlled and long-term extension periods of the pooled Studies 103, 301, and 302 was 0.8% (12/1493) for the < 10 mg/kg group and 0.9% (13/1449) for the 10 mg/kg group.

Reviewer comment: The incidence of death by person-years of exposure in aducanumab-assigned subjects in Studies 103, 301, and 302 was 4.7/1000 person-years (25 deaths/5309 person-years of exposure, where exposure in person-years by study in Pool B is noted by the applicant on page 45 of the ISS). The incidence of death from Alzheimer's disease in the U.S. in a community-based cohort of individuals with Alzheimer's disease has been reported to be 133.8/1,000 person-years.⁴ The incidence of death in aducanumab-assigned subjects in the pooled Studies 103, 301, and 302 does not exceed the incidence of death reported in a community-based population with Alzheimer's disease.

Death Narratives

I note four cases of death where ARIA preceded the deaths by less than four weeks (cerebellar infarction/lacunar infarction: (b) (6), cardiac arrest/renal failure: (b) (6), cardiac arrest: (b) (6), dementia Alzheimer's type: (b) (6). The reader is referred to the clinical review on ARIA-related events by Dr. Brian Trummer for a review of these narratives.

Another case of death involved cerebral hemorrhage and is also reviewed by Dr. Trummer in his clinical review (b) (6).

In the remaining 20 deaths occurring in aducanumab-treated subjects, I could not rule out a role for aducanumab in one death and summarize the death here.

Completed suicide, Study 301, (b) (6)

⁴ Ganguli M, Dodge H, Shen C, et al. Alzheimer's Disease and Mortality: A 15-Year Epidemiological Study. Arch Neurol 2005; 62(5): 779-784. doi: 10.1001/archneur.62.5.779.

75-year-old female with mild cognitive impairment due to Alzheimer's disease, back pain, dyslipidemia, insomnia, chronic gastritis, and spinal osteoarthritis who completed suicide by hanging on Day 430. The subject had received 16 doses of aducanumab prior to the event (two doses of 1 mg/kg, four doses of 3 mg/kg, two doses of 6 mg/kg, and eight doses of 10 mg/kg). The most recent dose (10 mg/kg) occurred 8 days prior to the event. The patient had no history of psychiatric illness or history of drug or alcohol abuse. No autopsy was performed. Concomitant medications included brotizolam, loxoprofen sodium dihydrate, and rosuvastatin.

Reviewer comment: A role for aducanumab in the event of suicide could not be ruled out given that the subject had no underlying risk factors such as previous history of psychiatric illnesses that could have contributed to the event of suicide.

I note one subject who did not have risk factors for the AE with fatal outcome of malignant lung neoplasm and summarize the narrative here.

Lung Neoplasm Malignant, Study 301, (b) (6)
59-year-old male with mild Alzheimer's disease dementia, history of basal cell carcinoma who was diagnosed with malignant lung neoplasm on Day 583 after hospitalization for weight loss and cough. The subject's most recent dose had occurred 302 days prior to the event (6 mg/kg) and the subject had received a total of 8 doses in the study. A history of tobacco use was not reported. A CT scan of the chest showed a primary bronchial neoplasm in the right lower lobe, with nodal involvement below the diaphragm. A head CT showed evidence of small vessel disease. The patient was discharged to home on palliative care on Study Day 590 and died of malignant lung neoplasm on Day 618. No autopsy was performed.

Reviewer comment: I did not identify a role for aducanumab in the event of malignant lung neoplasm; however, a role for aducanumab cannot be ruled out. The most recent dose occurred 302 days prior to the event.

The following table lists AEs with fatal outcome across the clinical program as well as risk factors for the fatal events.

Table 12. Deaths in Aducanumab-Treated Subjects Across the Clinical Program

Subject ID	Age, Sex	Dose ^a (mg/kg)	AE listed as cause of death	Risk factors
Study 302				
(b) (6)	80F	10	Cerebellar infarction Lacunar infarction	Dyslipidemia

Subject ID	Age, Sex	Dose ^a (mg/kg)	AE listed as cause of death	Risk factors
(b) (6)	74F	3	Pulmonary embolism	Hypercholesterolemia, hypertension, systemic lupus erythematosus, metastatic pancreatic carcinoma
	70M	6	Pleural mesothelioma	Age, gender
	73M	10	Cardiac arrest, renal failure	Arteriosclerosis, hyperlipidemia, type 2 diabetes.
	79M	10	Cardiac arrest	Hypercholesterolemia, hypertension, former smoker
	78M	1	Myocardial infarction	Coronary artery disease, hypercholesterolemia, sleep apnea
	81F	3	Dementia Alzheimer's type	Alzheimer's disease
	51M	6	Pulmonary aspiration Pulmonary sepsis	Alzheimer's disease
	75M	6	Cholangiocarcinoma	Age
	79M	3	Cerebrovascular accident	Hypertension, migraine with aura
	78M	3	Cardiac arrest	Hyperlipidemia, hypertension, coronary artery disease
	78M	3	Dystonia	Dementia with Lewy bodies, olanzapine use
	75F	10	Completed suicide	No risk factors
	59M	6	Lung neoplasm malignant	No risk factors
	81M	10	Dementia Alzheimer's type	Alzheimer's disease

Subject ID	Age, Sex	Dose ^a (mg/kg)	AE listed as cause of death	Risk factors
(b) (6)	81M	10	Pneumonia	Chronic bronchitis, dysphagia, lung adenocarcinoma, influenza
	72F	6	Myocardial infarction	Hypertension, cardiovascular disorder
	69M	6	Respiratory failure	Aspiration pneumonia, advanced dementia, Alzheimer's disease
	78M	6	Dementia Alzheimer's type	Alzheimer's disease
Study 103				
(b) (6)	76F	10	Cerebrovascular accident	Hypertension, hyperlipidemia, tobacco use
	79F	6	Dementia Alzheimer's type	Alzheimer's disease
	60F	3	Dementia Alzheimer's type	Alzheimer's disease
	74M	6	Myocardial infarction	Coronary artery disease, hyperlipidemia
	87F	10	Arteriosclerosis coronary artery	Hypertension, coronary artery disease, hypercholesterolemia
	84M	3	Cerebral hemorrhage	Concomitant medication use with acetylsalicylic acid, prior history of lacunar infarct

^aMost recent dose. M: male. F: female.

Deaths Occurring in Subjects After Study Withdrawal

The applicant notes an additional two deaths that occurred in aducanumab-treated subjects after withdrawal from Studies 301 and 302. I did not identify a role for aducanumab in the fatal events due to timing of the event or events preceding the deaths. One subject was diagnosed with stage IV breast cancer on Day 76 of the study (b) (6). Another subject had cardiopulmonary arrest that was preceded by the events of polycythemia vera, diagnosis of small cell lung cancer, subdural hematoma, and hyponatremia (b) (6).

90-Day Safety Update

No deaths were reported through the 90-Day Safety Update for Study 304.

8.4.2. Serious Adverse Events

The data sources I used for this summary of SAEs included the narrative summaries and case report forms submitted by the applicant.

The incidence of SAEs at all doses of aducanumab in the pooled Studies 301 and 302 is comparable to placebo. The most common SAEs were related to ARIA-E and superficial siderosis of the central nervous system in pooled Studies 301 and 302. Results from analysis of Study 302 alone are comparable to the findings of Studies 301 and 302 combined (the applicant's Pool A1). FDA analysis resulted in small differences in event numbers compared to the findings reported by the applicant. For example, FDA analysis shows SAEs of ARIA-E in 1.4% of aducanumab 10 mg/kg and 0.1% of placebo subjects in the placebo-controlled periods of Studies 301 and 302 combined whereas the applicant reported ARIA-E in 1.3% of aducanumab 10 mg/kg subjects and <0.1% of placebo subjects in Pool A1. The differences result from FDA reassignment to the 10 mg/kg group of 72 subjects that the applicant evaluated in the 6 mg/kg assigned treatment group for safety despite a protocol change but included in the 10 mg/kg treatment group for evaluation of efficacy as previously noted. FDA reassignment was performed to be consistent with the efficacy analysis. These differences do not lead to a difference in the conclusions. The combined placebo-controlled and long-term extension periods of pooled Studies 103, 301, and 302 showed infection, ARIA-E, arrhythmia, fall, and malignancy to be the most frequently occurring SAEs in the aducanumab 10 mg/kg arm.

Placebo-Controlled Period

In the placebo-controlled period of Study 302, there was not an excess of a subject experiencing at least one SAE in aducanumab-assigned groups compared to placebo, with approximately 13% in the aducanumab 10 mg/kg group and 15% in the placebo group experiencing at least one SAE. Similar findings were observed in Studies 301 and 302 combined. In the placebo-controlled period Study 103, the 10 mg/kg had a slightly higher incidence compared to placebo. The results are shown in the tables below.

Table 13. Incidence of A Subject Experiencing at Least One SAE in the Placebo-Controlled Period of Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
52 (14.1)	20 (11.4)	73 (13.3)	145 (13.3)	81 (14.8)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; STUDYID: 302; AESER: Y, TRTEMFL: Y; Group by USUBJID, POOLTR3 Reassigned.

Table 14. Incidence of A Subject Experiencing at Least One SAE in the Placebo-Controlled Periods of Pooled Studies 301 and 302.

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 (%)
105 (13.8)	43 (12.9)	152 (13.8)	300 (13.6)	151 (13.9)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; AESER: Y, TRTEMFL: Y; Group by USUBJID, POOLTR3 Reassigned.

Table 15. Incidence of A Subject Experiencing at Least One SAE in the Placebo-Controlled Period of Study 103.

ADU 1 mg/kg N=31 n (%)	ADU 3 mg/kg N=32 n (%)	ADU 6 mg/kg N=30 n (%)	ADU 10 mg/kg N=32 n (%)	ADU titration N=23 n (%)	ALL ADU N=148 n (%)	Placebo N=48 n (%)
4 (12.9)	4 (12.5)	4 (13.3)	12 (37.5)	4 (17.4)	28 (18.9)	16 (33.3)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; APHASE: Placebo-controlled; AESER= Y; Group by USUBJID, TRT01P.

In the placebo-controlled period of Study 302, the most frequently reported events included ARIA-E, hemorrhage, and malignancy. None of the SAEs in the 10 mg/kg arm had an incidence greater than 1.3% above placebo.

I note that the incidence of a subject experiencing an SAE related to intracranial hemorrhage in Study 302 was low, occurring in 0.2% of the aducanumab 10 mg/kg arm compared to no subjects on placebo. The reader is referred to the narratives section of the SAEs section for a review of narratives related to this topic and to the Intracranial Hemorrhage section of this review for a review of the incidence of AEs related to this topic.

Four subjects had SAEs of confusion, delirium, altered mental status, or disorientation in the placebo-controlled period of Study 302. Three of the four subjects had these SAEs within 40 days after ARIA events (b) (6). Further information related to these subjects is noted in the [Confusional State/Mental Status Changes/Delirium](#) narratives section of the Serious Adverse Events section of this review.

The following table lists SAEs in Study 302 occurring in at least 2 more subjects in the aducanumab 10 mg/kg arm compared to placebo.

Table 16. Serious Adverse Events Occurring in at Least 2 More Subjects in the Aducanumab 10 mg/kg Arm Compared to Placebo in Study 302

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	5 (1.4)	0	8 (1.5)	13 (1.2)	1 (0.2)
Hemorrhage FDA N MQG	2 (0.5)	3 (1.7)	6 (1.1)	11 (1)	3 (0.5)
Malignancy FDA B MQG	9 (2.4)	5 (2.9)	9 (1.6)	23 (2.1)	6 (1.1)
Inguinal Hernia	2 (0.5)	0	3 (0.5)	5 (0.5)	0
Superficial Siderosis Of Central Nervous System	1 (0.3)	0	3 (0.5)	4 (0.4)	0
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	4 (1.1)	0	2 (0.4)	6 (0.5)	0
Cardiac Arrest	0	0	2 (0.4)	2 (0.2)	0
Sepsis MQG	0	0	2 (0.4)	2 (0.2)	0
Cellulitis, Erysipelas MQG	2 (0.5)	0	2 (0.4)	4 (0.4)	0
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	2 (0.5)	0	2 (0.4)	4 (0.4)	0
Elevated Blood Urea Nitrogen or Creatinine, Anuria, Acute Renal Failure, Chronic Renal Failure, Oliguria MQG	0	0	2 (0.4)	2 (0.2)	0
Pancreatitis FDA N MQG	1 (0.3)	0	3 (0.5)	4 (0.4)	1 (0.2)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; AESER: Y, TRTEMFL = Y; StudyID: 302; Group by USUBJID, AEDECOD; POOLTR3 Reassigned A1. MQG: MedDRA query group.

Analysis 2 of the aducanumab 10 mg/kg and placebo arms of Study 302, presented at the Peripheral and Central Nervous System Drugs Advisory Committee meeting on November 6, 2020, resulted in no change in the incidence of subjects experiencing any SAE or the most common SAEs presented (ARIA-E, Hemorrhage FDA N MQG, Malignancy FDA B MQG, inguinal hernia, and superficial siderosis of the central nervous system).

The placebo-controlled periods of pooled Studies 301 and 302 were similar to Study 302 alone in that ARIA-E was the most frequently reported event. None of the SAEs in the 10 mg/kg arm had an incidence greater than 1.3% above placebo. A similar incidence was seen in the

aducanumab 10 mg/kg arm in the pooled Studies 301 and 302 as compared to Study 302 alone for ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis.

The applicant had similar finding of most frequent SAEs in their analysis of pooled Studies 301 and 302 (Pool A1: ARIA-E, superficial siderosis, inguinal hernia, and ARIA-microhemorrhages and hemosiderin deposits). The incidence of those SAEs in the aducanumab 10 mg/kg arm was similar between the applicant and FDA analyses (difference no greater than 0.1%). The incidence of ARIA-E in the applicant's Pool A1 analysis was 1.3% in the aducanumab 10 mg/kg arm compared to <0.1% on placebo.

The following table lists SAEs in pooled Studies 301 and 302 occurring in at least 2 more subjects in the aducanumab 10 mg/kg arm compared to placebo.

Table 17. Serious Adverse Events Occurring in at Least 2 More Subjects in the Aducanumab 10 mg/kg Arm Compared to Placebo in Pooled 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 (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	6 (0.8)	1 (0.3)	15 (1.4)	22 (1)	1 (0.1)
Superficial Siderosis Of Central Nervous System	1 (0.1)	0	5 (0.5)	6 (0.3)	0
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	4 (0.5)	0	4 (0.4)	8 (0.4)	0
Cardiac Arrest	1 (0.1)	0	4 (0.4)	5 (0.2)	0
Inguinal Hernia	2 (0.3)	0	4 (0.4)	6 (0.3)	0
Pre-Syncope Or Syncope MQG	6 (0.8)	2 (0.6)	10 (0.9)	18 (0.8)	6 (0.6)
Hemorrhage FDA N MQG	2 (0.3)	4 (1.2)	11 (1)	17 (0.8)	8 (0.7)
Sepsis	0	0	3 (0.3)	3 (0.1)	0
Pulmonary Embolism MQG	1 (0.1)	0	7 (0.6)	8 (0.4)	3 (0.3)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	2 (0.3)	1 (0.3)	3 (0.3)	6 (0.3)	0
Basal Cell Carcinoma	1 (0.1)	1 (0.3)	2 (0.2)	4 (0.2)	0
Deep Vein Thrombosis	2 (0.3)	0	4 (0.4)	6 (0.3)	2 (0.2)
Diverticulitis	0	0	2 (0.2)	2 (0.1)	0
Gastroenteritis	0	0	2 (0.2)	2 (0.1)	0

Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Difficile MQG	2 (0.3)	0	6 (0.5)	8 (0.4)	3 (0.3)
Bronchospasm FDA N MQG	0	0	2 (0.2)	2 (0.1)	0
Respiratory Depression FDA B MQG	0	1 (0.3)	2 (0.2)	3 (0.1)	0
Conduction Disturbance MQG	1 (0.1)	0	3 (0.3)	4 (0.2)	1 (0.1)
Pancreatitis FDA N MQG	3 (0.4)	0	3 (0.3)	6 (0.3)	1 (0.1)

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

ARIA-E and superficial siderosis were the two most frequent SAEs reported in Study 103. These events occurred at a higher incidence in Study 103 compared to Study 302. ARIA-E was reported at an incidence of 15.6% in Study 103 compared to 1.5% in Study 302 in the aducanumab 10 mg/kg arm. Superficial siderosis was reported at an incidence of at 9.4% in Study 103 compared to 0.5% in Study 302 in the aducanumab 10 mg/kg arm. The higher incidence of these SAEs may be due in part to the fixed dose design of Study 103 as compared to the titrated dose design that occurred in Study 302. The higher incidence may also be due smaller treatment arms in Study 103 compared to 302.

Other SAEs occurring with at least a 3% or higher incidence in the 10 mg/kg group compared to the placebo group were arthritis, ARIA-microhemorrhages and hemosiderin deposits, and encephalopathy.

I note two subjects with SAEs of falls; however, I did not identify a role for aducanumab in the events due to underlying risk factors. One subject fell during physical therapy after undergoing an elective hip replacement (b) (6). This subject later experienced a cerebrovascular accident, which led to death and is described in the Deaths section of this review. A second subject developed a hip fracture and had osteoporosis as a risk factor for the fracture (b) (6).

The following table lists SAEs in Study 103 occurring with higher incidence in the aducanumab 10 mg/kg arm compared to placebo.

Table 18. Serious Adverse Events Occurring with Higher Incidence in the 10 mg/kg Group Compared to Placebo in Placebo-Controlled Period of Study 103

Adverse Event	ADU 1 mg/kg N=31 n (%)	ADU 3 mg/kg N=32 n (%)	ADU 6 mg/kg N=30 n (%)	ADU 10 mg/kg N=32 n (%)	ADU titration N=23 n (%)	ALL ADU N=148 n (%)	Placebo N=48 n (%)

Amyloid Related Imaging Abnormality-Edema/Effusion	1 (3.2)	1 (3.1)	4 (13.3)	5 (15.6)	1 (4.3)	12 (8.1)	0
Superficial Siderosis Of Central Nervous System	1 (3.2)	0	2 (6.7)	3 (9.4)	0	6 (4.1)	0
Arthritis FDA B MQG	0	0	0	2 (6.3)	0	2 (1.4)	1 (2.1)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	0	0	2 (6.7)	1 (3.1)	0	3 (2)	0
Encephalitis, Encephalopathy MQG	0	0	0	1 (3.1)	0	1 (0.7)	0
Fall	1 (3.2)	0	0	1 (3.1)	0	2 (1.4)	1 (2.1)
Diverticular Disease MQG	0	1 (3.1)	0	1 (3.1)	0	2 (1.4)	1 (2.1)
Solid Neoplasia, All (Benign, Malignant, Unknown) MQG	1 (3.2)	0	0	1 (3.1)	0	2 (1.4)	1 (2.1)
Stroke, Transient Ischemic Accident MQG	1 (3.2)	0	0	1 (3.1)	0	2 (1.4)	1 (2.1)
Fracture MQG	1 (3.2)	0	0	1 (3.1)	0	2 (1.4)	1 (2.1)
Arrhythmia FDA B MQG	0	0	0	1 (3.1)	1 (4.3)	2 (1.4)	1 (2.1)
Syncope	0	0	0	1 (3.1)	0	1 (0.7)	1 (2.1)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; APHASE: Placebo-controlled; AESER= Y; Group by USUBJID, AEDECOD, TRT01P; tabulated on TRT01P. MQG: MedDRA query group.

Combined Placebo-Controlled and Long-Term Extension Periods

In the combined placebo-controlled and long-term extension periods of Study 302, the incidence of a subject experiencing at least one SAE in the 10 mg/kg group was similar to the < 10 mg/kg group (15.2% versus 15.9%, respectively) and slightly higher when compared to the placebo-controlled period alone (15.2% versus 13.3%, respectively). The higher incidence in the combined placebo-controlled and long-term extension periods compared to the placebo-controlled period alone is likely due to the longer study follow up.

In the combined placebo-controlled and long-term extension period of Study 302, the SAEs with the highest incidence in the aducanumab 10 mg/kg arm included infection, fall, malignancy, and ARIA-E, but none had an incidence of more than 2%.

ARIA-E occurred with similar incidence in the aducanumab 10 mg/kg arm in the combined placebo-controlled and long-term extension period of Study 302 as compared to the placebo-controlled period alone (1.3% versus 1.5%, respectively).

Unlike the combined placebo-controlled and long-term extension periods of Study 302, the SAEs of infection and fall were not among the most common SAEs in the placebo-controlled period alone. This was due to lower incidences in the aducanumab 10 mg/kg arm compared to placebo in the placebo-controlled period of Study 302. Infection occurred with incidence of 1.5% in the aducanumab 10 mg/kg arm compared to 1.6% on placebo. Fall occurred with incidence of 0.7% in the aducanumab 10 mg/kg arm compared to 2.2% on placebo.

Overall, I note that the incidences of infection and malignancy SAEs in the aducanumab 10 mg/kg arm were similar between the combined placebo-controlled and long-term extension periods of Study 302 compared to the placebo-controlled period alone (infection 1.9% versus 1.5%; malignancy 1.5% versus 1.6%, respectively).

Fall occurred at higher incidence in the combined placebo-controlled and long-term extension periods of Study 302 compared to the placebo-controlled period of Study 302 alone (1.6% versus 0.7%, respectively). The higher incidence of fall in the combined placebo-controlled and long-term extension periods of Study 302 may be due in part to the longer study follow up.

The following table lists SAEs in the combined placebo-controlled and long-term extension periods of Study 302 with incidence of at least 1% in the aducanumab 10 mg/kg arm.

Table 19. Serious Adverse Events Occurring in at Least 1% of the Aducanumab 10mg/kg Group in the Combined Placebo-Controlled and Long-Term Extension Periods of Study 302

Adverse Event	ADU < 10 mg/kg N=674 n (%)	ADU 10 mg/kg N=679 n (%)
Infection, All MQG	13 (1.9)	13 (1.9)
Fall	12 (1.8)	11 (1.6)
Malignancy FDA B MQG	20 (3)	10 (1.5)
Amyloid Related Imaging Abnormality-Edema/Effusion	5 (0.7)	9 (1.3)
Hemorrhage FDA N MQG	7 (1)	9 (1.3)
Fracture MQG	9 (1.3)	9 (1.3)
Arrhythmia FDA B MQG	6 (0.9)	8 (1.2)

Acute Coronary Syndrome FDA B MQG	3 (0.4)	7 (1)
Pre-Syncope Or Syncope MQG	4 (0.6)	7 (1)
Stroke, Transient Ischemic Attack MQG	7 (1)	7 (1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; AESER= Y; StudyID: 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

The combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302 had similar findings of the most frequently reported SAEs as compared to the combined placebo-controlled and long-term extension periods of Study 302 alone. Infection, ARIA-E, and malignancy were among the most frequently reported SAEs, which was similar to the combined placebo-controlled and long-term extension periods of Study 302 alone. The following table lists SAEs in the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302 with incidence of at least 1% in the aducanumab 10 mg/kg arm.

Table 20. Serious Adverse Events Occurring in at Least 1% in the Aducanumab 10 mg/kg Group in the Combined Placebo-Controlled and Long-Term Extension Periods of Pooled Studies 301 and 302

Adverse Event	ADU < 10 mg/kg N=1371 n (%)	ADU 10 mg/kg N=1386 n (%)
Total with at least one SAE	229 (16.7)	219 (15.8)
Infection, All MQG	30 (2.2)	33 (2.4)
Arrhythmia FDA B MQG	23 (1.7)	20 (1.4)
Amyloid Related Imaging Abnormality-Edema/Effusion	9 (0.7)	18 (1.3)
Malignancy FDA B MQG	32 (2.3)	18 (1.3)
Fall	34 (2.5)	17 (1.2)
Fracture MQG	27 (2)	17 (1.2)
Hemorrhage FDA N MQG	12 (0.9)	15 (1.1)
Pre-Syncope Or Syncope MQG	12 (0.9)	14 (1)
Acute Coronary Syndrome FDA B MQG	9 (0.7)	14 (1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; AESER= Y; StudyID:301 and 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

The combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 had a slightly higher incidence of a subject experiencing at least one SAE in the aducanumab 10 mg/kg arm as compared to Study 302 alone (17% versus 13.3%, respectively). This may be in part due to the longer study follow up in the long-term extension period. The combined placebo-controlled and long-term extension period of Studies 103, 301, and 302 had a similar incidence of a subject experiencing at least one SAE in the 10 mg/kg arm as compared to the <

10 mg/kg arm (17% versus 19.1%, respectively).

The combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 had similar findings of the most frequently reported SAEs as compared to the combined placebo-controlled and long-term extension periods of Study 302 alone. Infection, ARIA-E, and fall were among the most frequently reported SAEs, which was similar to the combined placebo-controlled and long-term extension periods of Study 302 alone. The difference in incidences for the SAEs of infection, ARIA-E, and fall in the aducanumab 10 mg/kg arm in the combined Studies 103, 301, and 302 compared to Study 302 alone was no greater than 1.1%.

The following table lists SAEs in the combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 with incidence of at least 1% in the aducanumab 10 mg/kg arm.

Table 21. Serious Adverse Events Occurring in at Least 1% in the Aducanumab 10mg/kg Group by Preferred Term in the Combined Placebo-Controlled and Long-Term Extension Periods of Studies 103, 301, and 302

Adverse Event	ADU < 10 mg/kg N=1493 n (%)	ADU 10 mg/kg N=1449 n (%)
Infection, All MQG	44 (2.9)	37 (2.6)
Amyloid Related Imaging Abnormality-Edema/Effusion	21 (1.4)	25 (1.7)
Arrhythmia FDA B MQG	33 (2.2)	24 (1.7)
Fall	39 (2.6)	21 (1.4)
Malignancy FDA B MQG	33 (2.2)	21 (1.4)
Fracture MQG	29 (1.9)	21 (1.4)
Hemorrhage FDA N MQG	20 (1.3)	16 (1.1)
Acute Coronary Syndrome FDA B MQG	11 (0.7)	16 (1.1)
Pre-Syncope Or Syncope MQG	21 (1.4)	15 (1)
Dyspepsia FDA B MQG	8 (0.5)	14 (1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; AESER= Y; StudyID: 103, 301, and 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

Analyses of SAEs by Maximum Dose Received

In the placebo-controlled period of Study 302, the most frequently reported SAEs in the aducanumab 10 mg/kg arm by maximum dose received were inguinal hernia (incidence in the aducanumab 10 mg/kg arm of 0.7% vs 0 on placebo) and syncope (incidence in the aducanumab 10 mg/kg arm of 0.9% vs 0.5% on placebo). I note that ARIA-E had a higher incidence in the 3 mg/kg maximum dose received (2.2%) compared to the 10 mg/kg maximum

dose received (0.4%); however, this could be in part due to study design as ARIA-E as subjects could discontinue treatment after developing ARIA.

In the placebo-controlled periods of Studies 301 and 302, the most frequently reported SAEs in the aducanumab 10 mg/kg arm by maximum dose received were similar to Study 302 alone (inguinal hernia, ARIA-E, syncope, and cardiac arrest).

Approach to Review of Narratives

I reviewed the narratives of SAEs related to events of special interest across the clinical program, SAEs occurring in subjects with at least a three-fold increase above placebo across the clinical program, most common SAEs reported in the placebo-controlled period of Study 302 across Studies 103, 301, and 302, and narratives of potentially medically significant events across the clinical program.

For narratives of events of special interest, I note the following topics: ARIA-E; ARIA-microhemorrhages and hemosiderin deposits; superficial siderosis of the central nervous system; intracranial hemorrhage, immunogenicity; hypersensitivity; injuries and accidents; syncope; encephalopathy; psychosis, delusions, hallucinations; and pulmonary embolism. For narratives related to ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system, the reader is referred to the clinical review by Dr. Brian Trummer. For narratives of immunogenicity, hypersensitivity, and injuries and accidents, the reader is referred to their subsequent sections in this review.

For narratives related to most common SAEs occurring in the placebo-controlled period of Study 302, I identified the following preferred terms or MQGs that had an incidence of 0.3% or greater in the aducanumab 10 mg/kg arm compared to placebo: Hemorrhage FDA N MQG; Malignancy FDA B MQG; Hernia MQG; Cellulitis, Erysipelas MQG; Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG; Cardiac Arrest, Elevated Blood Urea Nitrogen or Creatinine, Anuria, Acute Renal Failure, Chronic Renal Failure, Oliguria MQG; and Sepsis MQG.

Overall, a review of narratives of SAEs showed that SAEs of intracranial hemorrhage were frequently potentially related to ARIA. I note one SAE of confusional state and one SAE of seizure that were likely related to aducanumab, both occurring in the setting of symptomatic ARIA-E. Because of the presence of confounding factors, which included concomitant medication use, past medical history, and contributory events preceding the SAEs, I did not establish a role for aducanumab in SAEs of hemorrhage unrelated to intracranial hemorrhage; hernia; cellulitis, erysipelas; cardiac arrest; renal failure; sepsis; conduction disturbance; syncope; encephalitis, encephalopathy; psychosis, delusions, hallucinations; pulmonary embolism or SAEs identified as potentially medically significant (respiratory failure, pancreatitis, rhabdomyolysis, and asthmatic crisis).

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Hemorrhage

Preferred terms within the MQG of Intracranial Hemorrhage also occurred within the MQG of Hemorrhage FDA N. I summarize events related to intracranial hemorrhage and then other events that are also included within the MQG of Hemorrhage FDA N.

Overall, I note that SAEs of intracranial hemorrhage were frequently related to ARIA.

Fourteen SAEs belonging to the MQG of Intracranial Hemorrhage were reported in 12 aducanumab-assigned subjects across the clinical program. The following preferred terms were reported: cerebral hemorrhage (n=5), cerebral hematoma (n=4), subarachnoid hemorrhage (n=4), and hemorrhage intracranial (one only).

Nine out of 14 SAEs were potentially related to ARIA. Six SAEs reported Amyloid Related Imaging Abnormality-Hemorrhage (ARIA-H), macrohemorrhage as the reported term

(b) (6) (n=2), (b) (6). In an email discussion with Dr. Ranjit Mani dated October 8, 2020, two cases of cerebral hemorrhage (b) (6) and one case of cerebral hematoma (b) (6) were also identified as likely related to ARIA. The reader is referred to the clinical review by Dr. Trummer for a summary of the narratives of these nine cases.

In the remaining 5 out of 14 SAEs of intracranial hemorrhage, I note fall as a contributory factor in each of the cases. Two subjects had subarachnoid hemorrhage (b) (6). One subject had intracranial hemorrhage and also had as a contributory factor use of alcohol (b) (6). One subject had subarachnoid hemorrhage and cerebral hemorrhage and also reported the SAE of intraventricular hemorrhage at the time of the fall (b) (6).

The reader is referred to the section on Intracranial Hemorrhage for a review of the incidence of SAEs and TEAEs related to intracranial hemorrhage.

In the remaining events within the MQG Hemorrhage FDA N within Studies 103, 301, and 302, I did not identify a role for aducanumab due to confounding with concomitant medications, past medical history, or contributory events preceding the SAEs.

After excluding preferred terms related to intracranial hemorrhage, 28 SAEs within the MQG Hemorrhage FDA N remained (occurring in 25 subjects in Studies 103, 301, and 302). The following preferred terms were reported: subdural hematoma (n=12), hemorrhoidal hemorrhage (n=3), gastrointestinal hemorrhage (n=2), aortic aneurysm rupture, blood loss anemia, bone contusion, contusion, duodenal ulcer hemorrhage, extradural hematoma, gastric ulcer hemorrhage, hemothorax, intraventricular hemorrhage, Mallory-Weiss syndrome, and

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melena (each one event).

In the 12 SAEs of subdural hematoma, I note 9 SAEs (occurring in seven subjects) that were preceded by the risk factor of fall or accident occurring within two months (b) (6). One case also reported the SAE of extradural hematoma on the same day as the subdural hematoma (b) (6).

In the remaining three cases of subdural hematoma, after discussion by email with Ranjit Mani (October 8, 2020), a role for aducanumab could not be established because of preceding head trauma in one case (b) (6) and the underlying risk factor of age in the two remaining cases (age 78 years: (b) (6) and age 79 years: (b) (6)).

The one event intraventricular hemorrhage had as a risk factor fall occurring on the same day (b) (6).

In the three events of hemorrhoidal hemorrhage, I note underlying risk factors for hemorrhage (rivaroxaban use: (b) (6), history of diverticulosis/concomitant medication use with acetylsalicylic acid and meloxicam: (b) (6), and acute colitis in setting of history of colitis: (b) (6)).

In the two events of gastrointestinal hemorrhage, I note underlying risk factors for hemorrhage (initiation of ibuprofen within 17 days of event/concomitant medication use with acetylsalicylic acid: (b) (6) and hospitalization for right ureteral stone three days prior to the event: (b) (6)).

The cases of duodenal ulcer hemorrhage, gastric ulcer hemorrhage, melena, and Mallory-Weiss tear had contributing factors for the events of hemorrhage (concomitant medication use with naproxen: (b) (6), initiation of acetylsalicylic acid within four days of the event/concomitant medication use with naproxen and enoxaparin: (b) (6), history of duodenal ulcer: (b) (6) and episode of coughing and vomiting due to aspirating water while snorkeling 1 month before: (b) (6)). The case of Mallory-Weiss tear, found on an elective endoscopy, did not have active bleeding or oozing on exam, which was supportive of a subacute etiology.

I did not identify a role for aducanumab in the cases of hemothorax, contusion, and bone contusion as the events were preceded by a fall and the subjects had risk factors for falls (Parkinsonism: (b) (6), history of falls: (b) (6), and history of orthostatic hypotension: (b) (6)).

I did not identify a role for aducanumab in the events of aortic aneurysm rupture and blood loss

anemia because I identified the presence of risk factors (hypertension, hyperlipidemia, history of tobacco use for aortic aneurysm rupture: (b) (6) or concomitant medication use (rivaroxaban use for blood loss anemia: (b) (6)

Malignancy

The reader is referred to the section on Human Carcinogenicity for a review of the topic.

Hernia

Ten SAEs were reported within the MQG of Hernia and were reported in 10 aducanumab-treated subjects (preferred terms of inguinal hernia (n=9) and inguinal hernia strangulated (n=1)) in Studies 103, 301, and 302.

I did not identify a role for aducanumab in the SAEs of hernia because of the presence of underlying medical history of hernia or because of increased risk due to age, sex, and race. Five of the ten subjects had a history of inguinal hernia as risk factor for developing hernia

(b) (6)
The remaining five subjects had either white race, male sex, or age >60 years as risk factors for developing hernia (b) (6)

Cellulitis, Erysipelas

Six SAEs of cellulitis and one SAE of erysipelas were reported in seven aducanumab-treated subjects within the MQG of Cellulitis, Erysipelas in Studies 103, 301, and 302.

I did not identify a role for aducanumab in the SAEs of cellulitis and erysipelas because of events preceding the AE or underlying risk factors. Two of the seven subjects had an injury secondary to fall within six days preceding the development of cellulitis (b) (6). Three of seven subjects had one of the following risk factors for developing cellulitis: diabetes mellitus, tinea cruris, and peripheral edema (b) (6) respectively). One subject had as a potential risk factor a fall from bed 19 days before that resulted in left rib fractures and thoracic and lumbar vertebral fractures prior to the development of left sided facial cellulitis (b) (6). The last subject developed cellulitis of the hand and was noted on exam to have evidence of a healing injury to a digit on the hand (b) (6)

Confusion, Delirium, Altered Mental Status, Disorientation, and Coma

Ten SAEs were reported in ten aducanumab-treated subjects within the MQG of Confusion, Delirium, Altered Mental Status, Disorientation, and Coma in Studies 103, 301, and 302. The following preferred terms were reported: delirium (n=4), mental status changes (n=3), and confusional state (n=3).

I identified one case of confusional state where a role for aducanumab in the event was likely and one case of delirium where a role for aducanumab could not be ruled out. I summarize the narratives here.

Confusional State, (b) (6)

67-year-old female with mild cognitive impairment due to Alzheimer's disease, history of central nervous system hemorrhage, gastroesophageal reflux disease, hypertension, type 2 diabetes mellitus, drug hypersensitivities to amoxicillin/clavulanate potassium, codeine, meperidine, erythromycin, bacitracin/neomycin/polymyxin B, penicillin, and sulfamethoxazole who developed confusional state in the setting of symptomatic ARIA-E. The subject was diagnosed with asymptomatic ARIA-microhemorrhages and hemosiderin deposits and asymptomatic ARIA-E on Day 99. An MRI scan on that day showed severe new vasogenic edema (locations: left frontal; left parietal; and left temporal, nonhippocampal), >10 new microhemorrhages(locations: left parietal and left temporal), no superficial siderosis, and no macrohemorrhage. At the time of the event, she had received 4 doses of aducanumab. Her most recent dose had been 12 days prior to the events (dose of 3 mg/kg). Concomitant medications included acetylsalicylic acid, atorvastatin, cetirizine hydrochloride, losartan, metformin, naproxen, oxybutynin, and ranitidine. Study treatment was permanently discontinued because of the event of ARIA-microhemorrhages and hemosiderin deposits. On Day 114, the subject complained of a headache and was diagnosed with symptomatic ARIA-E. An MRI showed severe vasogenic edema which had increased in size compared to the previous scan.

Five days later, the patient was hospitalized for confusion, dragging right leg, and headache. She noted that her balance was off. She had forgotten how to turn on the dryer and had forgotten the code to open her phone. She also had difficulty with word finding and walking. The headache was rated as 5/10 and accompanied by sensitivity to bright lights. Her exam on admission showed right homonymous hemianopsia, short-term memory difficulties, transcortical sensory aphasia, right-sided hypertonia, and right leg weakness. An MRI scan showed severe vasogenic edema, which had increased in size in the motor area since the previous MRI scan.

She was treated with methylprednisolone 1 gram daily intravenously for 5 days for symptomatic ARIA-E. On Day 123, an MRI scan showed decrease in size to the vasogenic edema. She was discharged from the hospital on Day 123. The events of confusional state, gait disturbance, and headache were reported as resolved on Day 126. She was started on an oral prednisone taper on Day 127 (scheduled to last for 5.5 weeks). On Day 129, physical exam showed improvement with no field cut, no drift to right arm, and no dragging of right foot. An MRI scan of the same day showed severe vasogenic edema which had increased in size. On Day 156, an MRI scan showed decrease in size to vasogenic edema. On Day 186, an MRI showed

complete resolution of vasogenic edema and ARIA-E was reported as resolved.

Reviewer comment: A role for aducanumab in the event of confusional state is likely based on temporal sequence to the development of symptomatic ARIA-E.

Delirium, (b) (6)

A 75-year-old male with mild Alzheimer's disease, bradycardia, syncope, cardiac pacemaker insertion, hallucinations, hypertension, and incontinence developed the SAE of delirium 38 days after being diagnosed with symptomatic ARIA-E.

The applicant notes that the subject had a diagnosis of Alzheimer's for two years and over the course of time, the subject had deterioration of his condition as evidenced by aggressive behavior, restlessness, sleep disorders, memory disorders, disorientation, visual hallucinations, and anxiety.

On Day 127, the subject developed the non-serious event of delirium after presenting with symptoms of hallucinations and aggression. The event was assessed as moderate in severity and treatment was interrupted because of the event.

On Day 153, the subject was diagnosed with symptomatic ARIA-E. He had received 5 doses of aducanumab prior to the event. The most recent dose had been 41 days prior to the event (6 mg/kg). Concomitant medications included donepezil, metamizole sodium, and metoprolol. The subject began treatment for delirium on the same day with quetiapine fumarate. The subject also received aripiprazole for treatment of delirium. An MRI scan that day showed moderate new vasogenic edema (location: right parietal), 1 microhemorrhage, no superficial siderosis, and no macrohemorrhage. The event was reported as resolved on Day 188 when an MRI on that day showed complete resolution of vasogenic edema.

Study treatment was interrupted as a result of the event and led to the subject's withdrawal from the study.

On Day 224, the subject developed worsening symptoms of aggressive behavior and hallucinations and became unable to eat independently. The applicant noted that the disorientation and memory disorders suddenly became worse.

On Day 226, the delirium worsened to severe and the subject was hospitalized. Findings on exam showed impaired attention and impaired orientation to person, place, and time. Comprehension and concentration were severely impaired, and he had gait ataxia. He had received five doses of aducanumab prior to the event. The most recent dose had been 114 days prior to the event (6 mg/kg). Concomitant medications included aripiprazole, donepezil, metamizole sodium, metoprolol, quetiapine fumarate, and torsemide. The subject did not

consume alcohol, nicotine, or drugs and had not had previous hospital stays for psychiatric symptoms.

Over the next several days, the subject displayed increased agitation, irritability, confusion, and visual hallucinations. The subject was started on pregabalin and risperidone and the delirium, unrest, and irritability gradually improved. The subject remained disoriented to time and place.

He was discharged on Study Day 238 with the final diagnosis of behavioral disorder and delirium due to dementia associated with delayed onset Alzheimer's disease. The event of delirium remained unresolved. Study treatment was permanently discontinued as a result of the event.

Reviewer comment: Confounding factors in this case exist as the subject may have had worsening of his Alzheimer's disease that contributed to the delirium and had as past medical history symptoms of hallucinations (although none had required hospitalization previously). A role for aducanumab in the event of delirium cannot be ruled out as the symptoms started within a month of being diagnosed with symptomatic ARIA-E. Although repeat MRI scan showed resolution of ARIA-E, it is possible that the event of ARIA-E contributed to worsening delirium.

I did not identify a role for aducanumab in the remaining eight SAEs within the MQG of Confusion, Delirium, Altered Mental Status, Disorientation, and Coma based on events preceding the SAEs or underlying past medical history. Six of the eight subjects developed the SAEs in the setting of acute events of acute bronchitis (b) (6), acute COPD exacerbation (b) (6), gastroenteritis (b) (6), urinary tract infection (b) (6), alcohol intoxication/motor vehicle accident (b) (6), and after a dose of lorazepam as premedication for an MRI (b) (6). One subject had ongoing anxiety and insomnia that were likely contributory to the development of delirium (b) (6). Another subject experienced anxiety and delirium and was ultimately diagnosed with behavioral disturbances and delirium secondary to Alzheimer's disease (b) (6).

Cardiac arrest

Six SAEs with the preferred term of cardiac arrest were reported in six aducanumab-treated subjects in Studies 103, 301, and 302.

One case reported events of seizure, cardiac arrest, and symptomatic ARIA. I note a likely role for aducanumab in the event of seizure in a subject with symptomatic ARIA-E and summarize the narrative here. A role for aducanumab in the event of cardiac arrest cannot be established due to the confounding event of seizure which preceded cardiac arrest.

Cardiac arrest, Severe Symptomatic ARIA-E, Seizure, Symptomatic ARIA-H (microhemorrhage),

Symptomatic ARIA-H (macrohemorrhage) (b) (6)

72-year-old white male with history of dementia Alzheimer's type, hypertension who experienced the SAEs of severe symptomatic ARIA-E, seizure, and cardiac arrest on Day 465. The subject had received 3 doses of aducanumab with most recent dose occurring 17 days prior to the events (3 mg/kg). On Day 464, the patient was noted to be non-coherent and combative with a decline in mental status. On Day 465, he was transported by medics to the hospital and had a seizure that led to cardiac arrest. The subject was reported to have stopped breathing and become pulseless for 3 minutes. Prior to the cardiac arrest, the subject's blood pressure was 198/78 mmHg with a heart rate of 67 beats per minute. His pulse returned after CPR was initiated. Upon arrival to the ER, he was combative, non-verbal, and not responsive to voice commands or touch. ECG and EEG were unremarkable (results not provided). His cardiac enzymes were negative (values not provided). He was intubated in the ER for seizure and was admitted to the intensive care unit. An MRI scan showed severe vasogenic edema (locations: left occipital, right occipital, left temporal, and right temporal lobes), no microhemorrhage, no superficial siderosis, and no macrohemorrhage. A CT scan showed low attenuation in the left temporal lobe consistent with an acute infarct and senescent changes. He was treated with propofol, levetiracetam, acyclovir, vancomycin, piperacillin/tazobactam, and midazolam hydrochloride. He was extubated on Day 467 but remained sedated. Concomitant medications prior to the events of symptomatic ARIA-E, cardiac arrest, and seizure included donepezil, doxazosin, finasteride, hydrochlorothiazide/lisinopril, iron, naproxen sodium, and sildenafil.

Reviewer comment: A role for ARIA in the event of seizure seems likely given MRI findings at the time of the seizure. The event of cardiac arrest was likely a result of the seizure and a role for aducanumab cannot be established.

In the remaining five cases, I did not identify a role for aducanumab in the events based on underlying risk factors. Risk factors included hypertension, hyperlipidemia, coronary atherosclerosis, or diabetes mellitus (b) (6)

Three of the five events had a fatal outcome and are noted in the Deaths section of this review (b) (6)

Elevated Blood Urea Nitrogen or Creatinine/Acute Renal Failure/Chronic Renal Failure

Four treatment-emergent SAEs within the MQG of Elevated Blood Urea Nitrogen or Creatinine/Acute Renal Failure/Chronic Renal Failure were reported in four aducanumab-treated subjects in Studies 103, 301, and 302. The following preferred terms were reported: acute kidney injury (n=2); renal failure, prerenal failure (each one event).

I did not identify a role for aducanumab in the events of renal failure based on events preceding the events of renal failure. One event was fatal and was associated with cardiac arrest for which

the subject had underlying risk factors of arteriosclerosis, hyperlipidemia, and diabetes mellitus type 2 (b) (6). The remaining three events had contributing factors to renal failure (episode of diarrhea and vomiting 5 days prior to the event: (b) (6), ureteral stone: (b) (6), and poor oral intake/elbow effusion/cellulitis: (b) (6)

Sepsis

Nine SAEs within the MQG of Sepsis were reported in eight aducanumab-treated subjects in Studies 103, 301, and 302. The following preferred terms were reported: sepsis (n=6), pulmonary sepsis (n=2), and urosepsis (n=1).

I did not identify a role for aducanumab in the SAEs of sepsis because of events preceding the episodes of sepsis or because of underlying risk factors. One subject with fatal outcome was a resident of a nursing home who developed aspiration pneumonia in the setting of a suspected diazepam overdose, then developed the event of sepsis and death (b) (6) (see section on Deaths for further details on subject). Two subjects with history of urinary tract infections developed sepsis in the setting of a urinary tract infection (b) (6). The event of pneumonia preceded the development of sepsis in three subjects and each of the subjects had risk factors for developing pneumonia, which included chronic obstructive pulmonary disease (b) (6) and asthma/tobacco use (b) (6). One subject developed sepsis after an injury from a dog bite (b) (6). One subject was diagnosed with sepsis; however, a causative agent was never identified (b) (6).

Conduction Disturbance

For narratives of SAEs occurring with three-fold higher incidence in the 10 mg/kg arm compared to placebo, I identified the MQG of Conduction Disturbance (occurred in Studies 301 and 302 combined).

Six treatment-emergent SAEs of conduction disturbance were reported in six aducanumab-treated subjects in Studies 103, 301, and 302. The following preferred terms were included: atrioventricular block complete (n=2), atrioventricular block (n=2), atrioventricular block second degree, and bundle branch block right (each one event).

I identified one case where I could not rule out a role for aducanumab in the event of complete atrioventricular block because of temporal association with aducanumab administration.

Atrioventricular block complete, (b) (6)

A 76-year-old male with mild cognitive impairment due to Alzheimer's disease, dyslipidemia, hypertension, first degree atrioventricular block was hospitalized on Day 589 for complete atrioventricular block that started on the same day of as his second dose of aducanumab

infusion (1 mg/kg). Concomitant medications included amlodipine, beclomethasone, clonazepam, Ginkgo biloba, ipratropium bromide, isoprenaline, lactulose, memantine, metamizole sodium, metoclopramide, minerals NOS/vitamins NOS, paracetamol, perindopril, quetiapine, sertraline, simvastatin, sodium picosulfate, and tramadol. After lunch on that day, the patient developed pallor and sweating before losing consciousness. He was transported to the ER where several hours later he developed another self-limited episode similar to the previous one with a heart rate at 18 beats per minute. He was given atropine and follow up heart rate was 20 to 30 beats per minute. Labs showed sodium 142 mmol/L (reference range: 136 to 145 mmol/L), potassium 4.4 mmol/L (reference range: 3.5 to 5.1 mmol/L, calcium 1.11 mmol/L (reference range: 1.12 to 1.32 mmol/L), troponin I <0.16 µg/L (reference range <0.16 µg/L). An ECG showed findings suggestive of third-degree AV block. He had insertion of a temporary pacemaker and was given atropine, isoprenaline, metoclopramide, and sodium chloride. On Day 593, he was diagnosed with community acquired pneumonia and began treatment with amoxicillin-clavulanate acid. On Day 596, he had insertion of a pacemaker and the event of AV block was reported as resolved. He was discharged on Day 597. The event of respiratory tract infection was reported as resolved on Day 600. No action was taken with study treatment as a result of either event. The subject also experienced the SAEs of community-acquired pneumonia and left pleural effusion (Day 249 through Day 281) during the study.

Reviewer comment: Confounding factors in this case for the development of AV block include dyslipidemia, hypertension, first degree atrioventricular block, and a diagnosis of community acquired pneumonia within several days of the AV block. A role for aducanumab in the event of AV block cannot be ruled out given temporal association with drug administration and event onset.

In the remaining five cases of conduction disturbance, I note that the subjects had concomitant medication use or medical comorbidities as risk factors for developing conduction disturbances. One subject with atrioventricular block (type not specified) had hypertension and concomitant medication use with donepezil, which has a Warnings and Precautions Statement for atrioventricular block (b) (6). Another subject with complete atrioventricular block had concomitant medication use with donepezil and timolol which have been associated with atrioventricular block (b) (6). Another subject who reported the SAE of right bundle branch block had the risk factors of hypertension, hyperlipidemia, first degree atrioventricular block, aortic and tricuspid valve incompetence, and history of cardiac ablation (b) (6). Another subject who had reported the SAE of second degree atrioventricular block had a myocardial infarction and stent placed to his coronary arteries at the time of atrioventricular block and also had medical history of diabetes mellitus type 2, hypertension, and hyperlipidemia (b) (6). The remaining subject who reported the SAE of complete atrioventricular block had arteriosclerosis, left and right bundle branch block, hyperlipidemia, tobacco use, and concomitant donepezil use as risk factors

(b) (6)

Syncope

Forty-one SAEs with preferred terms of syncope (n=35), presyncope (n=5), or loss of consciousness (one event) were reported in 36 aducanumab-assigned subjects in Studies 103, 301, and 302.

I did not identify a role for aducanumab in my review of narratives related to syncope because of underlying risk factors. The most common causes for syncope in the cases included vasovagal syncope, arrhythmia, orthostatic hypotension, and dehydration. In cases where arrhythmia was the most likely cause for syncope, subjects had underlying risk factors for developing arrhythmias including history of myocardial infarction, left bundle branch block, post-operative status, diabetes mellitus, hypertension, and hyperlipidemia.

Encephalitis, Encephalopathy

Three SAEs within the MQG of Encephalitis, Encephalopathy occurred in three aducanumab-assigned subjects. Preferred terms included encephalopathy (n=2) and metabolic encephalopathy.

I did not identify a role for aducanumab in the events of encephalopathy. One case was related to overdose with an antidepressant (b) (6). Another case involved a subject who was hospitalized for nausea, vomiting, and acute changes in mental status (b) (6). Laboratory studies upon hospitalization showed elevation to his liver enzymes (total bilirubin of 1.3 mg/dL (reference range: 0.3 to 1.2 mg/dL), alanine aminotransferase of 64 IU/L (reference range: 17 to 63 IU/L), and aspartate aminotransferase (AST) of 91 IU/L (reference range: 15 to 41 IU/L)). Six weeks later, the subject was diagnosed with suspected common bile duct stone which was treated with needle knife papillotomy and stent placement. The acute mental status changes that caused the subject's initial hospitalization may have been due to an undiagnosed common bile duct stone. The third case involved a subject who was hospitalized for acute encephalopathy that was characterized by delirium and generalized weakness (b) (6). The workup, including CT of the brain, MRI of the brain, lumbar puncture, head and neck CT angiography, and EEG, was unrevealing. His symptoms resolved 6 days later. Discharge diagnosis included acute encephalopathy in the setting of amyloidosis noted on PET CT and transient delirium.

Psychosis, Delusions, Hallucinations

Four SAEs occurred within the MQG of Psychosis, Delusions, Hallucinations and occurred in four aducanumab-assigned subjects in Studies 103, 301, and 302. Preferred terms included psychotic disorder (n=2) and delusion (n=2).

In the two cases of psychotic disorder, a role for aducanumab could not be established due to

the presence of contributing or confounding factors. In one case, the subject's history of paranoid schizophrenia was a likely contributory factor (b) (6) and in the second case, discontinuation of escitalopram and initiation of duloxetine within four weeks of the event was a potential confounding factor (b) (6).

In the two cases of delusion, a role for aducanumab could not be established due to a lack of information. One case lacked results of laboratory tests, such as a comprehensive metabolic panel, vitamin B12 level, thyroid stimulating hormone, and tests to rule out infectious disease, and imaging, such as CT or MRI imaging, upon hospitalization (b) (6). The second case lacked information of the delusional disorder and results of laboratory tests or imaging (b) (6).

Pulmonary Embolism

Twelve SAEs with the preferred term of pulmonary embolism occurred in 11 subjects in Studies 103, 301, and 302.

I did not identify a role for aducanumab in the event of pulmonary embolism primarily due to underlying risk factors. I note two cases where age (> 70 years) was the only risk factor. Both cases lacked results for of laboratory assessment for a hypercoagulable state and a role for aducanumab could not be established (b) (6). In the other cases, the risk factors existed for thromboembolism existed including obesity (b) (6), tobacco use (b) (6), metastatic pancreatic carcinoma (b) (6), and hospitalization for pneumonia and sepsis a month before the event (b) (6).

Potentially Medically Significant SAEs

I did not identify any SAEs of aplastic anemia, agranulocytosis, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, Stevens Johnson syndrome, Toxic Epidermal Necrolysis, sudden death, or thrombotic thrombocytopenia purpura. I identified SAEs of respiratory failure, pancreatitis, rhabdomyolysis, and asthmatic crisis; however, I did not identify a role for aducanumab in the cases primarily because of contributory factors such as medical history, concomitant medication use, or events preceding the SAEs. I summarize the narratives here.

Respiratory failure

Six treatment-emergent SAEs related to respiratory failure were reported in six aducanumab-treated subjects in Studies 103, 301, and 302. The following preferred terms were reported: respiratory failure (n=3), acute respiratory failure (n=2), and postoperative respiratory failure (n=1).

I did not identify a role for aducanumab in the SAEs of respiratory failure due to events preceding the development of respiratory failure and the presence of risk factors in the subjects for those events. Two subjects had risk factors for respiratory failure of asthma/chronic obstructive pulmonary disease and obstructive sleep apnea (b) (6), respectively). One subject had advanced dementia and Alzheimer's disease as risk factor for developing aspiration pneumonia which led to respiratory failure (b) (6). Three subjects had cardiovascular events that led to the development of respiratory failure (aortic aneurysm rupture: (b) (6), atrial fibrillation: (b) (6), and aortic dissection: (b) (6). Each of the subjects had at least one risk factor for the development of cardiovascular events (such as hypertension, hyperlipidemia, and mitral valve incompetence).

Pancreatitis

Four SAEs of pancreatitis were reported in four aducanumab-treated subjects (preferred term: acute pancreatitis (n=2), pancreatitis (n=2)) in Studies 103, 301, and 302.

I did not identify a role for aducanumab in the SAEs of pancreatitis due to temporal disassociation between the event and drug, confounding with concomitant medication use, and underlying risk factors. In one of the cases, the event of pancreatitis occurred 293 days after the last dose of aducanumab (b) (6). In the remaining three cases, subjects had concomitant medication use with medications associated with pancreatitis including benazepril, enalapril, atorvastatin, corticosteroids, donepezil, metformin, and hydrochlorothiazide (b) (6). In addition, two of the subjects also had history of alcohol or tobacco use (b) (6).

Rhabdomyolysis

In the one SAE of rhabdomyolysis in Studies 103, 301, and 302, I did not identify a role for aducanumab based on the contributory factor of fall (b) (6). In this case, the subject had underlying risk factors for fall including alcohol abuse, lumbar spinal stenosis, foot drop, and joint contractures.

Asthmatic Crisis

In the one SAE of asthmatic crisis in Studies 103, 301, and 302, I did not identify a role for aducanumab due to events preceding the SAE (exposure to interior paint, (b) (6)).

90-Day Safety Update

No SAEs were reported through the 90-Day Safety Update for Study 304.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to study withdrawal were reported at a low incidence in aducanumab-

treated subjects in the placebo-controlled period of Study 302 and pooled Studies 301 and 302 (no higher than 4%). The most frequent AEs reported to lead to study withdrawal in Studies 302 and pooled Studies 301 and 302 included superficial siderosis of the central nervous system and ARIA-microhemorrhages and hemosiderin deposits. In Study 103, adverse events were reported to lead to study withdrawal in approximately 5% of aducanumab-treated subjects.

Adverse events leading to treatment discontinuation were driven by protocol for ARIA events in Studies 103, 301, and 302. Discontinuations did not necessarily lead to study withdrawal, as discussed in the section below. AEs leading to treatment discontinuation occurred in approximately 8% of aducanumab-treated subjects in Study 302 and 9% in pooled Studies 301 and 302. The most frequent AEs leading to treatment discontinuation in Study 302 and pooled Studies 301 and 302 were ARIA-microhemorrhages and hemosiderin deposits, superficial siderosis of the central nervous system, and ARIA-E. In Study 103, adverse events were reported to lead to treatment discontinuation in approximately 14% of aducanumab-treated subjects.

Study Withdrawal

Withdrawal of a subject from the study was required in Studies 103, 301, and 302 if a subject withdrew consent or was unwilling or unable to comply with the protocol, or at the discretion of the Investigator or Applicant.

In Study 302, approximately 54% of subjects completed the placebo-controlled period. Adverse events were reported to lead to study withdrawal in 4% of subjects in the aducanumab 10 mg/kg arm compared to 2% on placebo. The following table shows reasons for study withdrawal in the safety population of the placebo-controlled period for Study 302. I note the reason for study withdrawal in the “other” category was due to the applicant’s decision to terminate the study in over 95% of the cases. In subjects who withdrew consent, I reviewed specific reasons and note that adverse events leading to withdrawal of consent were mentioned with similar frequency across treatment arms (range between 20% to 27%). Examples of reasons included withdrawal after SAE of subdural hematoma, withdrawal due to recurrent symptom of previous SAE, and withdrawal due to ARIA (see the [Appendix](#) for a list of statements of AEs potentially leading to withdrawal of consent and a table with frequency of subjects with statements where AEs potentially led to study withdrawal in Study 302).

Table 22. Disposition Related to Study Withdrawal in Study 302.

Reason	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Subjects Who Completed the Study	202 (55)	90 (51)	295 (54)	587 (54)	287 (52)

Reason	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Subjects Who Withdrew from the Study	167 (45)	85 (49)	252 (46)	504 (46)	260 (48)
Adverse Event	9 (2)	4 (2)	20 (4)	33 (3)	10 (2)
Change of Treatment	0	0	1 (0)	1 (0)	0
Consent Withdrawn	20 (5)	12 (7)	26 (5)	58 (5)	15 (3)
Death	0	0	6 (1)	6 (1)	5 (1)
Disease Progression	0	0	1 (0)	1 (0)	2 (0)
Investigator Decision	1 (0)	1 (1)	5 (1)	7 (1)	2 (0)
Lost to Follow-Up	0	1 (1)	3 (1)	4 (0)	3 (1)
Other	130 (35)	64 (37)	183 (33)	377 (35)	216 (39)
Relocation	1 (0)	0	1 (0)	2 (0)	1 (0)
Study Visit Burden	6 (2)	2 (1)	5 (1)	13 (1)	2 (0)
Withdrawal by Parent/Guardian	0	1 (1)	1 (0)	2 (0)	4 (1)

The reviewer created this from the ISS ADSLI joined with the Study 302 ADSL, Subset on Study 302, POOLC=POOLA1, Tabulated on DCP01RS, POOLTR3 Reassigned PC Pool A1.

The placebo-controlled periods of pooled Studies 301 and 302 had a similar frequency of subjects who completed the placebo-controlled period as compared to Study 302 alone (55% versus 54%, respectively). Adverse events were reported to lead to study withdrawal in approximately 4% of subjects across aducanumab arms and 2% on placebo. Similar to Study 302 alone, the “other” category accounted for approximately 35% of study withdrawals and among those, the applicant’s decision to terminate the study was the primary reason for study withdrawal.

In Study 103, approximately 70-80% of subjects across all aducanumab arms and placebo completed the study. Adverse events were reported to lead to study withdrawal in approximately 5% of aducanumab-treated subjects and approximately 6% of subjects on placebo. The higher incidence of adverse events causing study withdrawal in Study 103 relative to Studies 301 and 302 may in part be due to the fixed dosing of design of Study 103 as opposed to the titrated dose design of Studies 301 and 302.

In the combined placebo-controlled and long-term extension periods of Study 302, adverse events were reported to lead to study withdrawal in approximately 4% (29/679) of aducanumab 10 mg/kg-treated subjects, which was the same as the incidence reported in the placebo-controlled period alone (4%).

In the combined placebo-controlled and long-term extension periods of pooled Studies 301 and

302 and pooled Studies 103, 301, and 302, adverse events were reported to lead to study withdrawal in approximately 5% of aducanumab 10 mg/kg-treated subjects (66/1386 for pooled Studies 301 and 302 and 75/1449 for pooled Studies 103, 301, and 302) and was similar to the incidence reported in the Study 302 alone (4%).

In the placebo-controlled period of Study 302, the most frequently reported TEAEs leading to study withdrawal were superficial siderosis of the central nervous system; ARIA-microhemorrhages and hemosiderin deposits; cardiac arrest; Psychosis, Delusions, Hallucinations MQG; and Malignancy FDA B MQG, and each were reported to lead to discontinuation in 1.3%, 0.5%, 0.4%, 0.5%, and 0.5% of subjects given aducanumab 10 mg/kg, respectively. The reader is referred to the section on [Human Carcinogenicity](#) in this review for a review of the topic of malignancy. The two events of cardiac arrest that were reported to lead to study withdrawal are discussed in the [Cardiac Arrest](#) section of the Serious Adverse Events section of this review (b) (6)

Three events occurring in aducanumab-treated subjects belonged to the MQG Psychosis, Delusions, Hallucinations. The preferred terms included delusion (n=2) and hallucination. One of the three events was a serious adverse event and is discussed in the [Psychosis, Delusions, Hallucinations](#) section of the Serious Adverse Events section of this review (delusion, (b) (6)). A role for aducanumab in the event could not be established due to a lack of results of an evaluation for other causes. In the remaining two events, a role for aducanumab could not be established due to past medical history of delusions and hallucinations in a subject with delusions (b) (6) and concomitant medication use with alprazolam, history of anxiety, depression, insomnia, Alzheimer's dementia in a subject with hallucination (b) (6).

The following table lists TEAEs reported to lead to study withdrawal in the placebo-controlled period of Study 302.

Table 23. TEAEs Leading to Study Withdrawal with Incidence in the Aducanumab 10 mg/kg Arm of at Least 0.3% Higher than Placebo in Study 302.

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Superficial Siderosis Of Central Nervous System	0	0	7 (1.3)	7 (0.6)	0
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	2 (0.5)	0	3 (0.5)	5 (0.5)	0
Cardiac Arrest	0	0	2 (0.4)	2 (0.2)	0

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Psychosis, Delusions, Hallucinations MQG	0	0	3 (0.5)	3 (0.3)	1 (0.2)
Malignancy FDA B MQG	1 (0.3)	2 (1.1)	3 (0.5)	6 (0.5)	1 (0.2)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; AEWD=1; StudyID: 302; Group by USUBJID, MedDRA query group; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

In the placebo-controlled periods of Studies 301 and 302, the most frequently reported TEAEs leading to study withdrawal were superficial siderosis of the central nervous system, ARIA-microhemorrhages and hemosiderin deposits, and ARIA-E, and each led to discontinuation in 1%, 0.5%, and 0.6% of aducanumab 10 mg/kg-treated subjects, respectively. The following table lists TEAEs reported to lead to study withdrawal with incidence in the aducanumab 10 mg/kg arm of at least 0.2% higher than placebo in Studies 301 and 302.

Table 24. TEAEs Leading to Study Withdrawal with Incidence in the Aducanumab 10 mg/kg Arm of at Least 0.2% Higher than Placebo in Pooled 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 (%)
Superficial Siderosis Of Central Nervous System	4 (0.5)	0	11 (1)	15 (0.7)	0
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	8 (1.1)	0	5 (0.5)	13 (0.6)	0
Amyloid Related Imaging Abnormality-Edema/Effusion	4 (0.5)	1 (0.3)	7 (0.6)	12 (0.5)	1 (0.1)
Cardiac Arrest	1 (0.1)	0	2 (0.2)	3 (0.1)	0
Psychosis, Delusions, Hallucinations MQG	0	0	3 (0.3)	3 (0.1)	1 (0.1)
Hemorrhage FDA N MQG	0	0	3 (0.3)	3 (0.1)	1 (0.1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; AEWD=1; Grouped by USUBJID, MedDRA query group; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

In the placebo-controlled period of Study 103, the TEAEs of ARIA-E, cerebrovascular accident, and syncope were each reported to lead to study withdrawal in one aducanumab 10 mg/kg-treated subject.

Superficial siderosis of the central nervous system was the most frequent AEs reported to lead to study withdrawal in the combined placebo-controlled and long-term extension periods of Study 302, pooled Studies 301 and 302, and pooled Studies 103, 301, and 302. Superficial siderosis of the central nervous system was reported to lead to study withdrawal in 1.2% of the aducanumab 10 mg/kg arm in Study 302, 0.9% in pooled Studies 301 and 302, and 0.8% in pooled Studies 103, 301, and 302.

Treatment Discontinuations

Adverse events leading to treatment discontinuation were driven by protocol for ARIA events in Studies 103, 301, and 302.

In Studies 301 and 302, discontinuation of study treatment was required if a subject developed any of the following: ARIA-E with serious clinical symptoms; symptomatic ARIA-microhemorrhages and hemosiderin deposits with serious clinical symptoms; symptomatic ARIA-H with serious clinical symptoms; ARIA-H with greater than or equal to 10 microhemorrhages or greater than two focal areas of superficial siderosis; any new incident macrohemorrhage; pregnancy; withdrew consent; experienced a medical emergency that necessitated permanent discontinuation of study treatment or unblinding of the treatment's assignment; any AE that did not resolve or required continued treatment that met exclusionary criteria; severe infusion reaction; at the discretion of the Investigator for medical reasons; at the discretion of the Investigator or Applicant for noncompliance. Subjects who discontinued study treatment were not automatically withdrawn from the study. The subject was to remain in the study and continue with a follow up visit 18 weeks after the final dose.

In Study 103, discontinuation of study treatment was required if a subject developed any of the following: mild, moderate, or severe ARIA-E, ARIA-H of less than or equal to 9 cumulative microhemorrhages or less than or equal to two cumulative areas of superficial siderosis accompanied by serious clinical symptoms; ARIA-H consisting of greater than or equal to 10 cumulative microhemorrhages or greater than or equal to two cumulative areas of superficial siderosis; any incident macrohemorrhage, pregnancy; withdrew consent; experienced a medical emergency that necessitated permanent discontinuation of study treatment or unblinding of the treatment's assignment; at the discretion of the Investigator for medical reasons; at the discretion of the Investigator or Applicant for noncompliance.

The following table shows reasons for treatment discontinuations in the safety population of the placebo-controlled period for Study 302. Treatment discontinuations due to adverse events had a higher incidence in the aducanumab 10 mg/kg group compared to placebo (9% versus 3%, respectively). The applicant's decision to terminate the study was listed as the reason for study discontinuation in the "other" category in greater than 95% of the cases. In subjects who withdrew consent, I reviewed specific reasons and note that adverse events leading to

withdrawal of consent were mentioned with similar frequency across treatment arms (range between 14% to 25%). (See the [Appendix](#) for a list of statements of AEs potentially leading to withdrawal of consent and a table with frequency of subjects with statements where AEs potentially led to treatment discontinuation in Study 302).

Table 25. Reasons Leading to Treatment Discontinuations in Study 302.

Reason	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Adverse Event	29 (8)	13 (7)	49 (9)	91 (8)	17 (3)
Change of Treatment	0	0	2 (0)	2 (0)	0
Consent Withdrawn	13 (4)	9 (5)	20 (4)	42 (4)	6 (1)
Death	0	0	5 (1)	5 (0)	5 (1)
Disease Progression	0	0	1 (0)	1 (0)	1 (0)
Investigator Decision	1 (0)	2 (1)	6 (1)	9 (1)	2 (0)
Lost to Follow-Up	0	1 (1)	2 (0)	3 (0)	2 (0)
Other	124 (34)	63 (36)	175 (32)	362 (33)	215 (39)
Relocation	1 (0)	0	1 (0)	2 (0)	1 (0)
Study Visit Burden	7 (2)	0	4 (1)	11 (1)	2 (0)
Withdrawal by Parent/Guardian	0	1 (1)	0	1 (0)	3 (1)

The reviewer created this from the ISS ADSLI joined with the Study 302 ADSL, Subset on Study 302, POOLC=POOLA1, Tabulated on DCT01RS, POOLTR3 Reassigned PC Pool A1.

In the placebo-controlled periods of Studies 301 and 302 combined, adverse events were reported to lead to treatment discontinuation in approximately 9% of subjects across aducanumab arms and 4% on placebo. Similar to Study 302 alone, the “other” category accounted for approximately 35% of treatment discontinuations and among those, the applicant’s decision to terminate the study was the primary reason for study withdrawal. Approximately 45% of subjects discontinued study treatment overall.

In Study 103, adverse events leading to treatment discontinuation occurred at a higher incidence in aducanumab-treated subjects of the placebo-controlled period as compared to the aducanumab-treated subjects of the placebo-controlled period of Study 302 (14% versus 8%, respectively). The 10 mg/kg treatment arm of the placebo-controlled period of Study 103 had a higher incidence of adverse events causing treatment discontinuation compared to the 10 mg/kg treatment arm of Study 302 (31% versus 9%, respectively). The higher incidence is likely due to the fixed-dose treatment design of Study 103. Approximately 20-30% of subjects across all aducanumab arms and placebo had a treatment discontinuation.

In the placebo-controlled period of Study 302, the most frequently reported TEAEs leading to treatment discontinuation were ARIA-microhemorrhages and hemosiderin deposits, superficial siderosis of central nervous system, and ARIA-E, and each led to discontinuation in 2.9%, 2.9%, and 0.9% of subjects given aducanumab 10 mg/kg, respectively. The following table lists most frequent TEAEs reported to lead to treatment discontinuation in the placebo-controlled period of Study 302.

Table 26. TEAEs Leading to Treatment Discontinuation With Incidence in the Aducanumab 10 mg/kg Group of at Least 0.4% Higher Than Placebo in Study 302.

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	10 (2.7)	1 (0.6)	16 (2.9)	27 (2.5)	0
Superficial Siderosis Of Central Nervous System	7 (1.9)	1 (0.6)	16 (2.9)	24 (2.2)	0
Amyloid Related Imaging Abnormality-Edema/Effusion	5 (1.4)	2 (1.1)	5 (0.9)	12 (1.1)	1 (0.2)
Psychosis, Delusions, Hallucinations MQG	0	0	3 (0.5)	3 (0.3)	0
Hemorrhage FDA N MQG	1 (0.3)	0	3 (0.5)	4 (0.4)	0
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	0	1 (0.6)	2 (0.4)	3 (0.3)	0

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; AEDISC=1; StudyID: 302; Group by USUBJID, MedDRA query group; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

In the placebo-controlled periods of Studies 301 and 302, the most frequently reported TEAEs leading to treatment discontinuation were superficial siderosis of the central nervous system, ARIA-microhemorrhages and hemosiderin deposits, and ARIA-E, and each led to discontinuation in 3%, 2.4%, and 1.5% of subjects given aducanumab 10 mg/kg.

Preferred terms for adverse events within the MQG of Allergic Reaction, Hypersensitivity included urticaria and angioedema. Two of the four adverse events (urticaria, angioedema) were SAEs. Both of these SAEs were reported in one subject where a role for aducanumab was likely based on temporal sequence with aducanumab infusion (b) (6). The reader is referred to the [Hypersensitivity Reaction](#) section of this review for a narrative of these events.

Three cases of deep vein thrombosis occurring in three aducanumab-treated subjects were

reported to lead to treatment discontinuation (b) (6)

(b) (6) Two of the three events were serious. I did not identify a role for aducanumab in the cases of deep vein thromboses due to underlying risk factors. I note age as a risk factor in all three cases as subjects were over 70 years of age. One case also had the risk factor of prolonged sitting (b) (6) and a second case the risk factors of obesity and testosterone supplementation (b) (6). None of the cases reported results of laboratory assessments to evaluate for hypercoagulable state.

The following table lists TEAEs leading to treatment discontinuation with incidence of at least 0.2% higher in the aducanumab 10 mg/kg arm compared to placebo in combined Studies 301 and 302.

Table 27. TEAEs Leading to Treatment Discontinuation Occurring With Incidence in the 10 mg/kg Group of at Least 0.2% Higher Than Placebo in Pooled 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 (%)
Superficial Siderosis Of Central Nervous System	16 (2.1)	2 (0.6)	33 (3)	51 (2.3)	2 (0.2)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	23 (3)	2 (0.6)	27 (2.4)	52 (2.4)	0
Amyloid Related Imaging Abnormality-Edema/Effusion	9 (1.2)	3 (0.9)	17 (1.5)	29 (1.3)	1 (0.1)
Psychosis, Delusions, Hallucinations MQG	0	0	3 (0.3)	3 (0.1)	0
Deep Vein Thrombosis	0	1 (0.3)	2 (0.2)	3 (0.1)	0
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	0	2 (0.6)	2 (0.2)	4 (0.2)	0
Allergic Reaction, Hypersensitivity MQG	1 (0.1)	0	3 (0.3)	4 (0.2)	1 (0.1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; AEDISC=1; Grouped by USUBJID, MedDRA query group; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

In the placebo-controlled period of Study 103, the most frequently reported TEAEs leading to treatment discontinuation were ARIA-E, Superficial Siderosis, and ARIA-microhemorrhages and hemosiderin deposits, and each were reported to lead to discontinuation in 15.6%, 12.5%, and 6.3% of subjects given fixed dose of aducanumab 10 mg/kg, respectively.

In the combined placebo-controlled and long-term extension periods of Study 302, adverse

events were reported to lead to treatment discontinuation in approximately 9% of aducanumab 10 mg/kg-treated subjects. This incidence was the same as the incidence of AEs causing treatment discontinuation in the aducanumab 10 mg/kg arm of the placebo-controlled period alone.

In the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302, adverse events were reported to lead to treatment discontinuation in 10% of aducanumab 10 mg/kg-treated subjects which was similar to the incidence reported in Study 302 alone.

In the combined placebo-controlled and long-term extension periods of pooled Studies 103, 301, and 302, adverse events were reported to lead to treatment discontinuation in 11% of aducanumab 10 mg/kg-treated subjects which was similar to the incidence reported in Study 302 alone.

ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis were the most frequent AEs reported to lead to treatment discontinuation in the combined placebo-controlled and long-term extension periods of Study 302, pooled Studies 301 and 302, and pooled Studies 103, 301, and 302.

8.4.4. Significant Adverse Events

Overall, evaluation of significant AEs did not identify a new safety signal.

Most TEAEs were mild or moderate, with approximately 15% considered severe across studies. In Study 302, the preferred terms for the severe AEs with the highest frequency were ARIA-edema/effusion, ARIA-microhemorrhages and hemosiderin deposits, superficial siderosis of central nervous system that each occurred in approximately 3% of aducanumab 10 mg/kg treated subjects and in none of the placebo-treated subjects.

Severity of adverse event in Studies 103, 301, and 302 was assessed using the definitions in the table below.

Table 28. Definition for Severity of Adverse Events for Studies 103, 301, and 302.

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

The above table was taken from the Applicant's submission: Study 103 Protocol, Version 11.0, Section 15.3.2; Study 301 Protocol, Version 6.0, Section 15.2.3; Study 302 Protocol, Version 6.0, Section 15.2.3.

In the placebo-controlled periods of Study 302, pooled Studies 301 and 302, and Study 103, approximately 15% of patients had TEAEs that were severe. Severity did not appear to be dose related. The incidence of a subject experiencing a severe TEAE was higher in the aducanumab 10 mg/kg arm compared to placebo. The findings for Study 302 are shown in the table below.

Table 29. Incidence of a Subject Experiencing a TEAE by Severity in Study 302.

Severity	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Mild	322 (87)	139 (79)	487 (89)	948 (87)	451 (82)
Moderate	206 (56)	85 (49)	309 (56)	600 (55)	246 (45)
Severe	55 (15)	17 (10)	80 (15)	152 (14)	47 (9)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; StudyID: 302; Grouped by USUBJID, AESEV, POOLTR3 Reassigned A1; Tabulate by AESEV and POOLTR3 Reassigned A1

The reader is referred to the appendix for tables on the incidence of TEAEs by severity in the placebo-controlled periods of pooled Studies 301 and 302 and in Study 103 ([Appendix 13.2](#)).

In the placebo-controlled period of Study 302, the most frequent severe TEAEs were ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system.

Findings in the placebo-controlled period of pooled Studies 301 and 302 were consistent with these. In Study 103, severe headache and syncope each occurred in 2 of 148 aducanumab-treated patients (1.4%), and each occurred in 1 of 32 subjects (3.1%) in the aducanumab 10 mg/kg arm versus none in the 48 placebo-treated subjects.

The most frequent severe TEAEs in the combined placebo-controlled and long-term extension periods of Study 302 and pooled Studies 301 and 302 were ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis, which was consistent with the placebo-controlled periods of Study 302 and pooled Studies 301 and 302.

In the placebo-controlled period of Study 302, two cases with preferred term of encephalopathy occurred in two aducanumab-treated subjects. Overall, I did not identify a role for aducanumab in these cases. Narratives of these cases are summarized in the [Encephalitis, Encephalopathy section](#) of the Serious Adverse Events section of this review (b) (6)

The following table shows the most frequently occurring severe TEAEs in the placebo-controlled period of Study 302.

Table 30. Severe TEAEs With Incidence at Least 0.4% Higher in Aducanumab 10 mg/kg Arm Compared to Placebo in Study 302

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	10 (2.7)	2 (1.1)	18 (3.3)	30 (2.7)	0
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	12 (3.3)	1 (0.6)	16 (2.9)	29 (2.7)	0
Superficial Siderosis Of Central Nervous System	9 (2.4)	1 (0.6)	14 (2.6)	24 (2.2)	0
Malignancy FDA B MQG	5 (1.4)	4 (2.3)	7 (1.3)	16 (1.5)	4 (0.7)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	1 (0.3)	0	3 (0.5)	4 (0.4)	0
Cardiac Arrest	0	0	2 (0.4)	2 (0.2)	0
Encephalopathy	0	0	2 (0.4)	2 (0.2)	0

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; AESEV= severe; StudyID: 302; Grouped by USUBJID, AEDECOD, POOLTR3 Reassigned A1 for individual preferred terms and by USUBJID, MedDRA query group, and POOLTR3 Reassigned A1 from grouped terms. MQG: MedDRA query group.

The reader is referred to the Appendix for tables of the most frequent severe TEAEs in the placebo-controlled periods of pooled Studies 301 and 302, and the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302 ([Appendix 13.2](#)).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs across all trials were ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system. In the placebo-controlled portion of Studies 301 and 302, ARIA-E occurred in up to 35% of aducanumab 10 mg/kg subjects versus 3% for placebo. ARIA-microhemorrhages and hemosiderin deposits occurred in up to 19% of aducanumab 10 mg/kg subjects versus 7% for placebo. Superficial siderosis occurred in up to 15% of aducanumab 10 mg/kg subjects versus 2% for placebo. The incidence of these TEAEs in Study 302 alone was similar to pooled Studies 301 and 302. In Study 103, a higher incidence of ARIA-E was seen in subjects in the aducanumab 10 mg/kg arm relative to placebo (41% versus 0, respectively) compared to Study 302 (34% versus 2%, respectively). The combined placebo-controlled and long-term extension periods did not identify other TEAEs as being the most common except for infection. Infection occurred at similar incidence in the long-term extension periods as compared to the placebo-controlled period alone. Infection was not among the most frequently occurring TEAEs in the placebo-controlled periods of pooled Studies 301 and 302 as the incidence was similar in all aducanumab arms compared to placebo.

Placebo-Controlled Period

In the placebo-controlled period of Study 302, subjects who received aducanumab 10 mg/kg had a higher incidence of experiencing at least one TEAE compared to subjects who received placebo. Similar findings were observed in Pooled Studies 301 and 302. In Study 103, subjects treated with aducanumab 10 mg/kg had a slightly lower incidence of experiencing at least one TEAE when compared to placebo (91% versus 98%, respectively).

In the placebo-controlled period of Study 302, the most frequently reported TEAEs by preferred term in the aducanumab 10 mg/kg arm included ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system.

The reader is referred to the section of the review titled [Subjects Without ARIA-E, ARIA-Microhemorrhages and Hemosiderin Deposits, or Superficial Siderosis](#) for an analysis of the incidence of most common AEs in subjects who did not have ARIA events during the clinical studies.

Similar findings were observed in pooled Studies 301 and 302. I note that the difference in incidence of the TEAE of fall between aducanumab 10 mg/kg-treated subjects and placebo-treated subjects was higher in pooled Studies 301 and 302 compared to Study 302 alone. In pooled Studies 301 and 302, fall occurred in 15% of aducanumab 10 mg/kg-treated subjects compared to 12% of placebo-treated subjects. In Study 302 alone, fall occurred in 14% of aducanumab 10 mg/kg-treated subjects compared to 13% of placebo-treated subjects. In Study

301 alone, fall occurred in 15% of aducanumab 10 mg/kg-treated subjects compared to 11% of placebo-treated subjects.

Reviewer comment: The higher incidence of falls in the aducanumab 10 mg/kg arm is of significance as falls are a known risk factor for hip fracture.⁵ In addition, hip fracture is significant for patients with Alzheimer's disease due to an association with higher mortality. A study by Baker et al. demonstrated a 1.5-fold increased mortality rate in patients with hip fracture and Alzheimer's disease compared to patients with hip fracture without Alzheimer's disease.⁶

In the placebo-controlled period of Study 103, I note dose-dependent responses were seen for ARIA-E, headache, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system. Dose-dependent responses were likely seen in part because of the different study design of Study 103 as compared to Studies 301 and 302, as most subjects in Study 103 were assigned to a fixed dose of aducanumab rather than a titrated dose. ARIA-E was seen at a higher incidence in subjects in Study 103 in the aducanumab 10 mg/kg arm relative to placebo (41% versus 0, respectively) compared to Study 302 (34% versus 2%, respectively). I also note that in Study 103 constipation occurred in 9% (3/32) of subjects in the aducanumab 10 mg/kg group vs none (0/48) in the placebo patients and urinary tract infection occurred in 16% of subjects in the aducanumab 10 mg/kg group vs 10% in the placebo group. Baseline demographics in Study 103 differed from Studies 301 and 302 in that subjects were more impaired at baseline. This may in part explain the higher incidence of urinary tract infection in Study 103. The small number of subjects in Study 103 limits the conclusions that can be drawn from that study. The reader is referred to the [Appendix](#) for the frequency of TEAEs reported in the placebo-controlled period of Study 103.

The following table shows the most frequently occurring TEAEs in the placebo-controlled period of Study 302.

Table 31. TEAEs with Incidence of at Least 2% and at Least 2% Higher in the Aducanumab 10 mg/kg Arm Compared to Placebo in Study 302.

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Total with at least one TEAE	337 (91)	150 (86)	509 (93)	996 (91)	478 (87)

⁵ Vieira E, Palmer R, Chaves P. Prevention of falls in older people living in the community. BMJ 2016;353:i1419 doi: 10.1136/bmj.i1419

⁶ Baker N, Cook M, Arrighi M, et al. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. Age and Ageing 2011; 40: 49–54 doi: 10.1093/ageing/afq146

Adverse Event	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	109 (30)	31 (18)	188 (34)	328 (30)	13 (2)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	68 (18)	19 (11)	108 (20)	195 (18)	37 (7)
Superficial Siderosis Of Central Nervous System	46 (12)	6 (3)	73 (13)	125 (11)	14 (3)
Headache FDA B MQG	92 (25)	32 (18)	121 (22)	245 (22)	95 (17)
Vertigo FDA B MQG	46 (12)	11 (6)	75 (14)	132 (12)	57 (10)
Diarrhea FDA N MQG	31 (8)	7 (4)	44 (8)	82 (8)	30 (5)
Nasal Congestion	2 (1)	3 (2)	15 (3)	20 (2)	6 (1)
Nausea, Vomiting MQG	37 (10)	7 (4)	48 (9)	92 (8)	37 (7)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	21 (6)	6 (3)	40 (7)	67 (6)	27 (5)
Visual Disturbance MQG	10 (3)	4 (2)	16 (3)	30 (3)	6 (1)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 302; For TEAEs by preferred term, grouped by USUBJID, AEDECOD; POOLTR3 Reassigned A1. For TEAEs by MedDRA query group, grouped by USUBJID, MedDRA query group, POOLTR3 Reassigned A1. MQG: MedDRA query group.

Compared to the above table, the most frequent adverse events in Study 302 presented at the Peripheral and Central Nervous System Drugs Advisory Committee meeting (AC meeting) on November 6, 2020, had small differences in frequency for Confusion, Delirium, Altered Mental Status, Disorientation MQG and Diarrhea MQG (differences no greater than 1%). Differences for the Confusion, Delirium, Altered Mental Status, Disorientation MQG were due to reassignment of subjects to different treatment arms (Analysis 2). Diarrhea was reported at a higher frequency in the placebo arm at the AC meeting because of differences in rounding methods (6% compared to 5%).

The following table shows the most frequently reported TEAEs in pooled Studies 301 and 302.

Table 32. 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	700 (92)	281 (84)	1012 (92)	1993 (91)	945 (87)
Amyloid Related Imaging Abnormality-Edema/Effusion	223 (29)	58 (17)	387 (35)	668 (30)	29 (3)
Superficial Siderosis Of Central Nervous System	91 (12)	12 (4)	162 (15)	265 (12)	24 (2)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	141 (19)	35 (11)	212 (19)	388 (18)	71 (7)
Headache FDA B MQG	181 (24)	50 (15)	242 (22)	473 (22)	183 (17)
Hemorrhage FDA N MQG	82 (11)	49 (15)	154 (14)	285 (13)	123 (11)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	50 (7)	20 (6)	86 (8)	156 (7)	51 (5)
Fall	105 (14)	43 (13)	162 (15)	310 (14)	128 (12)
Diarrhea FDA N MQG	62 (8)	25 (8)	96 (9)	183 (8)	74 (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.

A review of the Hemorrhage FDA N MQG indicated that terms related to contusion contributed greatest to the group. Terms related to contusion were analyzed separately from the other terms that contributed to the group of Hemorrhage FDA N MQG as they were thought to be distinct from hemorrhage. After the terms were excluded, Hemorrhage FDA N MQG no longer met criteria for inclusion in the table. The terms related to contusion also did not meet criteria for inclusion in the table. The reader is referred to the [Appendix](#) for a list of preferred terms related to contusion and the frequency of Hemorrhage FDA N MQG after TEAEs related to contusion were excluded in pooled Studies 301 and 302.

The following table includes recommendations for groupings of terms for labeling purposes for pooled Studies 301 and 302 (see footnotes below the table for preferred terms included in the groupings).

Table 33. TEAEs with Incidence of at Least 2% and at Least 2% Higher in the Aducanumab 10 mg/kg Arm Compared to Placebo in Pooled Studies 301 and 302 with Groups of Preferred Terms Specific for Labeling.

Adverse Event	ADU 10 mg/kg N=1105 %	Placebo N=1087 %
Amyloid Related Imaging Abnormality-Edema	35	3
Amyloid Related Imaging Abnormality-H Superficial Siderosis	15	2
Amyloid Related Imaging Abnormality-H Microhemorrhages	19	7
Headache ^a	21	16
Confusion, Delirium, Altered Mental Status, Disorientation ^b	8	4
Fall	15	12
Diarrhea ^c	9	7

The portion of this table with the preferred terms was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD or grouping of preferred terms; POOLTR3 Reassigned A1 ^aGroup includes the preferred terms headache, head discomfort, migraine, and occipital neuralgia. ^bGroup includes confusion postoperative, confusional state, depressed level of consciousness, disorientation, delirium, disturbance in attention, mental impairment, mental status changes, and somnolence. ^cGroup includes diarrhea and infectious diarrhea.

The MQG of Headache FDA B was used for headache for the label. Preferred terms of post lumbar puncture syndrome and procedural headache were excluded from the label as the etiology for these events was not thought to be due to drug. For labeling purposes, the preferred terms sinus headache, tension headache, and thunderclap headache were also excluded from the MQG of Headache as these events occurred with equal or higher frequency on placebo compared to aducanumab 10 mg/kg. Although no subjects in the aducanumab 10 mg/kg arm reported the preferred term of migraine with aura, the term was included in the MQG of Headache as it was similar to the preferred term of migraine, which occurred with higher frequency in the aducanumab 10 mg/kg arm compared to placebo.

The MQG Confusion, Delirium, Altered Mental Status, Disorientation, Coma was used for the group Confusion, Delirium, Altered Mental Status, Disorientation. Coma was excluded from the group as the event, reported in one subject, could not be attributed with any degree of confidence to aducanumab per an email communication from Dr. Ranjit Mani, dated October 8, 2020. For labeling purposes, the preferred terms lethargy and transient global amnesia were also excluded as these events occurred with equal or higher frequency on placebo compared to aducanumab 10 mg/kg. Although no subjects in the aducanumab 10 mg/kg arm reported the preferred term altered state of consciousness, the term was included in the MQG as it was similar in meaning to other preferred terms in the group.

For labeling purposes, the name superficial siderosis of the CNS was changed to ARIA-H superficial siderosis as my review of the verbatim terms demonstrated that all the events were related to ARIA and the name Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits was changed to ARIA-H microhemorrhages as my review of the verbatim terms demonstrated that all the events were related to microhemorrhage.

Combined Placebo-Controlled and Long-Term Extension Periods

In the combined placebo-controlled and long-term extension periods of Study 302, the incidence of a subject experiencing at least one TEAE in the 10 mg/kg group was similar to the less than 10 mg/kg group (89% versus 88%, respectively). Similar results were seen in the combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 (incidence of 89% in both arms).

In the combined placebo-controlled and long-term extension periods of Study 302, the most frequent TEAEs in aducanumab 10 mg/kg group included infection, ARIA-E, headache, and ARIA-microhemorrhages and hemosiderin deposits, and they occurred with frequencies similar to those observed in the placebo-controlled portion of these trials (difference no greater than 2%).

Similar results were observed in the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302 and pooled Studies 103, 301, and 302. The reader is referred to [Appendix](#) for the incidence of TEAEs reported in the combined placebo-controlled and long-term extension periods of pooled Studies 301 and 302 and pooled Studies 103, 301, and 302.

Infection was among the most frequently reported TEAEs in the combined placebo-controlled and long-term extension periods of Study 302 but was not among the most frequently reported adverse events in the placebo-controlled period of Study 302 as the incidence in the placebo-controlled period in the aducanumab 10 mg/kg arm did not exceed placebo.

The incidence of fall was slightly higher in the combined placebo-controlled and long-term extension periods of Study 302 compared to the placebo-controlled period alone (16% versus 14%, respectively); however, this may be due to longer study follow-up.

The following table lists TEAEs in the combined placebo-controlled and long-term extension periods of Study 302 with an incidence of greater than 10% in the aducanumab 10mg/kg arm.

Table 34. TEAEs with an Incidence Greater than 10% in the Aducanumab 10mg/kg Group in the Combined Placebo-Controlled and Long-Term Extension Periods of Study 302

Adverse Event	ADU < 10 mg/kg N=674 n (%)	ADU 10 mg/kg N=679 n (%)
Total with at least one TEAE	592 (88)	602 (89)
Infection, All MQG	277 (41)	264 (39)
Amyloid Related Imaging Abnormality-Edema/Effusion	168 (25)	224 (33)
Headache FDA B MQG	147 (22)	142 (21)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	113 (17)	128 (19)
Arrhythmia FDA B MQG	89 (13)	111 (16)
Fall	93 (14)	109 (16)
Superficial Siderosis Of Central Nervous System	67 (10)	96 (14)
Vertigo FDA B MQG	68 (10)	91 (13)
Arthritis FDA B MQG	71 (11)	86 (13)
Hemorrhage FDA N MQG	82 (12)	78 (11)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; StudyID: 302; For preferred terms: Group by USUBJID, AEDECOD, POOLTR3 Reassigned B. For grouped terms: Group by USUBJID, MedDRA query group, POOLTR3 Reassigned B. MQG: MedDRA query group.

Analyses of TEAEs by Maximum Dose Received

In the placebo-controlled period of Study 302, the most frequently reported TEAEs by preferred term and maximum dose received in aducanumab 10 mg/kg group and with greatest difference from placebo included ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis of the central nervous system. The most common AEs and their frequencies analyzed in this way are similar to those identified when using the analysis by assigned dose, above. Similar findings are observed for the placebo-controlled periods of pooled Studies 301 and 302 and the combined placebo-controlled and long-term extension periods of Study 302 and pooled Studies 103, 301, and 302.

The frequency of TEAEs in the aducanumab 10 mg/kg arm by maximum dose received is similar to the frequency reported when analyzing incidences by assigned dose. Similar results were observed for in the placebo-controlled period of pooled Studies 301 and 302 and combined placebo-controlled and long-term extension periods of Study 302 and combined Studies 103, 301, and 302 in terms of most frequent TEAEs and frequency of those TEAEs. The reader is referred to the [Appendix](#) for tables on the incidence of TEAEs by maximum dose for these studies.

90-Day Safety Update

The incidence of a subject experiencing an AE in Study 304 reported through the 90-Day Safety Update was 9% (11/120). AEs reported were mild (6/120, 5%) or moderate (5/120, 4%) in severity. Reported preferred terms included: fatigue (n=2); cellulitis, diverticulitis, folliculitis, animal bite, arthropod sting, musculoskeletal pain, spinal pain, pruritis, rash, abdominal pain, constipation, tremor, anxiety (each once).

Reviewer comment: The low number of subjects in the safety population of Study 304 makes it difficult to draw further conclusions regarding TEAEs from this study.

8.4.6. Laboratory Findings

Overall, I did not identify a safety signal in a review of laboratory findings or of TEAEs belonging to the SOC Investigations.

I reviewed mean change from baseline, outlier shift analyses, and outlier analyses of potentially clinically significant changes in the applicant's response dated November 11, 2020, to an information request dated November 4, 2020 and analyses performed by Senior Clinical Analyst Dr. Rui Li. I also reviewed TEAEs belonging to the system organ classes (SOC) Investigation related to laboratory findings.

For hematology-related labs, chemistry-related labs, and urinalysis, I did not identify any clinically significant changes in analyses of mean change from baseline, outlier shift analyses, or outlier analyses of potentially clinically significant laboratory values because of small magnitudes of difference. The maximum differences between aducanumab 10 mg/kg and placebo arms in Study 302 were approximately 2% for hematology-related labs (shift to high for erythrocyte mean corpuscular volume (14.9% versus 13.0% and shift to low for lymphocytes (16.7% versus 14.8%, respectively)), 4% for chemistry-related labs (shift to low for glucose (32.0% versus 27.7%, respectively)), and 2% for urinalysis (shift to high for protein (31.2% versus 29.5%, respectively) between placebo and aducanumab 10 mg/kg arms. Pooled Studies 301 and 302 showed similar findings.

Laboratory analyses in Study 103 showed maximum differences between aducanumab 10 mg/kg arm and placebo in mean change from baseline, outlier shift analyses, and outlier analyses of potentially clinically significant laboratory values of approximately 25% for hematology-related labs (erythrocytes $\leq 3.5 \times 10^{12}/L$ (25.8% versus 2.1%, respectively)), 8% for chemistry-related labs (shift to high for gamma glutamyl transferase (22% versus 14%, respectively)), and 10% for urine analysis (shift to high for occult blood (16% versus 6.7%, respectively)). The difference was greater than that in Studies 301 and 302; however, this was likely due in part to the smaller number of subjects in each treatment arm in Study 103, and greater variability. I did not find the difference between the aducanumab 10 mg/kg arm and placebo for shift to high for gamma glutamyl transferase and shift to high for occult blood in the

urine analysis to be significant as the difference in percentages was a difference of approximately two subjects.

For aducanumab-treated subjects who had erythrocyte counts of less than or equal to $3.5 \times 10^{12}/L$, I did not establish a role for aducanumab for occurrence of this shift due to potential confounding factors or a lack of information. Five subjects had confounding or contributory factors including gastritis in the setting of pancreatic bile duct obstruction (b) (6), adenocarcinoma of the colon (b) (6), colitis and diverticulosis (b) (6), (b) (6) post sinus surgery status (b) (6) and diverticular perforation (b) (6). In the remaining four subjects, I did not identify a role due to a lack of information (b) (6).

In my review of TEAEs belonging to the system organ classes (SOC) Investigations and related to laboratory findings, I note that the aducanumab 10 mg/kg did not have an excess of TEAEs compared to placebo in Study 302 (incidence of 4% versus 6.2%, respectively). See the [Appendix](#) for a list of preferred terms related to laboratory findings. The following table shows the incidence of a subject experiencing at least one TEAE belonging to the SOC Investigations related to laboratory findings in the placebo-controlled period of Study 302.

Table 35. Incidence of A Subject Experiencing at Least One TEAE Belonging to the SOC Investigations Related to Laboratory Findings in Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
18 (4.9)	9 (5.1)	22 (4)	49 (4.5)	34 (6.2)

This table was created by the reviewer using ISS ADAE dataset, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; AESOC: Investigations; preferred terms related to laboratory findings (see the [Appendix](#)). StudyID: 302; Group by USUBJID, POOLTR3 Reassigned A1

Pooled Studies 301 and 302 had findings related to TEAEs belonging to the SOC Investigations similar to those in Study 302 alone in the aducanumab 10 mg/kg and placebo arms (4.1% and 6.6%, respectively).

The placebo-controlled and long-term extension periods of Study 302 had findings related to TEAEs belonging to the SOC Investigations related to laboratory findings similar to those in the placebo-controlled period of Study 302 alone in the aducanumab 10 mg/kg arm (4.9% versus 4%, respectively).

The placebo-controlled and long-term extension periods of Studies 103, 301 and 302 had a similar incidence of TEAEs belonging to the SOC Investigations in the aducanumab 10 mg/kg arm compared to Study 302 alone (5.7% versus 4.9%).

Hepatic-Related Events

I did not identify a safety signal for hepatic-related events in an analysis of maximum post-baseline liver enzyme values, hepatic-related adverse events, or Hy's law cases in Studies 301 and 302.

In Study 302, I note a similar incidence of maximum post-baseline values for liver enzymes in aducanumab 10 mg/kg arm compared to placebo (difference no greater than 0.4%). The following table shows the maximum post-baseline values for liver enzymes in the placebo-controlled period of Study 302.

Table 36. Maximum Post-Baseline Values For Liver Enzymes in the placebo-controlled period of Study 302

Lab Test	Cut Point	3 mg/kg (N = 369)	6 mg/kg (N = 175)	10 mg/kg (N = 547)	All Aducanumab (N = 1091)	Placebo (N = 547)
ALT	> 3*ULN	2 / 361 (0.6)	0 / 170 (0.0)	3 / 532 (0.6)	5 / 1063 (0.5)	3 / 541 (0.6)
	> 5*ULN	2 / 361 (0.6)	0 / 170 (0.0)	3 / 532 (0.6)	5 / 1063 (0.5)	1 / 541 (0.2)
	> 10*ULN	0 / 361 (0.0)	0 / 170 (0.0)	0 / 532 (0.0)	0 / 1063 (0.0)	0 / 541 (0.0)
AST	> 3*ULN	2 / 361 (0.6)	1 / 170 (0.6)	2 / 532 (0.4)	5 / 1063 (0.5)	3 / 541 (0.6)
	> 5*ULN	1 / 361 (0.3)	0 / 170 (0.0)	0 / 532 (0.0)	1 / 1063 (<0.1)	0 / 541 (0.0)
	> 10*ULN	0 / 361 (0.0)	0 / 170 (0.0)	0 / 532 (0.0)	0 / 1063 (0.0)	0 / 541 (0.0)
ALP	> 1.5*ULN	1 / 361 (0.3)	0 / 170 (0.6)	3 / 532 (0.9)	7 / 1063 (0.7)	1 / 541 (0.6)
BILI	> 2*ULN	0 / 361 (0.0)	0 / 170 (0.0)	1 / 532 (0.0)	1 / 1063 (<0.1)	1 / 541 (0.2)

This table was modified by the reviewer using analyses by Senior Clinical Analyst Dr. Rui Li.

I note similar findings of similar incidence of maximum post-baseline values for liver enzymes between aducanumab 10 mg/kg arm and placebo in Studies 301 and 302 compared to Study 302 alone (differences no greater than 0.2% between aducanumab 10 mg/kg and placebo).

In Study 103, I note that for the same analyses of maximum post-baseline values for liver enzymes, incidences in the aducanumab 10 mg/kg arm did not exceed placebo.

I note similar incidences of TEAEs related to liver investigations in the aducanumab 10 mg/kg and placebo arms in Studies 302 and Studies 301 and 302 (maximum difference no greater than 0.5%). Preferred terms included blood alkaline phosphatase increased, hepatic enzyme increased, blood bilirubin increased, liver function test increased, alanine aminotransferase

increased, bilirubin conjugated increased, aspartate aminotransferase increased, liver function test abnormal, and transaminases increased.

With regards to Hy's law cases in Studies 301 and 302, one aducanumab-assigned subject had elevated hepatic-related labs that met Hy's law criteria (elevation of AST or ALT of 3-fold or higher than the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal without initial findings of cholestasis). Upon review of the narrative, the etiology appeared likely due to gallstones (b) (6). The subject was an 80-year old man with history of hypertension who developed elevated liver enzymes on Day 339 after receiving 13 doses of aducanumab. On Day 344, he met Hy's law criteria when his ALT was 163 U/L (reference range: 0 to 41 U/L), AST was 73 U/L (reference range: 0 to 37 U/L), and his total bilirubin was 53 umol/L (reference range: 0 to 21 umol/L). His alkaline phosphatase was also elevated at 269 IU/L (reference range: 40 to 129 IU/L) and his direct bilirubin at 38 umol/L (reference range not provided). His liver enzymes subsequently trended downward on Day 357. On Day 391 the AE of choledocholithiasis was reported and the subject underwent stone extraction, stent placement, and cholecystectomy within the month. By Day 507, his ALT, AST, alkaline phosphatase, and total bilirubin had returned to normal values. Later in the study, the subject developed the SAE of pancreatic cancer (Day 952).

I did not identify any subjects that met Hy's Law criteria in Studies 101, 102, 103, 104, or 205.

I did not identify any SMQs related to hepatic safety with an incidence above 0.2% in the aducanumab 10 mg/kg arm compared to placebo in Study 302 and Studies 301 and 302.

My review agrees with the findings of the applicant who did not identify any significant trends in laboratory findings with aducanumab in Studies 301 and 302 in analyses of mean values, change from baseline values, outlier shift analysis, outlier analysis of potentially clinically significant laboratory values, and incidence of laboratory-related AEs.

8.4.7. Vital Signs

Overall, I did not identify a safety signal in an analysis of vital signs. Systolic blood pressure > 160 mm Hg was observed at a higher frequency in aducanumab 10 mg/kg arm compared to placebo in Study 302 (12.3% versus 10.1%, respectively) and diastolic blood pressure > 90 mmHg occurred at a higher frequency in aducanumab 10 mg/kg arm compared to placebo in Study 302 (20.9% versus 17.4%, respectively). In pooled Studies 301 and 302, these differences were less than 2% with systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mmHg between the aducanumab 10 mg/kg arm and placebo. An analysis of TEAEs and SAEs related to elevated blood pressure showed similar incidences between the aducanumab 10 mg/kg and placebo arms in Study 302 and pooled Studies 301 and 302.

For analysis of vital signs, I reviewed mean change from baseline, outlier shift analyses of potentially clinically significant values, and shift analyses from normal to high and normal to low in the applicant's response dated November 11, 2020, to an information request dated November 4, 2020 and the applicant's response dated November 30, 2020, to an information request dated November 23, 2020. I also reviewed TEAEs belong to the system organ classes (SOC) Investigation related to vital signs.

Blood Pressure

A review of mean change from baseline values in blood pressure values showed overall that blood pressure was lower across all study visits in comparison to baseline in all treatment arms in Study 302 and pooled Studies 301 and 302. In Study 302 relative to placebo, systolic blood pressure in the aducanumab 10 mg/kg arm decreased least at Week 68 (difference from placebo of 1.7 mmHg). By the end of the placebo-controlled period (Week 76), the difference in systolic blood pressure in the aducanumab 10 mg/kg arm from placebo had lessened to 0.4 mmHg. In Study 302 relative to placebo, diastolic blood pressure in the aducanumab 10 mg/kg arm decreased least at Week 52 (difference from placebo of 1.1 mmHg). By the end of the placebo-controlled period (Week 76), the difference had lessened (difference from placebo of 0.6 mmHg). Similar mean systolic and diastolic blood pressures were observed at baseline in the aducanumab 10 mg/kg and placebo arms (difference of no higher than 0.5 mmHg).⁷

Similar findings were observed in pooled Studies 301 and 302.

Systolic blood pressure > 160 mmHg was observed at a higher frequency in the aducanumab 10 mg/kg arm compared to placebo in Study 302 (12.3% versus 10.1%, respectively). Similar findings of systolic blood pressure > 160 mmHg were observed in pooled Studies 301 and 302 between the aducanumab 10 mg/kg arm and placebo at any point although the difference was less than 2% (13.0% versus 11.4%, respectively). The aducanumab 10 mg/kg and placebo arms had a similar incidence of systolic blood pressure > 160 mmHg at baseline in Study 302 and pooled Studies 301 and 302 (difference no higher than 0.3%).

An excess in the incidence of systolic blood pressure > 140 mmHg was not observed in aducanumab 10 mg/kg arm relative to placebo in Study 302 or pooled Studies 301 and 302.

A similar incidence of subjects with systolic blood pressure > 180 mmHg in the aducanumab 10 mg/kg arm and placebo was observed in Study 302 and pooled Studies 301 and 302 and noted by the applicant in a November 30, 2020, response to an information request dated November 23, 2020 (difference of no greater than 0.4%).

⁷ Data was taken from the applicant's response dated November 11, 2020, to an information request dated November 4, 2020, page 167 and 175.

Diastolic blood pressure > 90 mmHg was observed at a higher frequency in the aducanumab 10 mg/kg arm compared to placebo in Study 302 (20.9% versus 17.4%, respectively). A higher incidence of diastolic blood pressure > 90 mmHg was also seen in pooled Studies 301 and 302 in the aducanumab 10 mg/kg arm compared to placebo although the difference was less than 2% (18.9% versus 17.9%, respectively). The aducanumab 10 mg/kg and placebo arms had a similar incidence of diastolic blood pressure > 90 mmHg at baseline in Study 302 and pooled Studies 301 and 302 (difference no higher than 0.3%).

An excess in the incidence of diastolic blood pressure > 100 mmHg was not observed in aducanumab 10 mg/kg arm relative to placebo in Study 302 or pooled Studies 301 and 302.

The combined placebo-controlled and long term extension periods of Study 302 and pooled Studies 103, 301, and 302 showed similar findings in incidence of potentially clinically significant blood pressure values in the aducanumab 10 mg/kg arm compared to Study 302.

The placebo-controlled period of Study 103 did not show an excess of potentially clinically significant values with blood pressure in the aducanumab 10 mg/kg arm compared to placebo.

The following table shows the incidence of subjects with potentially clinically significant values for blood pressure in Study 302.

Table 37. Potentially Clinically Significant Values for Blood Pressure in Study 302

PCS category	ADU 3 mg/kg N=369 %	ADU 6 mg/kg N=175 %	ADU 10 mg/kg N=547 %	ALL ADU N=1091 %	Placebo N=547 %
SBP < 90 mmHg	0.8	1.2	1.1	1.0	2.2
SBP > 140 mmHg	62.2	60.5	60.3	61.0	62.8
SBP > 160 mmHg	15.2	12.2	12.3	13.3	10.1
DBP < 50 mmHg	5.2	2.3	3.1	3.7	3.1
DBP > 90 mmHg	25.3	14.5	20.9	21.4	17.4
DBP > 100 mmHg	2.7	0.6	2.2	2.1	2.6

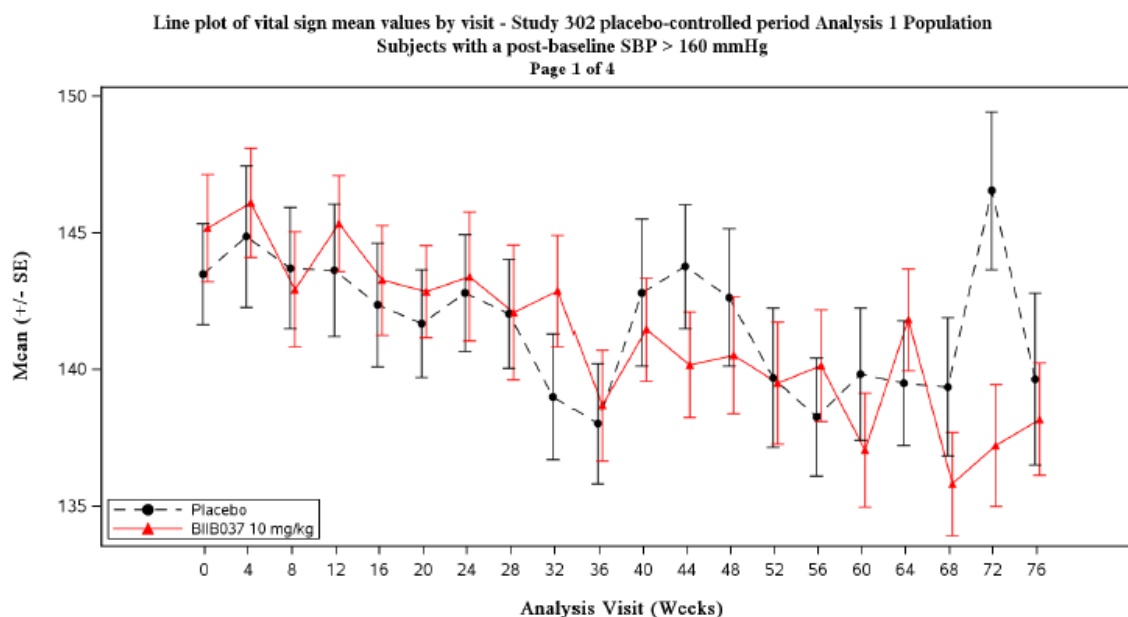
This table was created by the reviewer using data from analyses by Senior Clinical Analyst Dr. Rui Li. SBP: systolic blood pressure, DBP: diastolic blood pressure, PCS: potentially clinically significant.

In a November 30, 2020, response to an information request dated November 23, 2020, the applicant submitted line plots of mean systolic blood pressure values in subjects with systolic blood pressure > 160 mmHg and mean diastolic blood pressure in subjects with diastolic blood

pressure > 90 mmHg across study visits which showed similar mean blood pressure values between placebo and aducanumab 10 mg/kg arm across most study visits.

The following two figures of mean systolic blood pressure in subjects with systolic blood pressure > 160 mmHg and mean diastolic blood pressure in subjects with diastolic blood pressure > 90 mmHg in Study 302 were submitted by the applicant. Similar findings were observed in pooled Studies 301 and 302 (see the [Appendix](#)).

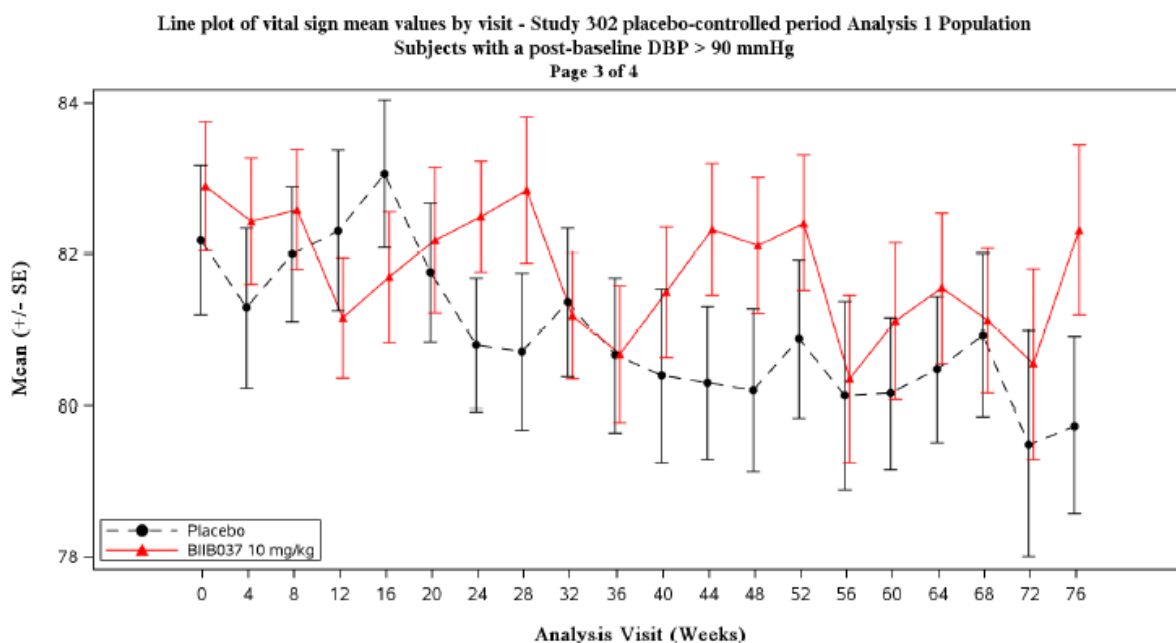
Figure 2. Line Plot of Mean Systolic Blood Pressure in Subjects with a Post-Baseline Systolic Blood Pressure of > 160 mmHg Across Study Visits in Study 302.



Abbreviation: SE = standard error, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

The above figure was submitted by the applicant in an information response dated November 30, 2020, to an information request dated November 23, 2020 (page 9).

Figure 3. Line Plot of Mean Diastolic Blood Pressure in Subjects with a Post-Baseline Diastolic Blood Pressure of > 90 mmHg Across Study Visits in Study 302.



Abbreviation: SE = standard error, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

The above figure was submitted by the applicant in an information response dated November 30, 2020, to an information request dated November 23, 2020 (page 11).

TEAEs belonging to the MQG of Hypertension, Blood Pressure Increased were reported at a higher incidence in the aducanumab 10 mg/kg and placebo arms in Study 302. In Study 302, Hypertension, Blood Pressure Increased occurred in 6.8% of the aducanumab 10 mg/kg arm compared to 5.9% of placebo. In pooled Studies 301 and 302, TEAEs of the MQG of Hypertension, Blood Pressure Increased were reported with similar frequency between the aducanumab 10 mg/kg arm and placebo (5.6% and 5.7%, respectively).

The following table shows the incidence of TEAEs related to the MQG of Hypertension, Blood Pressure Increased in Study 302.

Table 38. TEAEs related to MQG of Hypertension, Blood Pressure Increased in Study 302

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
20 (5.4)	10 (5.7)	37 (6.8)	67 (6.1)	32 (5.9)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y;

MQG=Hypertension, Blood Pressure Increased; StudyID=302; Group by USUBJID, MedDRA query group; POOLTR3 Reassigned A1. MQG: MedDRA query group.

No TEAEs belonging to the MQG of Hypertension, Blood Pressure Increased led to study withdrawal or treatment discontinuation in Studies 103, 301, or 302.

The incidence of SAEs belonging to the MQG of Hypertension, Blood Pressure Increased in the aducanumab 10 mg/kg arm did not exceed placebo in Study 302 or pooled Studies 301 and 302. In Study 302, SAEs occurred in no subjects in the aducanumab 10 mg/kg arm versus 3 subjects on placebo (0.5%). In Pooled Studies 301 and 302, SAEs occurred in 0.1% of the aducanumab 10 mg/kg arm (1 subject) compared to 0.4% of placebo (4 subjects).

In a review of narratives related to SAEs and the MQG of Hypertension, Blood Pressure Increased, I did not establish a role for aducanumab because of potential confounding factors. Three SAEs belonging to the MQG of Hypertension, Blood Pressure Increased were reported in aducanumab-treated subjects in Studies 103, 301, and 302. All three subjects had a history of hypertension. One subject with the preferred term of blood pressure increased had as potential confounding factor uncontrolled knee pain (b) (6). A second subject who reported hypertensive emergency had infection as a potential confounding factor given symptoms of increased sputum production and consolidation on a chest x-ray (b) (6). In the third case, a role for aducanumab appeared unlikely given resolution of hypertension over the course of a day without initiation of an antihypertensive agent (b) (6).

Similar frequencies were seen between the aducanumab 10 mg/kg arm and placebo arms in a review of TEAEs with preferred terms blood pressure abnormal, blood pressure decreased, blood pressure orthostatic abnormal in Study 302, pooled Studies 301 and 302, and Study 103 (difference no greater than 1.1%). Similar findings were seen in the combined placebo-controlled and long-term extension periods of Study 302 and pooled Studies 103, 301, and 302.

Reviewer comment: Overall, based on a review of mean blood pressure values, potentially clinically significant blood pressure values, and TEAEs and SAEs related to elevated hypertension, I did not identify a safety signal with elevated blood pressure.

Other Vital Signs

I did not identify any clinically significant trends in mean change from baseline for heart rate, temperature, weight, and respiratory rate because of the small magnitude of difference between aducanumab 10 mg/kg and placebo arms in the placebo-controlled periods of Studies 301 and 302. A larger magnitude of difference was seen between aducanumab 10 mg arm and placebo in Study 103 and at later visit dates during the long-term extension periods of Studies 301 and 302 likely in part because of smaller treatment arms.

I did not identify any clinically significant trends in outlier shift analyses of potentially clinically significant vital signs for heart rate, temperature, weight, and respiratory rate because of small magnitudes of difference in incidence between aducanumab 10 mg/kg and placebo arms in the placebo-controlled period of Study 302 and in pooled Studies 301 and 302. The greatest difference in incidence where the aducanumab 10 mg/kg arm exceeded placebo was with temperature $<36.0^{\circ}\text{C}$ in pooled Studies 301 and 302 (31.7% versus 29.2%).

Larger magnitudes of difference were seen between the aducanumab 10 mg/kg arm and placebo in Study 103 in potentially clinically significant trends likely in part because of smaller treatment arms.

The combined placebo-controlled and long-term extension periods of Study 302 had similar incidence of potentially clinically significant vital signs outliers as compared to the placebo-controlled period. The maximum difference in incidence was no greater than 4% in the aducanumab 10 mg/kg arm, which occurred with weight decrease $\leq 7\%$. The difference may in part be due to the longer study follow-up.

In Study 302 and pooled Studies 301 and 302, similar frequencies were seen between aducanumab 10 mg/kg arm and placebo arms in a review of TEAEs related to vital signs with preferred terms body temperature decreased, body temperature increased, heart rate abnormal, heart rate decreased, heart rate increased, heart rate irregular, weight decreased, and weight showed (difference no greater than 0.4%). Similar findings were seen in the placebo-controlled period of Study 103 and combined placebo-controlled and long-term extension periods of Study 302 and pooled Studies 103, 301, and 302.

8.4.8. Electrocardiograms (ECGs)

Overall, I did not identify a safety signal with ECGs based on a review of qualitative ECG parameters in Studies 301 and 302 and qualitative and quantitative ECG parameters in Study 102.

Studies 301 and 302

The applicant evaluated ECGs in Studies 301 and 302 by calculating the incidence of subjects who had shifts from normal or missing ECGs at baseline to abnormal ECGs postbaseline. The applicant categorized postbaseline abnormal ECGs as representing an adverse event or not. When calculating the incidence of abnormal ECGs with or without adverse events, subjects were only counted once under the most severe category. Quantitative ECG parameters were not measured in Studies 301 and 302.

Overall, I considered the applicant's approach to be acceptable.

In the placebo-controlled period of Study 302, the incidence of subjects with shift to abnormal

ECG was similar between aducanumab 10 mg/kg- and placebo-assigned subjects. The following table shows subjects with shift to abnormal ECG in the placebo-controlled period of Study 302. Similar results were observed for the placebo-controlled period of pooled Studies 301 and 302 and in the combined placebo-controlled and long-term extension periods of 302 and pooled Studies 301 and 302.

Table 39. Subjects with Shift to Abnormal ECG in Placebo-Controlled Period of Study 302

Shift	ADU 3 mg/kg N=223 n (%)	ADU 6 mg/kg N=92 n (%)	ADU 10 mg/kg N=329 n (%)	ALL ADU N=644 n (%)	Placebo N=320 n (%)
Shift to Abnormal, Adverse Event	4 (1.8)	4 (4.3)	7 (2.1)	15 (2.3)	5 (1.6)
Shift to Abnormal, Not Adverse Event	102 (45.7)	36 (39.1)	135 (41)	273 (42.4)	129 (40.3)

This table was created by the reviewer using ISS ADEG, POOLC=POOLA1; BASESEC=inverse of Abnormal; ABLFL=Inverse of Yes; for Shift to Abnormal Adverse Event: AVALC=Abnormal, Adverse Event; for Shift to Abnormal, not Adverse Event: AVALC=Abnormal, Not Adverse Event; Abnormal Adverse Event Flag POOLA1: Inverse of 1; StudyID: 302; Group by USUBJID, POOLTR3reassigned; tabulated on POOLTR3reassigned

Study 102

I reviewed quantitative ECG parameters from Study 102 because quantitative ECG measurements were not obtained in Studies 103, 301, or 302.

In Study 102, 28 healthy subjects were randomized to aducanumab 420 mg subcutaneously or aducanumab 6 mg/kg intravenously (IV). The applicant evaluated mean change from baseline for the following ECG parameters: heart rate; PR interval; QRS interval; QT interval; QT interval using Fridericia's Correction (QTcF). The applicant also evaluated QTcF interval outliers and calculated the incidence of subjects who had shifts from normal ECG at baseline to abnormal ECGs postbaseline.

I did not find a clinically significant difference in change from baseline for heart rate, PR interval, QRS interval, QT interval, and QTcF interval because of small magnitudes of difference seen. The following tables show the mean change from baseline for heart rate, PR interval, QRS interval, QT interval, and QTcF interval for aducanumab 6 mg/kg IV in Study 102 by study visit.

Table 40. Change from Baseline for Heart Rate for Subjects Treated with Aducanumab 6 mg/kg in Study 102.

Visit	Parameters	Change from Baseline (beats per minute)
1 hour Postdose (N=14)	Mean (SD)	-1.9 (8.7)

Visit	Parameters	Change from Baseline (beats per minute)
	Median	-2.0
	Min, Max	-23, 10
24 hours Postdose (N=14)	Mean (SD)	4.2 (9.1)
	Median	8.0
	Min, Max	-19, 12
85 days Postdose (N=13)	Mean (SD)	-0.8 (9.1)
	Median	2.0
	Min, Max	-22, 10

This table was created by the reviewer using Study 102 ADEG, SAFFL=Yes; PARAM=Mean HR; AVISIT=Day 1, Day 2, and Day 85; TRTA=IV.

Table 41. Change from Baseline for PR Interval for Subjects Treated with Aducanumab 6 mg/kg in Study 102.

Visit	Parameters	Change from Baseline (msec)
1 hour Postdose (N=14)	Mean (SD)	-0.9 (9.3)
	Median	0.0
	Min, Max	-17, 20
24 hours Postdose (N=14)	Mean (SD)	-4.1 (9.7)
	Median	-5.0
	Min, Max	-18, 14
85 days Postdose (N=13)	Mean (SD)	-4.8 (12.0)
	Median	-3.0
	Min, Max	-28, 12

This table was created by the reviewer using Study 102 ADEG, SAFFL=Yes; PARAM=PR Interval; AVISIT=Day 1, Day 2, and Day 85; TRTA=IV.

Table 42. Change from Baseline for QRS Interval for Subjected Treated with Aducanumab 6 mg/kg in Study 102.

Visit	Parameters	Change from Baseline (msec)
1 hour Postdose (N=14)	Mean (SD)	-0.3 (7.7)
	Median	0.5
	Min, Max	-21, 15
24 hours Postdose (N=14)	Mean (SD)	-0.1 (5.2)
	Median	-0.5
	Min, Max	-11, 8
85 days Postdose (N=13)	Mean (SD)	-0.9 (5.4)
	Median	-1.0

Visit	Parameters	Change from Baseline (msec)
	Min, Max	-5, 13

This table was created by the reviewer using Study 102 ADEG, SAFFL=Yes; PARAM=QRS Interval; AVISIT=Day 1, Day 2, and Day 85; TRTA=IV.

Table 43. Change from Baseline for QT Interval for Subjects Treated with Aducanumab 6 mg/kg in Study 102.

Visit	Parameters	Change from Baseline (msec)
1 hour Postdose (N=14)	Mean (SD)	3.8 (11.2)
	Median	4.0
	Min, Max	-17, 21
24 hours Postdose (N=14)	Mean (SD)	-14.9 (12.4)
	Median	-15.5
	Min, Max	-37, 4
85 days Postdose (N=13)	Mean (SD)	3.8 (20.0)
	Median	1.0
	Min, Max	-29, 54

This table was created by the reviewer using Study 102 ADEG, SAFFL=Yes; PARAM=QT Interval; AVISIT=Day 1, Day 2, and Day 85; TRTA=IV.

Table 44. Change from Baseline for QTcF Interval for Subjects Treated with Aducanumab 6 mg/kg in Study 102.

Visit	Parameters	Change from Baseline (msec)
1 hour Postdose (N=14)	Mean (SD)	-0.1 (11.1)
	Median	3.0
	Min, Max	-25, 13
24 hours Postdose (N=14)	Mean (SD)	-7.5 (13.4)
	Median	-3.0
	Min, Max	-39, 13
85 days Postdose (N=13)	Mean (SD)	2.5 (9.4)
	Median	2.0
	Min, Max	-12, 18

This table was created by the reviewer using Study 102 ADEG, SAFFL=Yes; PARAM=QTcF; AVISIT=Day 1, Day 2, and Day 85; TRTA=IV.

I reviewed the QTcF intervals and did not identify any intervals greater than 440 msec.

The incidence of subjects with shift to abnormal ECG was 23.1% in the IV aducanumab group (3/13). The applicant did not identify any adverse events occurring in subjects with shift to abnormal ECG by ECG interpretation. Comparison with placebo was not possible as the study

lacked a placebo group.

Overall, I did not identify a safety signal evaluating ECG parameters in Study 102. Applicability of the results of this study is limited because of the low number subjects exposed to IV aducanumab (n=14), difference in doses studied compared to proposed dose (6 mg/kg versus 10 mg/kg respectively), and differences in the study population (Study 102 was conducted in healthy subjects).

8.4.9. QT

In Study 102, where ECG parameters were measured quantitatively, analyses of QT and QTcF intervals showed no clinically significant findings (see discussion above). In accordance with ICH E14 guidelines for monoclonal antibodies that have a low likelihood of direct ion channel interactions, a dedicated QT study was not conducted.

8.4.10. Immunogenicity

Overall, the number of aducanumab-treated subjects in the placebo-controlled and long-term extension periods of Studies 301 and 302 with treatment emergent anti-aducanumab antibody (ADA) responses was low (0.6%, (15/2689)). Because of the low number of subjects with treatment emergent ADA responses, I did not find the database to be sufficient in assessing the immunogenicity with aducanumab.

The immunogenicity of aducanumab was evaluated using an in vitro assay for the detection of binding anti-aducanumab antibodies. In the placebo-controlled periods of Studies 301 and 302, ADA samples were collected at baseline, Day 1, Weeks 24, 32, 56, 78, and at the follow up visit 18 weeks after final dose. In the long-term extension period, ADA samples were collected at Weeks 80, 104, 128, 152, 182, 338, and at the follow-up visit 18 weeks after the final dose.

Reviewer comment: The Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019) recommends obtaining pre-treatment samples, samples at multiple intervals throughout the trial, and samples at approximately five half-lives after last exposure (~18 weeks given aducanumab's half-life of 25 days). The Guidance also recommends sampling at 9 to 14 days after the first exposure to detect an IgM response. The applicant sampled on Day 1 and then at Week 24, which would allow for detection of an IgG response, but not an IgM response.

In a response dated September 30, 2020, to an information request dated September 23, 2020, the applicant noted that a neutralizing antibody assay was not developed as the FDA had agreed with the applicant that subjects with neutralizing anti-aducanumab antibodies could be identified by correlating anti-aducanumab antibody positivity to changes in aducanumab exposure and efficacy in treated subjects.

A subject was considered to be ADA positive if the subject screened positive for anti-aducanumab antibody at any point. Treatment-emergent ADA responses were defined as a positive ADA response in a subject who had a negative response at baseline or in a subject who had a positive ADA response at baseline and had more than a 2-fold increase in their titer compared to baseline. Treatment-emergent ADA responses were further classified by the applicant as transient positive if a subject had only a single positive evaluation (excluding the last assessment), or if more than 1 positive evaluation occurred within < 112 days. Responses were classified as persistent positive if a subject had more than one positive evaluation occurring $\geq$ 112 days apart or if the subject had a positive evaluation at the last timepoint with no further negative results available.

In the placebo-controlled period of Study 302, the number of subjects with a treatment emergent ADA response was low. Seven aducanumab-assigned subjects and two placebo-assigned subjects had a treatment-emergent ADA response (7/1062 (0.7%) and 2/542 (0.4%), respectively). Aducanumab-treated subjects had a higher incidence of treatment emergent ADA responses compared to placebo (0.7% versus 0.4%, respectively).

Two of seven aducanumab-assigned subjects and one of two placebo-assigned subjects had persistent positive responses (2/1062 (0.2%) and 1/542 (0.2%), respectively).

The following table shows subjects who developed a treatment-emergent ADA response by visit week in the placebo-controlled period of Study 302.

Table 45. Number of Subjects with a Treatment Emergent ADA Response in Study 302.

Visit	ADU 3 mg/kg N=362 n (%)	ADU 6 mg/kg N=170 n (%)	ADU 10 mg/kg N=530 n (%)	ALL ADU N=1062 n (%)	Placebo N=542 n (%)
Week 24	2 (0.6)	1 (0.6)	1 (0.2)	4 (0.4)	2 (0.4)
Week 32	0	1 (0.6)	0	1 (0.1)	2 (0.4)
Week 56	0	1 (0.6)	1 (0.2)	2 (0.2)	1 (0.2)
Week 78	0	0	1 (0.2)	1 (0.1)	0
Week 80	0	0	0	0	0

This table was created by the reviewer using ISS ADAB, POOLC=POOLA1; PIMMUFL=Y; TEMP01FL=Y; StudyID: 302; Grouped on AVISIT, POOLTR3reassigned; Tabulated on POOLTR3reassigned, AVISIT

In the placebo-controlled periods of Studies 301 and 302, the number of subjects with a treatment emergent ADA response was low. Ten aducanumab-assigned subjects and two placebo-assigned subjects had a treatment-emergent ADA response (10/2151 (0.5%) and 2/1069 (0.2%), respectively).

Two of ten aducanumab-assigned subjects and one of two placebo-assigned subjects had persistent positive responses (2/2151 (0.1%) and 1/1069 (0.1%), respectively), with a pattern similar to that in Study 302 alone (with one patient having a positive response at week 80).

The combined placebo-controlled and long-term extension periods of Study 302 had the same incidence of subjects developing a treatment-emergent ADA response as compared to the placebo-controlled period of Study 302 (0.7%, 9/1312). Persistently positive treatment-emergent ADA responses occurred at a similar incidence in the combined placebo-controlled and long-term extension periods of Study 302 in the all-aducanumab treated group compared to the placebo-controlled period of Study 302 alone (0.3% and 0.2%, respectively).

In the combined placebo-controlled and long-term extension periods of Study 302, treatment emergent ADA responses were seen through Week 78.

The combined placebo-controlled and long-term extension periods of Studies 301 and 302 had similar findings in incidence of subjects developing a treatment-emergent ADA response as compared to Study 302 alone (0.6% (15/2689) versus 0.7% (9/1312), respectively). Additionally, findings were similar to those of Study 302 alone with development of treatment-emergent ADA responses by study visit, with occurrence through Week 128. Subjects were exposed to up to 180 weeks of aducanumab 10 mg/kg once monthly.

The incidence of developing a treatment-emergent ADA response among aducanumab-assigned subjects was higher in the placebo-controlled period of Study 103 compared to Study 302 (5.4% (8/147) versus 0.7% (7/1062), respectively). This may be in part due to the difference in study design as most subjects in Study 103 received fixed doses of aducanumab compared to titrated dosing in the Phase 3 studies. Treatment-emergent ADA responses occurred at higher incidence in aducanumab-treated subjects compared to placebo-treated subjects in Study 103 (5.4% versus 4.3%, respectively). Treatment-emergent ADA responses were seen through Week 52 of the placebo-controlled period of Study 103.

The incidence of treatment emergent ADA responses was higher in the combined placebo-controlled and long-term extension periods of Study 103 compared to the placebo-controlled period of Study 103 alone (8.7% (16/184) versus 5.4% (8/147), respectively). In the placebo-controlled and long-term extension period of Study 103, treatment-emergent ADA responses were seen through Week 332.

Because of the few treatment-emergent ADA responses observed, the frequency of TEAEs overall, and the frequency of TEAEs in ADA-positive patients (observed in all 7 aducanumab treated patients and both placebo-treated subjects in study 302, for example), it is not possible to determine the role, if any, of ADA antibodies in the occurrence of TEAEs.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Intracranial Hemorrhage

Intracranial hemorrhage was a topic of special interest as ARIA events were the most frequently reported adverse event in Studies 301 and 302.

Overall, I note a similar incidence of AEs related to intracranial hemorrhage in aducanumab- and placebo-assigned subjects in Studies 301 and 302. SAEs of intracranial hemorrhage in Study 302 occurred in fewer than 1% of subjects. In pooled Studies 301 and 302, the incidence of a subject experiencing an SAE of intracranial hemorrhage was 0.2% in the aducanumab 10 mg/kg arm compared to 0.3% on placebo. The incidence of a subject experiencing an SAE of intracranial hemorrhage in Study 302 in aducanumab 10 mg/kg arm was 0.2%, compared to 0 on placebo. SAEs of intracranial hemorrhage were frequently potentially related to ARIA.

My analysis for the MQG of Intracranial Hemorrhage includes the preferred terms cerebral hemorrhage, cerebral hematoma, subarachnoid hemorrhage, and hemorrhage intracranial. Terms that are frequently due to an underlying traumatic event, such as subdural hematoma and subdural hemorrhage, were excluded from my analysis. Terms selected for my analysis were based on a discussion with Dr. Ranjit Mani by email (October 8, 2020).

Of note, the applicant's event numbers differ slightly in comparison to FDA numbers. The applicant's group of intracranial hemorrhage, titled CNS Hemorrhage, includes subdural hematoma and subdural hemorrhage, which were excluded in my analyses. In addition, the applicant's calculation do not include FDA's reassignment of 72 subjects from the aducanumab 6 mg/kg arm to the 10 mg/kg arm in Studies 301 and 302.

I note a similar incidence of SAEs of intracranial hemorrhage between aducanumab and placebo arms. The following table shows the incidence of SAEs related to intracranial hemorrhage in the placebo-controlled period of Study 302.

Table 46. Incidence of A Subject Experiencing an SAE of the MQG of Intracranial Hemorrhage in Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
0	0	1 (0.2)	1 (0.1)	0

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; STUDYID: 302; AESER: Y, TRTEMFL: Y. Group by USUBJID, MedDRA query group, POOLTR3 Reassigned. MQG: MedDRA query group.

Pooled Studies 301 and 302 showed findings similar to Study 302 alone of a similar incidence of

SAEs of intracranial hemorrhage between aducanumab 10 mg/kg arm and placebo arms (0.2% versus 0.3%, respectively).

In Study 302, the difference in incidence of TEAEs related to intracranial hemorrhage in the aducanumab 10 mg/kg arm compared to placebo was small (less than 1%). I note that the four events of intracranial hemorrhage occurring in aducanumab-treated subjects had ARIA-H listed as the reported term for the events. The following table shows the incidence of TEAEs related to intracranial hemorrhage in the placebo-controlled period of Study 302.

Table 47. Incidence of A Subject Experiencing a TEAE of the MQG of Intracranial Hemorrhage in Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
1 (0.3)	0	3 (0.5)	4 (0.4)	0

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; STUDYID: 302; TRTEMFL: Y; EMQ grouping of intracranial hemorrhage. Group by USUBJID, MedDRA query group, POOLTR3 Reassigned, MQG: MedDRA query group.

Pooled Studies 301 and 302 showed similar findings of a low incidence of TEAEs of the MQG of Intracranial Hemorrhage (0.5% in both the aducanumab 10 mg and placebo arm, 0.4% in the all aducanumab group).

A review of narratives of SAEs related to intracranial hemorrhage occurring in aducanumab-treated subjects from Studies 103, 301, and 302 showed that a majority of events were related to ARIA (9 out of 14 SAEs). For a detailed review of narratives related to intracranial hemorrhage, the reader is referred to the [Hemorrhage section](#) of the Serious Adverse Events section of this review.

8.5.2. Subjects Without ARIA-E, ARIA-Microhemorrhages and Hemosiderin Deposits, or Superficial Siderosis of the Central Nervous System

The applicant noted that the most frequent TEAEs associated with symptomatic ARIA (all types) included headache, dizziness, and confusional state. These TEAEs were also among the most frequently reported TEAEs in the placebo-controlled period of Study 302 and the combined placebo-controlled periods of Studies 301 and 302.

In order to evaluate the most frequently reported TEAEs in subjects without reported events of ARIA, I calculated the incidence of TEAEs by preferred term and MQGs in subjects who did not report adverse events of ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, superficial

siderosis. I evaluated subjects from the placebo-controlled periods of Study 302, Studies 301 and 302, and Study 103.

Fall, hemorrhage, diarrhea, arthritis, and confusion/delirium/altered mental status/disorientation/coma were reported with highest frequency in subjects without ARIA in the placebo-controlled periods of pooled Studies 301 and 302. Fall, vertigo, and diarrhea were preferred terms that were reported with highest frequency in subjects without ARIA in the placebo-controlled period of Study 302.

In the placebo-controlled period of Study 302, the most frequent TEAEs with greatest difference from placebo in subjects without ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, or superficial siderosis assigned to aducanumab 10 mg/kg were fall, vertigo, and diarrhea. Fall was reported in 16% of the 10 mg/kg arm compared to 13% of placebo. Vertigo was reported in 13% of the 10 mg/kg arm compared to 10% of placebo. Diarrhea was reported in 9% of the 10 mg/kg arm compared to 6% of placebo. The following table lists TEAEs with incidence in the aducanumab 10 mg/kg arm of at least 2% higher than placebo in subjects without ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, or superficial siderosis in the placebo-controlled period of Study 302. The reader is referred to my analysis of blood pressure in the Vital Signs section of this review.

Table 48. TEAEs in Subjects Without ARIA-E, ARIA-Microhemorrhages and Hemosiderin Deposits, or Superficial Siderosis in the 10 mg/kg Aducanumab Arm with Incidence of at Least 2% and at Least 2% Higher Than Placebo in the Placebo-Controlled Period of Study 302

Adverse Event	ADU 3 mg/kg N=230 n (%)	ADU 6 mg/kg N=136 n (%)	ADU 10 mg/kg N=319 n (%)	ALL ADU N=685 n (%)	Placebo N=491 n (%)
Fall	24 (10)	13 (10)	50 (16)	87 (13)	64 (13)
Vertigo FDA B MQG	27 (12)	6 (4)	42 (13)	75 (11)	51 (10)
Diarrhea FDA N MQG	21 (9)	6 (4)	29 (9)	56 (8)	28 (6)
Cough	8 (3)	8 (6)	22 (7)	38 (6)	26 (5)
Neck Pain	1 (0)	1 (1)	12 (4)	14 (2)	10 (2)
Nasal Congestion	0	3 (2)	8 (3)	11 (2)	6 (1)
Paresthesia	4 (2)	2 (1)	8 (3)	14 (2)	7 (1)
Headache FDA B MQG	51 (22)	24 (18)	59 (18)	134 (20)	79 (16)
Arthritis FDA B MQG	20 (9)	12 (9)	49 (15)	81 (12)	66 (13)
Nausea, Vomiting MQG	17 (7)	5 (4)	25 (8)	47 (7)	30 (6)
Hypertension, Blood Pressure Increased MQG	13 (6)	6 (4)	23 (7)	42 (6)	27 (5)
Rash FDA B MQG	20 (9)	8 (6)	19 (6)	47 (7)	21 (4)

Adverse Event	ADU 3 mg/kg N=230 n (%)	ADU 6 mg/kg N=136 n (%)	ADU 10 mg/kg N=319 n (%)	ALL ADU N=685 n (%)	Placebo N=491 n (%)
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis MQG	8 (3)	6 (4)	18 (6)	32 (5)	21 (4)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; ARIA E, H, SS Subject Level Flag POOLA1: Inversion of 1; StudyID=302; Group by USUBJID, AEDECOD; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

In the placebo-controlled period of Studies 301 and 302, the most frequent TEAEs by preferred term in subjects without ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, or superficial siderosis assigned to aducanumab 10 mg/kg were similar to Study 302 alone and included fall, hemorrhage, and diarrhea. The incidence of fall and diarrhea in the aducanumab 10 mg/kg group was similar in the combined Studies 301 and 302 compared to Study 302 alone (fall: 15% versus 16%, diarrhea: 10% versus 9%, respectively). Hemorrhage occurred at a slightly higher frequency in Studies 301 and 302 compared to Study 302 alone in the aducanumab 10 mg/kg arm (13% versus 10%, respectively). Preferred terms that contributed to the grouping of hemorrhage with highest frequency included contusion and hematoma and combined contributed to approximately 40% of the grouped terms. The following table lists the most frequent TEAEs in subjects without ARIA for pooled Studies 301 and 302.

Table 49. TEAEs in Subjects Without ARIA-E, ARIA-Microhemorrhages and Hemosiderin Deposits, or Superficial Siderosis with Incidence in the Aducanumab 10 mg/kg Arm of at least 2% and at Least 2% Higher Than Placebo in Pooled Studies 301 and 302

Adverse Event	ADU 3 mg/kg N=486 n (%)	ADU 6 mg/kg N=258 n (%)	ADU 10 mg/kg N=651 n (%)	ALL ADU N=1395 n (%)	Placebo N=976 n (%)
Fall	60 (12)	31 (12)	100 (15)	191 (14)	113 (12)
Hemorrhage FDA N MQG	50 (10)	35 (14)	85 (13)	170 (12)	98 (10)
Diarrhea FDA N MQG	40 (8)	20 (8)	66 (10)	126 (9)	69 (7)
Arthritis FDA B MQG	52 (11)	22 (9)	88 (14)	162 (12)	121 (12)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	25 (5)	13 (5)	44 (7)	82 (6)	45 (5)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; ARIA E, H, SS Subject Level Flag POOLA1: Inversion of 1; Group by USUBJID, AEDECOD; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1. MQG: MedDRA query group.

I did not find analysis of the aducanumab 10 mg/kg arm of the placebo-controlled period of Study 103 informative due to a low number of subjects without ARIA (n=17).

I noted 8 cases of anemia occurring in aducanumab-treated subjects without ARIA. None of the cases were serious, resulted in study withdrawal, or discontinuation of study treatment.

Two of the eight subjects with anemia also had a gastrointestinal bleed. I did not establish a role for aducanumab in the events of anemia and gastrointestinal bleed in these two subjects due to medical comorbidities or a lack of additional information in the case narrative. One subject was diagnosed with adenocarcinoma of the colon (b) (6). The second subject reported hematochezia, had a normal endoscopy and colonoscopy, and was diagnosed with monoclonal gammopathy of unknown significance, iron deficiency, and chemical relapse of prostate cancer (b) (6).

In the remaining six cases of anemia, I did not establish a role for aducanumab due to a lack of information or presence of potential contributory factors. One case had potential contributory factors of diverticulosis and infectious colitis (b) (6). Another case reported the contributory factor of diverticulosis (b) (6). A third case reported history of anemia and recent events of fall from a wheelchair resulting in hip fracture (b) (6).

The remaining three cases of anemia did not have narratives (b) (6).

The reader is referred to the [Appendix](#) for a table on the most frequent TEAEs in subjects without ARIA for the placebo-controlled period of Study 103.

8.5.3. Suicide-Related Events

Overall, I did not identify a signal for suicide-related events based on the incidence of affirmative responses on the Columbia-Suicide Severity Rating Scale (C-SSRS) in aducanumab-assigned subjects compared to placebo-assigned subjects and based on a review of narratives of subjects with SAEs related to suicide.

Baseline Affirmative Responses on the C-SSRS

In the placebo-controlled period of Study 302, aducanumab-assigned subjects had lower incidence of affirmative responses on the C-SSRS related to suicidal ideation compared to placebo-assigned subjects at baseline (3.5% versus 4.6%, respectively). Affirmative responses on the C-SSRS related to suicidal behavior and self-injurious behavior were reported at similar incidence in aducanumab-assigned subjects compared to placebo (0.6% versus 0.7% and 0.2% versus 0.2%, respectively).

The placebo-controlled periods of Studies 301 and 302 had similar incidence of affirmative

responses on the C-SSRS related to suicidal ideation, suicidal behavior, and self-injurious behavior in aducanumab-assigned subjects compared to Study 302 alone (3.6% versus 4.1%, 0.6% versus 0.6%, and 0.1% versus 0.2%, respectively).

The placebo-controlled and long-term extension periods of Study 302 alone and Studies 301 and 302 combined had similar incidence of baseline affirmative responses on the C-SSRS compared to the placebo-controlled period of Study 302 alone (suicidal ideation: 3.8% and 3.7% versus 3.5%, suicidal behavior: 0.4% and 0.5% versus 0.6%, and self-injurious behavior: 0.1% and 0.1% versus 0.2%, respectively).

Post-Baseline Affirmative Responses on the C-SSRS

In the placebo-controlled period of Study 302, the incidence of affirmative responses on the C-SSRS related to suicidal ideation and suicidal behavior post-baseline in aducanumab 10 mg/kg-assigned subjects was not higher than placebo (3.1% versus 4.6% and 0% versus 0.2%, respectively). The incidence of affirmative responses on the C-SSRS for self-injurious behavior was low (0.2% in aducanumab 10 mg/kg arm and 0 on placebo).

In the placebo-controlled period of Studies 301 and 302, the incidence of affirmative responses on the C-SSRS related to suicidal ideation in the aducanumab 10 mg/kg group was not in excess of placebo (3.1% versus 4.5%, respectively). The incidence of affirmative responses on the C-SSRS related to suicidal behavior and self-injurious behavior in the aducanumab 10 mg/kg group was low (0.1%).

In the combined placebo-controlled and long-term extension periods of Study 302, the incidence of affirmative responses on the C-SSRS related to suicidal ideation and suicidal behavior in the aducanumab 10 mg/kg group was similar to the placebo-controlled period of Study 302 (2.7% and 0%, respectively). The incidence of affirmative responses on the C-SSRS for self-injurious behavior was low (0.2% in aducanumab 10 mg/kg group).

The placebo-controlled and long-term extension periods of Studies 301 and 302 had similar incidence of affirmative responses on the C-SSRS in responses related to suicidal ideation, suicidal behavior, and self-injurious behavior compared to Study 302 alone (3.9%, 0.2%, and 0 versus 3.3%, 0, and 0.1%, respectively).

SAEs Related to Suicide

Preferred terms among the serious adverse events related to suicide in Studies 103, 301, and 302 included completed suicide (n=1) and suicide attempt (n=2). I did not identify a role for aducanumab in the case of completed suicide (b) (6) as the subject had received multiple doses of aducanumab at the same dosage prior to the event (narrative summarized in the Deaths section of this review). I did not identify a role for aducanumab in the two events of attempted suicide because of the contributory factors of psychiatric comorbidities. I summarize

the two cases here.

Attempted Suicide, (b) (6)

A 65-year-old female with history of anxiety, depression experienced the SAE of attempted suicide on Day 350. On the day of the event, the subject had a fight with her husband. She refused to go to lunch with her husband and instead remained in the car. She subsequently started to drive and was involved in a car accident. She was brought to the emergency department and did not have any injuries. She had received 11 doses of aducanumab prior to the event with the most recent dose occurring 13 days before (3 mg/kg). Concomitant medications included clorazepate dipotassium, escitalopram, fluvoxamine, and Rivastigmine. She was seen by a psychiatrist two days later and the dose of her escitalopram was reduced and dipotassium clorazepate was discontinued. Treatment medications included risperidone, lorazepam, mirtazapine, and topiramate. The event of attempted suicide was considered resolved on the same day. Study treatment was discontinued, and the subject withdrew from the study as a result of the event. The participant was evaluated by a psychiatrist; the fight with the husband was considered a trigger for the impulsive behavior. During the study, the subject also experienced the nonserious adverse event of asymptomatic ARIA-E on Day 99 which resolved on Day 153.

Reviewer comment: A role for aducanumab in the event of attempted suicide cannot be established as the subject had past medical history (anxiety and depression) that were likely contributory factors.

Attempted Suicide, (b) (6)

72-year-old man with history of mild cognitive impairment due to Alzheimer's Disease and depression experienced the serious adverse events of drug overdose and suicide attempt. On Day 156, the subject was noted to have ingested alcohol in the morning and to be unarousable by 2 pm. The subject's wife noted that 15 mg to 20 mg of lorazepam was missing and that the subject had left a note. The subject was taken to the hospital via emergency medical services, treated for overdose with activated charcoal and flumazenil, and admitted to the psychiatric service. Events leading up to the event of attempted suicide included being more apathetic in the months preceding the event, having reoccurring obsessive ideas, feelings of guilt, and insomnia. The subject was diagnosed with confusional state and possible long-standing depression in addition to cognitive deterioration. The subject was started on risperidone. The event was considered resolved on Day 158. The subject had received 6 doses of aducanumab with the most recent dose occurring 15 days prior the event (3 mg/kg). Concomitant medications included bimatoprost/timolol maleate, citalopram, tamsulosin hydrochloride, and dutasteride. Study treatment was permanently discontinued, and the subject withdrew from the study as a result of the event.

Reviewer comment: A role for aducanumab in the events of overdose and suicide attempt

cannot be established because of the likely contributory factor of underlying history of depression.

Overall, I did not identify a signal for suicide-related events based on a similar incidence of baseline and post-baseline affirmative responses on the C-SSRS between aducanumab 10 mg/kg- and placebo-assigned subjects in Study 302 and the combined Studies 301 and 302 (difference in incidence no higher than 2%). In addition, I did not identify a signal for suicide-related events based on my review of narratives of SAEs related to suicide.

8.5.4. Hypersensitivity Reaction

Overall, I note small increase in incidence of TEAEs belonging to the Hypersensitivity SMQ (narrow) in pooled Studies 301 and 302 for aducanumab-all treated (9.2%) compared to placebo 8.1%), with the same incidence in the 10 mg/kg dose group compared to placebo (8.1%). Similar findings were observed in Study 302. Most TEAEs belonging to the Hypersensitivity SMQ were mild or moderate in severity. The most frequent hypersensitivity events were eczema (1.3% for aducanumab 10 mg/kg, 0.7% for placebo), rhinitis allergic (0.7% for aducanumab 10 mg/kg, 0.4% for placebo), and rash (2.6% for aducanumab 10 mg/kg, 2.4% for placebo) in Study 302 with similar findings in the other pools. The SAEs of angioedema and urticaria were reported in one subject in Study 301.

Two subjects in Studies 103, 301, and 302 had SAEs within the Hypersensitivity SMQ (narrow). I include the cases here.

Hypersensitivity (b) (6)

75-year-old woman with mild cognitive impairment due to Alzheimer's disease, history of dry eye, reflux, and penicillin allergy who was reported to have hypersensitivity reaction (reported preferred term, moderate in severity) while undergoing an infusion of aducanumab 3 mg/kg on Day 689. Eight minutes into the infusion, she developed back pain (moderate in severity), chest pain (moderate in severity), and shortness of breath. Her blood pressure at the time of the event was 156/69 mmHg and her heart rate was 69 beats per minute. She was given normal saline; however, continued to have dyspnea and back pain. She was placed on oxygen 5 liters via nasal cannula and was given an infusion of methylprednisolone for allergic reaction. The chest pain resolved, and the back pain and shortness of breath improved after receiving methylprednisolone. Vital signs upon presentation to the ER included heart rate of 69 beats per minute, blood pressure of 197/93 mmHg, respiratory rate of 18 breaths per minute, and temperature of 97.2°F. Labs were significant for blood urea nitrogen 20 mg/dL (reference range: 7 to 17 mg/dL), WBC $5.4 \times 10^9/L$ (reference range: 4.5 to $11.0 \times 10^9/L$), hemoglobin 14.4 g/dL (reference range: 12.5 to 16.5 g/dL), and troponin I level 0.00 ng/mL (reference range: 0.00 to 0.08 ng/mL). CT angiography of the chest showed a hiatal hernia and no evidence of pulmonary embolism. Her ECG was normal. The subject still had some pain to the right scapula that worsened with movement and with inspiration. The events of chest pain, back pain, and

hypersensitivity were considered resolved the same day. She had received 23 doses of aducanumab prior to the event. Concomitant medications included ascorbic acid, bupropion, cyclosporin, curcumin, escitalopram, omeprazole/sodium bicarbonate, paracetamol, ubiquinol, vitamin B12 NOS, and vitamin D NOS. The event of hypersensitivity led to the subject's withdrawal from the study.

Reviewer comment: The symptoms of back pain, chest pain, and shortness of breath are potentially consistent with a hypersensitivity reaction given onset during a drug infusion, improvement/resolution with methylprednisolone, and negative workups for alternate etiologies (normal troponin, normal ECG, CT angiography of the chest without acute findings). Alternate diagnoses for the chest and back pain include musculoskeletal etiology given worsening of symptoms with movement. A role for aducanumab in the events of back pain, chest pain, and hypersensitivity cannot be ruled out given onset during aducanumab infusion.

Urticaria, Angioedema (b) (6)

A 77-year-old male with mild cognitive impairment due to Alzheimer's disease with history of gastroesophageal reflux disease, myocardial ischemia, angina with acute myocardial infarction and stent placement, cough, osteoarthritis, and hay fever developed the SAEs of urticarial rash and angioedema on Day 393 during infusion of aducanumab. He had received a total of 15 doses of aducanumab prior to the event (2 doses of 1 mg/kg and 13 doses of 3 mg/kg). He developed swollen lips and a nonpruritic rash to the anterior chest and inner arms ~ 55 minutes into the infusion. He also experienced mild chest tightness. The infusion was stopped, and he was given IV hydrocortisone and oral cetirizine. He was admitted to the hospital the same day. Concomitant medications included acetylsalicylic acid, atorvastatin calcium, carbohydrates NOS/choline/fats NOS/minerals NOS/proteins NOS/uridine phosphate/vitamins NOS, dutasteride/tamsulosin hydrochloride, glyceryl trinitrate, latanoprost, and ranitidine hydrochloride. Five hours after treatment with hydrocortisone, he developed a rash and started to itch. His blood pressure was 125/82 mmHg, pulse rate 61 bpm, respiratory rate 21 breaths per minute, and oxygen saturation of 98%. Lab testing showed eosinophils at 0.14 (unit and reference range not reported). Additional lab values or other investigatory tests were not reported. He was treated with methylprednisolone. On Day 394, his eosinophil count was 0.0 (unit not reported). The angioedema was considered resolved on that day and he was discharged on prednisone. Study treatment was permanently discontinued as a result of the event and the event led to subsequent study withdrawal by the subject.

Reviewer comment: The symptoms of swollen lips, rash, and chest tightness that developed during a drug infusion appear consistent with a hypersensitivity reaction. A role for aducanumab in the event of urticaria and angioedema is likely given onset of symptoms during infusion of aducanumab.

I evaluated the incidence of a subject experiencing at least one TEAE belonging to the Hypersensitivity SMQ (narrow).

In the placebo-controlled period of Study 302, the all-aducanumab treated group had a higher incidence of subjects reporting at least one TEAE belonging to the Hypersensitivity SMQ (narrow) compared to placebo.

The following tables show the incidence of a subject experiencing at least one TEAE belonging to the SMQ Hypersensitivity (narrow) in the placebo-controlled period of Study 302.

Table 50. Incidence of A Subject Reporting at Least One TEAE Belonging to the Hypersensitivity SMQ (Narrow) in the Placebo-Controlled Period of Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
35 (9.5)	18 (10.3)	40 (7.3)	93 (8.5)	41 (7.5)

This table was created by the reviewer using ISS ADAE table with SMQs added with MAED, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; SMQ name: Hypersensitivity; NarrowSE: Yes; StudyID: 302; Group by USUBJID, POOLTR3 Reassigned A1.

In the placebo controlled portion of Study 302, eczema (1.3% for aducanumab 10 mg/kg, 0.7% for placebo), rhinitis allergic (0.7% for aducanumab 10 mg/kg, 0.4% for placebo) and rash (2.6% for aducanumab 10 mg/kg, 2.4% for placebo) were among the most frequently observed hypersensitivity reactions.

The duration of TEAEs belonging to the hypersensitivity SMQ in the combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 ranged between 1 and 547 days (25% quartile of 5 days, 50% quartile of 17 days, 75% quartile of 59 days). In subjects who experienced only one TEAE belonging to the SMQ hypersensitivity, approximately 25% had onset within 6 days of their most recent dose. Approximately 75% of subjects had onset within 28 days of their most recent dose.

In the August 10, 2020, response to an information request dated June 10, 2020, the applicant summarized rashes in Studies 103, 301, and 302 that were identified in a search of TEAEs using the high-level term of Rashes, eruptions and exanthems NEC. The applicant noted that concomitant treatment was given for approximately half of the rashes and included topical steroids.

Pooled Studies 301 and 302, and the placebo-controlled and long-term extension periods of Study 302 and Studies 103, 301, and 302 had similar incidences of TEAEs within the hypersensitivity SMQ as the placebo-controlled period of Study 302 in the aducanumab 10

mg/kg arm and the all-aducanumab group. In pooled Studies 301 and 302, subjects in the aducanumab 10 mg/kg arm and placebo reported the same frequency of TEAEs belonging to the hypersensitivity SMQ (8.1%). The incidence of TEAEs belonging to the hypersensitivity SMQ for all aducanumab arms combined was 9.2%. Eczema (1.3% for aducanumab 10 mg/kg, 0.7% for placebo), rhinitis allergic (0.8% for aducanumab 10 mg/kg, 0.5% for placebo) and rash maculo-papular (0.2% for aducanumab 10 mg/kg, 0 for placebo) were among the most frequently observed hypersensitivity reactions.

The TEAEs belonging to the SMQ Hypersensitivity (Narrow) in Study 302 were mild (89%) or moderate (11%) in severity in aducanumab-treated subjects.

Similar findings were observed in the combined Studies 301 and 302 and in the combined placebo-controlled and long-term extension periods of Studies 103, 301, and 302 with fewer than 1% of subjects having severe reactions. Fewer than 0.5% of aducanumab-treated subjects across Studies 103, 301, and 302 had TEAEs of hypersensitivity contributing to either study withdrawal or treatment discontinuation was low.

I note two subjects who reported an anaphylactic reaction and two subjects who reported circulatory collapse in Studies 103, 301, and 302.

I did not establish a role for aducanumab in the cases of anaphylactic reaction. One case was related to a bee sting (b) (6). The second case involved a subject who had been exposed to the quinolone antibiotic (garenoxacin) for a cold he had developed within two days prior to the anaphylactic reaction. His most recent dose of aducanumab had been 8 days prior to the event. He was treated with epinephrine, dexchlorpheniramine, famotidine, methylprednisolone, and fexofenadine (b) (6). The event of anaphylactic reaction was considered related to garenoxacin. The subject received one additional dose of aducanumab prior to termination of the study by the applicant and did not experience reoccurrence of anaphylaxis.

I did not establish a role for aducanumab in the events of circulatory collapse. In the 08/10/2020 response to an information request dated 06/10/2020, the applicant noted that both cases involved subjects enrolled at sites in Germany and “the reported event ‘circulatory collapse’ in German is ‘Kreislaufskollaps’, which can be synonymous to ‘syncope’ or ‘fainting’ in English.” In both cases, the subjects went on to receive greater than 15 additional doses of aducanumab without reoccurrence of symptoms (b) (6).

8.5.5. Infusion Site Reactions

Overall, I did not identify a safety signal with aducanumab and infusion site reactions in a review of the applicant's analyses for potential infusion reactions and in a comparison of the

incidence of TEAEs belonging to the high-level term Infusion Site Reaction in placebo- and aducanumab-assigned subjects in Studies 301 and 302.

The applicant performed a custom MedDRA query search for AEs that were considered potential infusion reactions and did not find an imbalance between aducanumab and placebo-assigned subjects in Studies 301 and 302. The applicant also searched for AEs that occurred within 24 hours of an infusion and resolved within two days of onset and did not find an imbalance in AEs between aducanumab- and placebo-assigned subjects.

I performed a search of TEAEs occurring with the high-level term Infusion Site Reaction and did not find an imbalance in TEAEs occurring in aducanumab and placebo-assigned subjects in the controlled trials. The placebo controlled and long-term extension pools had findings in incidence of TEAEs within the Infusion Site Reaction HLT similar to those in the controlled trials. The following table shows the incidence of a subject experiencing at least one TEAE within the Infusion Site Reaction AEHLT in the placebo-controlled period of Study 302.

Table 51. Incidence of A Subject Reporting at Least One TEAE Within the Infusion Site Reaction HLT in the Placebo-Controlled Period of Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
6 (1.6)	2 (1.1)	9 (1.6)	17 (1.6)	8 (1.5)

This table was created by the reviewer using ISS ADAE table, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; AEHLT: Infusion Site Reaction; StudyID: 302; Group by USUBJID, POOLTR3 Reassigned A1.

8.5.6. Evaluation of Injuries and Accidents

The topic of injury and accidents was a topic of interest as the most frequently reported TEAEs in aducanumab-assigned subjects in Studies 301 and 302 occurred within the MQG of Confusion, Delirium, Altered Mental Status, Disorientation, Coma and Vertigo FDA.

I note a slightly higher incidence of road traffic accidents occurring in aducanumab 10 mg compared to placebo in Study 302 (1.5% versus 0.9%, respectively) and in pooled Studies 301 and 302 (1.6% versus 1%, respectively). One road traffic accident occurred in a subject who had likely symptomatic ARIA as a potential contributory factor to the event.

I evaluated the incidence of TEAEs related to injury residing within the SOC Injury, Poisoning, and Procedural Complications in Studies 301 and 302. The reader is referred to the [Appendix](#) for a listing of preferred terms that were included in this grouping. I also reviewed narratives of SAEs related to road traffic accidents.

In pooled Studies 301 and 302, TEAEs related to injury were reported at higher incidence in the all-aducanumab group compared to placebo (23% versus 21%, respectively). The following table shows the incidence of a subject experiencing at least one TEAE related to injury in Studies 301 and 302.

Table 52. Incidence of A Subject Experiencing a TEAEs Related to Injury in Studies 301 and 302.

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 (%)
175 (23)	83 (25)	258 (23)	516 (23)	229 (21)

This table was created by the reviewer using ISS ADAE table, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; TEAEs with potential traumatic etiology selected from the SOC Injury, poisoning, and procedural complications; Group by USUBJID, POOLTR3 Reassigned A1.

In Study 302, the incidence of TEAEs related to injury in the aducanumab 10 mg/kg arm was the same as placebo (22%).

The most frequently reported TEAEs related to injury in Study 302 included bone contusion, head injury, and fall. Pooled Studies 301 and 302 showed similar findings. The incidence of TEAEs of road traffic accident in Study 302 in the aducanumab 10 mg/kg group was 1.5% compared to 0.9% on placebo. In pooled Studies 301 and 302, the incidence of road traffic accident was similar to Study 302 (1.6% in aducanumab 10 mg/kg versus 1% on placebo). The following table shows TEAEs related to injury with at least 0.5% higher incidence in the aducanumab 10 mg/kg group compared to placebo in Study 302.

Table 53. TEAEs Related to Injury with at Least 0.5% Incidence Higher in Aducanumab 10 mg/kg Group Compared to Placebo, by Preferred Term in Study 302

Preferred Term	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Bone contusion	3 (0.8)	1 (0.6)	8 (1.5)	12 (1.1)	1 (0.2)
Head injury	5 (1.4)	1 (0.6)	8 (1.5)	14 (1.3)	3 (0.5)
Fall	48 (13)	20 (11.4)	76 (13.9)	144 (13.2)	71 (13)
Road traffic accident	6 (1.6)	1 (0.6)	8 (1.5)	15 (1.4)	5 (0.9)
Skin wound	1 (0.3)	0	3 (0.5)	4 (0.4)	0
Tooth fracture	3 (0.8)	3 (1.7)	4 (0.7)	10 (0.9)	1 (0.2)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; TEAEs with potential traumatic etiology selected from the SOC Injury, poisoning, and procedural complications; Group by

USUBJID, AEDECOD; POOLTR3 Reassigned A1; tabulated on POOLTR3 Reassigned A1.

Road Traffic Accidents

No driving studies were conducted to evaluate the effects of aducanumab on driving ability.

No TEAEs of road traffic accident resulted in study withdrawal or treatment discontinuation in Studies 103, 301, and 302. I identified 3 SAEs of road traffic accident involving a motor vehicle. Each of the cases had contributory factors, which included alcohol use (b) (6) cycle racing during wet conditions (b) (6) and obstructive sleep apnea (b) (6)

I note a fourth case of traffic accident that I note in the Serious Adverse Events section of this review of a subject with a likely ARIA event (b) (6). In this case, the subject experienced traffic accident in the setting of hemianopsia and was subsequently hospitalized for a cerebral hemorrhage. I summarize the case here.

Cerebral hemorrhage, (b) (6)

67-year-old male with history of anemia, hyperlipidemia, hypertension, memory disorder, blood in stool, prediabetes, occasional alcohol use, who developed a cerebral hemorrhage. On Day 207, a year before the event, he was diagnosed with non-serious asymptomatic ARIA-E and non-serious asymptomatic ARIA-microhemorrhages and hemosiderin deposits that involved the left occipital lobe (events resolved after 2 and 4 months, respectively). He had received 8 doses of placebo prior to the event with most recent dose being 3 days before the event. On Study day 599, the subject experienced left occipital intraparenchymal hemorrhage. He had received two doses of aducanumab prior to the event. The most recent dose was 8 days prior to the event (1 mg/kg). He awoke with a bad headache, got into the car to drive, and backed into wife's car, backed into trashcans. The next day he drove into a vehicle parked on the side of the road. Each accident had occurred on the right side. He reported difficulty seeing. On Day 600, he was hospitalized and was found to have right-sided visual deficits. He was hypertensive to the 190s mmHg. CT angiography of the head and neck showed left occipital intraparenchymal hemorrhage. ECG showed sinus rhythm. He had a negative drug screen. A CT scan showed acute 3.4 cm intraparenchymal hemorrhage in the left occipital lobe. A brain MRI on Day 601 showed stable appearance to the hemorrhage. The patient was evaluated by neurology and advised to stop acetylsalicylic acid. The cerebral hemorrhage was considered to be resolved on Day 601 and he was discharged from the hospital and it was recommended that he no longer continue study drug as the event was thought related to the drug. Concomitant medication included acetylsalicylic acid, atorvastatin, donepezil, fexofenadine, ketotifen, losartan, and melatonin. On Day 626, the subject noted that he continued to experience right-sided visual field cut and he no longer drove a vehicle. Blood pressure readings were 110-150's/60-80's. On Day 694, the subject continued to experience bilateral hemianopsia and had not been driving.

The study treatment was permanently discontinued as a result of the event. On Day 786, he was diagnosed with asymptomatic ARIA-H microhemorrhage and asymptomatic ARIA-H, left occipital macrohemorrhage. An MRI scan showed no vasogenic edema, 3 microhemorrhages in the left occipital cortex, one of which was new compared to the prior scan, no superficial siderosis, and moderate new microhemorrhage in the left occipital cortex. He had received no additional doses of aducanumab since the diagnosis of cerebral hemorrhage. The events of ARIA-H remained unresolved for the remainder of the study.

Reviewer comment: Per an email discussion with Dr. Ranjit Mani dated October 8, 2020, the event of cerebral hemorrhage likely represented an ARIA event. A role for ARIA in the event of traffic accident seems likely given the subject's symptoms of hemianopsia from the cerebral hemorrhage. A role for aducanumab in the event of traffic accident cannot be established due to the likely preceding event of ARIA.

I note a road traffic accident that occurred in a subject with ongoing symptomatic ARIA and I summarize the case here.

Road Traffic Accident, (b) (6)

A 68-year-old white male with mild cognitive impairment due to Alzheimer's disease, restless leg syndrome, sleep apnea syndrome, was involved in a road traffic accident on Day 113. At the time of the event, the subject had ongoing symptomatic ARIA-E that started Day 99. An MRI on that day showed moderate new vasogenic edema (locations: right occipital cortex, right parietal, and right temporal, nonhippocampal). The subject was considered symptomatic as he experienced the symptom of increased headache (moderate in severity) at the time. Prior to the event of ARIA-E, the subject had received 4 doses of aducanumab, with the most recent dose occurring 13 days before (3 mg/kg). Concomitant medications included biotin, calcium pantothenate, choline bitartrate, cyanocobalamin, folic acid, inositol, nicotinamide, pyridoxine hydrochloride, riboflavin, thiamine mononitrate, cholecalciferol, donepezil, fexofenadine hydrochloride, iron, paracetamol, and prucalopride succinate. Study treatment was interrupted as a result of the events of ARIA-E and headache.

On Day 113, the subject experienced a road traffic accident (further details not provided). On Day 122, he was started on nortriptyline for headache. On Day 127, he experienced a fall (further details not provided). The applicant noted that neither the fall nor the road traffic accident resulted in hospitalization.

On Day 127, the subject was diagnosed with symptomatic ARIA-H (microhemorrhage). An MRI scan on that day showed moderate vasogenic edema which had increased in size compared to previous MRI (locations: right frontal; right occipital cortex; right parietal; and right temporal, nonhippocampal) and 5 new microhemorrhages in the right occipital cortex. The event of ARIA-

H was considered symptomatic as the subject had experienced a road traffic accident on Day 113 and a fall on Day 127.

On Day 131, he started dexamethasone for ARIA-E. The headache resolved on Day 131. On Day 141, the event of ARIA-H was reported as resolved/stabilized (MRI scan showed decreased moderate vasogenic edema and 5 stable microhemorrhages. ARIA-E resolved on Day 211 (MRI scan showed complete resolution of vasogenic edema).

The subject experienced another event of symptomatic ARIA-E on Day 659. An MRI scan showed new mild vasogenic edema in the left occipital cortex. He had received 20 doses of aducanumab with the most recent dose occurring 14 days prior to the event (3 mg/kg). He began treatment for agitation with lorazepam on Day 666. The event of ARIA-E was considered symptomatic because of events of fall and increased headache that had occurred on Day 689 (both moderate in severity). Study treatment was interrupted as a result of ARIA-E. ARIA-E was considered resolved on Day 742 when an MRI showed complete resolution of vasogenic edema.

Reviewer comment: Potential contributory factors in this case include concomitant medication use with donepezil and fexofenadine, which can be sedating, and the subject's history of sleep apnea. A role for aducanumab in the event of road traffic accident cannot be established due to the event of ARIA and other potential contributory factors.

The applicant concluded that the incidence of road traffic accident was similar between placebo- and aducanumab-assigned subjects in Studies 301 and 302 (1.0% versus 1.4%, respectively) and that overall, the data suggested no apparent effect of aducanumab on the ability to drive or operate machinery. I note that a role for aducanumab could not be established in the cases of road traffic accident due to the presence of potential contributory factors.

8.6. Safety Analyses by Demographic Subgroups

8.6.1. Sex, Age, Race, Region, Body Mass Index, Baseline Clinical Stage, Use of Alzheimer's Disease Medications at Baseline

I evaluated the most common TEAEs reported in pooled Studies 301 and 302 by the following demographic parameters: sex, age group, race, region, BMI, and baseline clinical stage of Alzheimer's disease. The most common TEAEs in pooled Studies 301 and 302 included ARIA-microhemorrhages and hemosiderin deposits, ARIA-E, confusional state, diarrhea, dizziness, fall, headache, and superficial siderosis of the CNS.

Overall, I note the following findings in the aducanumab 10 mg/kg arm compared to placebo. With regards to sex, superficial siderosis of the central nervous system was reported less frequently in women compared to men. With regards to age, ARIA-E was reported more

frequently in younger age groups compared to older age groups. With regards to race, Asians had a lower incidence of ARIA-E and superficial siderosis of the CNS compared to Whites. With regards to region, Asia had a lower incidence of ARIA-E and diarrhea compared to Europe/Canada/Australia or the United States. In Europe/Canada/Australia, fall was reported with lower frequency compared to the United States and superficial siderosis of the CNS with higher frequency compared to Asia. With regards to body mass index, common TEAEs were reported with similar frequency in the lowest BMI quartile compared to the highest BMI quartile. With regards to baseline clinical stage of Alzheimer's disease, ARIA-microhemorrhages and hemosiderin deposits and headache were reported at lower frequency in subjects with mild dementia compared to mild cognitive impairment.

With regards to sex, superficial siderosis of central nervous system was reported less frequently in women compared to men in the aducanumab 10 mg/kg arm (11% versus 19%, respectively). The following table shows the incidence of common TEAEs in pooled Studies 301 and 302 by sex.

Table 54. Incidence of Common TEAEs in Pooled Studies 301 and 302 by Sex

Preferred Term	ADU 10 mg/kg		Placebo	
	F N=577 %	M N=528 %	F N=575 %	M N=512 %
ARIA-microhemorrhages and hemosiderin deposits	20	18	6	7
ARIA-E	34	36	2	3
Confusional State	4	5	2	3
Diarrhea	9	8	7	7
Dizziness	10	9	9	9
Fall	18	11	15	8
Headache	22	18	17	14
Superficial Siderosis of CNS	11	19	2	3

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1. F: female. M: male.

With regards to age group in the aducanumab 10 mg/kg arm, ARIA-E occurred with higher incidence in age ≤ 64 years compared to age ≥ 75 years (37% versus 31%, respectively). The following table shows the incidence of the most common TEAEs in pooled Studies 301 and 302 by age group.

Table 55. Incidence of Common TEAEs in Pooled Studies 301 and 302 by Age Group (Years)

Preferred Term	ADU 10 mg/kg			Placebo		
	≤64 N=238 %	65-74 N=514 %	≥75 N=353 %	≤64 N=232 %	65-74 N=498 %	≥75 N=357 %
ARIA-microhemorrhages and hemosiderin deposits	16	19	21	4	7	8
ARIA-E	37	37	31	2	4	2
Confusional State	4	5	4	0	2	4
Diarrhea	7	9	8	6	8	6
Dizziness	8	10	11	9	8	10
Fall	8	15	18	8	11	15
Headache	28	20	15	23	15	10
Superficial Siderosis of CNS	14	16	13	0	3	3

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1.

With regards to race, differences in incidence of common TEAEs reported in aducanumab-treated subjects were noted however the number of subjects in some race categories was low. I report on the race categories of Asian and White as other categories had low numbers by treatment arm (< 10 subjects). In the aducanumab 10 mg/kg arm, Asians compared to Whites had a lower incidence of ARIA-E (24% versus 36%, respectively) and superficial siderosis of the CNS (8% versus 15%, respectively). A potential confounding factor was region as most Asians were from the region of Asia and most whites were from the regions of Europe/Canada/Australia or the United States (>90% in both cases). The following table shows the incidence of common TEAEs in pooled Studies 301 and 302 by race.

Table 56. Incidence of Common TEAEs in Pooled Studies 301 and 302 by Race

Preferred Term	ADU 10 mg/kg		Placebo	
	Asian N=107 %	White N=838 %	Asian N=102 %	White N=839 %
ARIA-microhemorrhages and hemosiderin deposits	17	19	5	7
ARIA-E	24	36	3	3
Confusional State	1	5	0	3
Diarrhea	5	9	7	7
Dizziness	6	11	5	10

Preferred Term	ADU 10 mg/kg		Placebo	
	Asian N=107 %	White N=838 %	Asian N=102 %	White N=839 %
Fall	11	15	7	12
Headache	11	21	3	16
Superficial Siderosis of CNS	8	15	1	2

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1.

With regards to region, ARIA-E and diarrhea were reported at lower frequency in Asia compared to Europe/Canada/Australia or the United States in the aducanumab 10 mg/kg arm. In Europe/Canada/Australia, fall occurred with lower frequency compared to the United States (12% versus 19%, respectively) and superficial siderosis of the CNS occurred with higher frequency compared to Asia (16% versus 9%, respectively). A potential confounding factor was race as most Asians were from the region of Asia and most Whites were from the regions of Europe/Canada/Australia or the United States. The following table shows the incidence of common TEAEs in pooled Studies 301 and 302 by region.

Table 57. Incidence of Common TEAEs in the Pooled Studies 301 and 302 by Region

Preferred Term	ADU 10 mg/kg			Placebo		
	Asia N=100 %	ECA N=535 %	US N=470 %	Asia N=95 %	ECA N=527 %	US N=465 %
ARIA-microhemorrhages and hemosiderin deposits	16	19	20	4	6	8
ARIA-E	24	37	35	3	3	3
Confusional State	1	4	6	0	1	4
Diarrhea	4	9	9	7	6	7
Dizziness	6	8	12	5	8	11
Fall	11	12	19	7	12	13
Headache	10	21	21	3	18	15
Superficial Siderosis of CNS	9	16	14	1	2	2

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1. ECA: Europe/Canada/Australia, US: United States.

With regards to body mass index, I created BMI categories based on quartile groupings of BMI of the safety population (all treatment arms combined) of pooled Studies 301 and 302. Common TEAEs were reported with similar frequency in the lowest BMI quartile compared to the highest BMI quartile (difference < 5%). The following table shows the incidence of common TEAEs in pooled Studies 301 and 302 by body mass index.

Table 58. Incidence of Common TEAEs in Pooled Studies 301 and 302 by Body Mass Index (kg/m²)

Preferred Term	ADU 10 mg/kg				Placebo			
	<22.5 N=284 %	22.5 to <24.9 N=289 %	24.9 to < 27.9 N=257 %	≥27.9 N=273 %	<22.5 N=276 %	22.5 to <24.9 N=262 %	24.9 to < 27.9 N=275 %	≥27.9 N=270 %
ARIA-microhemorrhages and hemosiderin deposits	20	20	19	18	6	7	7	6
ARIA-E	31	34	41	34	2	3	2	4
Confusional State	4	3	6	5	3	2	3	2
Diarrhea	7	10	8	9	7	7	8	6
Dizziness	11	10	12	7	8	11	10	7
Fall	14	14	17	14	10	14	12	11
Headache	20	21	20	18	14	16	16	15
Superficial Siderosis of CNS	12	14	18	15	2	2	2	3

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1.

Dementia, by definition, includes an impairment of daily functioning, whereas mild cognitive impairment, by definition, does not. The pathology of Alzheimer's Disease is therefore expected to be at least somewhat more severe in those with mild dementia than in those with mild cognitive impairment and differences in drug-related effects may be important. With regards to baseline clinical stage of Alzheimer's disease in the aducanumab 10 mg/kg arm, ARIA-microhemorrhages and hemosiderin deposits and headache were reported at lower frequency in subjects with mild dementia compared to subjects with mild cognitive impairment. The following table shows the incidence of common TEAEs in pooled Studies 301 and 302 by baseline clinical stage of Alzheimer's disease.

Table 59. Incidence of Common TEAEs in Pooled Studies 301 and 302 by Baseline Clinical Stage of Alzheimer's Disease

Preferred Term	ADU 10 mg/kg		Placebo	
	Mild Alzheimer's N=223 %	MCI N=882 %	Mild Alzheimer's N=202 %	MCI N=885 %
ARIA-microhemorrhages and hemosiderin deposits	16	20	8	6
ARIA-E	33	35	2	3
Confusional State	4	5	4	2
Diarrhea	9	9	8	7
Dizziness	12	9	9	9
Fall	13	15	10	12
Headache	15	21	16	15
Superficial Siderosis of CNS	15	15	2	2

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL = Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD; Demographic parameter, POOLTR3 Reassigned A1. MMCI: mild cognitive impairment

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

I did not identify an imbalance in the incidence of AEs belonging to the SOC Neoplasm between aducanumab 10 mg/kg and placebo arms; however, I note that the duration of exposure in the clinical database may not have been sufficient to identify any drug-induced carcinogenicity (mean exposure to aducanumab 10 mg/kg dose was less than 73 weeks). A conclusion about the carcinogenic potential of aducanumab cannot be drawn.

In terms of exposure, among the 679 subjects in Study 302 who were assigned to aducanumab 10 mg/kg in either the placebo-controlled period or the long-term extension period, the average duration of time within the study was 73 weeks. Approximately 20% of the 679 subjects were assigned to placebo in the placebo-controlled period of Study 302, and therefore, were not exposed to aducanumab 10 mg/kg until the long-term extension period (132/679).

In an analysis of the incidence of subject reporting an AE within the SOC Neoplasm in Study 302, aducanumab 10 mg/kg-assigned subjects did not have a higher incidence compared to placebo (5.9% versus 7.9%, respectively).

I grouped AEs belonging to the SOC Neoplasm by organ system and did not find a grouping in the aducanumab 10 mg/kg arm that exceeded placebo by more than 0.4% in Study 302. The following table shows AEs belonging to the SOC Neoplasm grouped by organ or organ system in the placebo-controlled period of Study 302.

Table 60. AEs Belonging to the SOC of Neoplasm in the Placebo-Controlled Period of Study 302

Preferred Term	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Skin	11 (3)	5 (2.9)	20 (3.7)	36 (3.3)	27 (4.9)
Skin papilloma	0	0	3 (0.5)	3 (0.3)	0
Dysplastic nevus	0	0	2 (0.4)	2 (0.2)	0
Malignant melanoma in situ	0	0	2 (0.4)	2 (0.2)	0
Melanocytic nevus	1 (0.3)	0	3 (0.5)	4 (0.4)	2 (0.4)
Basal cell carcinoma	6 (1.6)	3 (1.7)	12 (2.2)	21 (1.9)	12 (2.2)
Cholesteatoma	0	1 (0.6)	0	1 (0.1)	0
Seborrheic keratosis	0	1 (0.6)	2 (0.4)	3 (0.3)	2 (0.4)
Squamous cell carcinoma of skin	1 (0.3)	0	2 (0.4)	3 (0.3)	2 (0.4)
Bowen's disease	0	0	1 (0.2)	1 (0.1)	2 (0.4)
Lip squamous cell carcinoma	1 (0.3)	0	0	1 (0.1)	1 (0.2)
Malignant melanoma	1 (0.3)	0	0	1 (0.1)	1 (0.2)
Benign neoplasm of skin	1 (0.3)	0	0	1 (0.1)	2 (0.4)
Squamous cell carcinoma	0	0	1 (0.2)	1 (0.1)	5 (0.9)
Reproductive and Breast	4 (1.1)	2 (1.1)	4 (0.7)	10 (0.9)	6 (1.1)
Benign breast neoplasm	0	0	0	0	2 (0.4)
Breast cancer	0	1 (0.6)	0	1 (0.1)	2 (0.4)
Intraductal papillary mucinous neoplasm	1 (0.3)	0	0	1 (0.1)	0
Invasive ductal breast carcinoma	0	0	1 (0.2)	1 (0.1)	1 (0.2)
Invasive lobular breast carcinoma	1 (0.3)	0	1 (0.2)	2 (0.2)	0
Endometrial cancer ^a	0	0	1 (0.4)	1 (0.2)	0

Preferred Term	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Ovarian cancer ^a	0	0	1 (0.4)	1 (0.2)	0
Uterine leiomyoma ^a	0	0	1 (0.4)	1 (0.2)	1 (0.3)
Endometrial adenocarcinoma ^a	0	0	0	0	1 (0.3)
Prostate cancer recurrent ^a	0	0	1 (0.4)	1 (0.2)	0
Prostate cancer ^a	2 (1.1)	1 (1.1)	1 (0.4)	4 (0.7)	1 (0.4)
Gastroenterology	2 (0.5)	1 (0.6)	3 (0.5)	6 (0.5)	2 (0.4)
Adenocarcinoma of colon	0	0	1 (0.2)	1 (0.1)	0
Gastrointestinal neoplasm	0	0	1 (0.2)	1 (0.1)	0
Pancreatic carcinoma metastatic	0	0	1 (0.2)	1 (0.1)	0
Benign pancreatic neoplasm	1 (0.3)	0	0	1 (0.1)	0
Esophageal carcinoma	0	1 (0.6)	0	1 (0.1)	0
Colon adenoma	1 (0.3)	0	0	1 (0.1)	1 (0.2)
Gastric cancer	0	1 (0.6)	0	1 (0.1)	1 (0.2)
Pulmonary	2 (0.5)	0	1 (0.2)	3 (0.3)	1 (0.2)
Pleural mesothelioma	0	0	1 (0.2)	1 (0.1)	0
Lung neoplasm malignant	1 (0.3)	0	0	1 (0.1)	0
Small cell lung cancer	1 (0.3)	0	0	1 (0.1)	0
Lung adenocarcinoma stage IV	0	0	0	0	1 (0.2)
Vascular	2 (0.5)	2 (1.1)	2 (0.4)	6 (0.5)	2 (0.4)
Benign vascular neoplasm	0	0	1 (0.2)	1 (0.1)	0
Hemangioma	1 (0.3)	1 (0.6)	1 (0.2)	3 (0.3)	1 (0.2)
Hemangioma of skin	0	1 (0.6)	0	1 (0.1)	0
Hemangioma of liver	1 (0.3)	0	0	1 (0.1)	1 (0.2)
Heme	2 (0.5)	1 (0.6)	1 (0.2)	4 (0.4)	0
Chronic lymphocytic leukemia	0	0	1 (0.2)	1 (0.1)	0
Diffuse large B-cell lymphoma	1 (0.3)	0	0	1 (0.1)	0
Polycythemia vera	1 (0.3)	0	0	1 (0.1)	0
T-cell lymphoma	0	1 (0.6)	0	1 (0.1)	0
Head and neck	1 (0.3)	1 (0.6)	0	2 (0.2)	1 (0.2)
Salivary gland cancer	0	1 (0.6)	0	1 (0.1)	0
Squamous cell carcinoma of the oral cavity	1 (0.3)	0	0	1 (0.1)	0
Nasal cavity cancer	0	0	0	0	1 (0.2)
Bladder	1 (0.3)	1 (0.6)	0	2 (0.2)	1 (0.2)
Bladder papilloma	0	1 (0.6)	0	1 (0.1)	0

Preferred Term	ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
Transitional cell carcinoma	1 (0.3)	0	0	1 (0.1)	0
Bladder cancer	0	0	0	0	1 (0.2)
Connective tissue	0	0	2 (0.4)	2 (0.2)	0
Chondromatosis	0	0	1 (0.2)	1 (0.1)	0
Osteoma cutis	0	0	1 (0.2)	1 (0.1)	0
Thyroid	1 (0.3)	1 (0.6)	0	2 (0.2)	0
Benign neoplasm of thyroid gland	0	1 (0.6)	0	1 (0.1)	0
Medullary thyroid cancer	1 (0.3)	0	0	1 (0.1)	0
Miscellaneous	1 (0.3)	0	2 (0.4)	3 (0.3)	8 (1.5)
Metastases to bone	1 (0.3)	0	0	1 (0.1)	0
Metastases to spine	1 (0.3)	0	0	1 (0.1)	0
Metastatic neoplasm	1 (0.3)	0	0	1 (0.1)	0
Adrenal adenoma	0	0	0	0	1 (0.2)
Benign neoplasm of eye	0	0	0	0	2 (0.4)
Lipoma	0	0	1 (0.2)	1 (0.1)	2 (0.4)
Neuroendocrine tumor	0	0	0	0	1 (0.2)
Thymoma malignant	0	0	0	0	1 (0.2)
Tumor pain	0	0	0	0	1 (0.2)
Paraganglion neoplasm benign	0	0	1 (0.2)	1 (0.1)	0

This table was created by the reviewer using ISS ADAE dataset, POOLC=POOLA1; AESOC=neoplasm; StudyID: 302; Group by USUBJID, POOLTR3reassigned. ^a Sex-specific denominators used.

Similar to Study 302, there was not an excess of AEs belonging to the SOC Neoplasm in the aducanumab 10 mg/kg group compared to placebo in pooled Studies 301 and 302 (6.4% versus 8.6%, respectively).

In the placebo-controlled and long-term extension periods of Study 302, the incidence of a subject experiencing at least one AE within the SOC Neoplasm in the aducanumab 10 mg/kg arm was slightly higher than in the placebo-controlled period alone (7.1% versus 5.9%, respectively). The higher incidence seen in the placebo-controlled and long-term extension periods of Study 302 is likely due in part to longer study follow-up.

The placebo-controlled and long-term extension periods of Studies 103, 301, and 302 had a similar incidence of a subject experiencing at least one AE within the SOC Neoplasm as compared to Study 302 alone for the aducanumab 10 mg/kg arm (8.1% versus 7.1%, respectively).

The incidence of a subject experiencing an SAE within the SOC Neoplasm was similar in the aducanumab 10 mg/kg arm and placebo in Study 302 (1.6% (9/547) and 1.3% (7/547), respectively).

Similar to Study 302, the aducanumab 10 mg/kg group and placebo arms in pooled Studies 301 and 302 had similar incidences of a subject reporting an SAE belonging to the SOC Neoplasm (1.3% versus 1.6%, respectively).

8.8.2. Human Reproduction and Pregnancy

There is no safety data on the use of aducanumab in pregnant women. The applicant notes that no pregnancies have been reported in any clinical study of aducanumab.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Overall, I did not identify a safety signal for abuse potential in a search of TEAEs related to abuse potential in Studies 103, 301, and 302.

I identified four cases with the preferred term overdose in a search of TEAEs within the HLT of Overdoses NEC in Studies 103, 301, and 302. No cases involved overdose with aducanumab. One case involved overdose with donepezil (b) (6), another with Klonopin (b) (6), another with paracetamol (b) (6), and another with lorazepam (b) (6).

Drug Abuse Potential

I did not identify a safety signal for drug abuse potential with aducanumab in a review of the incidence of TEAEs related to abuse potential.

I searched for TEAEs related to abuse potential using the following preferred terms: abnormal dreams; apathy; depersonalization/derealization disorder; dysphoria; euphoric mood; feeling abnormal; feeling drunk; hallucination; hallucination visual; hallucination auditory; illusion; mental impairment.

A similar incidence of TEAEs related to abuse potential were seen in aducanumab arms compared to placebo in Study 302. The following table shows the incidence of TEAEs related to abuse potential in the placebo-controlled period of Study 302.

Table 61. Incidence of A Subject Reporting at Least One TEAE Related to Abuse Potential in Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
7 (1.9)	2 (1.1)	13 (2.4)	22 (2)	13 (2.4)

This table was created by the reviewer using ISS ADAE; POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; StudyID: 302; Group by USUBJID, POOLTR3 Reassigned A1.

Studies 301 and 302 showed similar findings of a similar incidence of TEAEs related to abuse potential in aducanumab 10 mg/kg arm compared to placebo (2.6% and 2.3%, respectively).

The placebo-controlled and long-term extension periods of Study 302 and Studies 103, 301, and 302 had similar incidence of TEAEs relate to abuse potential (2.4% and 2.9%, respectively), which was similar to the placebo-controlled periods.

With regards to hallucinations, aducanumab arms did not have an excess of TEAEs related to hallucinations compared to the placebo arm in Study 302. The following table shows the incidence of TEAES related to hallucinations in the placebo-controlled period of Study 302.

Table 62. Incidence of A Subject Reporting at Least One TEAE Related to Hallucinations in the Placebo-Controlled Period of Study 302.

ADU 3 mg/kg N=369 n (%)	ADU 6 mg/kg N=175 n (%)	ADU 10 mg/kg N=547 n (%)	ALL ADU N=1091 n (%)	Placebo N=547 n (%)
4 (1.1)	0	6 (1.1)	10 (0.9)	7 (1.3)

This table was created by the reviewer using ISS ADAE; POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; AEDECOD: hallucination, hallucination auditory, hallucination visual; StudyID: 302; Group by USUBJID, POOLTR3 Reassigned A1.

Pooled Studies 301 and 302, similar to Study 302 alone, did not have an excess of TEAEs related to hallucinations in the aducanumab 10 mg/kg arm compared to placebo (incidence of 0.9% for both arms).

Withdrawal and Rebound

Overall, I did not establish that aducanumab was associated with withdrawal and rebound symptoms. No clinical studies have been conducted to evaluate the withdrawal or rebound effect of aducanumab. I note fatigue and nasopharyngitis were reported at higher incidence in the follow-up period of Study 302 compared to the entire trial period (by calculating difference from placebo for aducanumab 10 mg/kg arm). The magnitude of difference was low (difference

did not exceed 3%).

The FDA Guidance for Industry “Assessment of Abuse Potential of Drugs” (January 2017) states that the assessment of physical dependence in humans does not typically involve a dedicated study. Instead, physical dependence is usually assessed at the conclusion of a phase 2/3 clinical efficacy study through a monitored discontinuation period. The applicant did not identify a safety signal for withdrawal and rebound in a search of TEAEs occurring in subjects starting 28 days after treatment was discontinued to the end of the study. AEs were recorded up to 18 weeks in the placebo-controlled periods of Studies 301 and 302 after final dosing. The applicant noted that the incidence of AEs in the follow-up period was lower than when compared to the entire study. Additionally, the types of AEs that were noted were similar to those observed during the study.

The applicant’s approach differs from my approach in that the applicant calculated the incidence of AEs per 100 subject-years whereas I calculated the incidence per subject. Additionally, my approach includes adverse events occurring within 28 days of the last treatment.

Similar to the applicant, I note a lower incidence of AEs occurring in aducanumab 10 mg/kg and placebo arms in the follow-up period compared to the entire study period of Study 302, with similar findings in pooled Studies 301 and 302. The following table shows the incidence of a subject experiencing at least one AE in the follow-up period compared to the entire study of the placebo-controlled period of Study 302.

Table 63. Incidence of A Subject Reporting at Least One AE in the Follow-Up Period Compared to the Entire Study of the Placebo-Controlled Period of Study 302.

Follow-Up Period		Entire Study	
ADU 10 mg/kg N=265 n (%)	Placebo N=254 n (%)	ADU 10 mg/kg N=547 n (%)	Placebo N=547 n (%)
131 (49)	76 (30)	509 (93)	478 (87)

This table was created by the reviewer using ISS ADAE dataset, POOLC=POOLA1; Treatment Discontinuation Subject Level flag A1 = 1; Epoch= follow up; StudyID: 302; Group by USUBJID, POOLTR3reassigned. The denominator is the number of subjects who discontinued treatment in the placebo-controlled period.

In the follow-up period of Study 302, AEs with greatest difference from placebo in the aducanumab 10 mg/kg included ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, superficial siderosis of the CNS, and headache. These AEs were similar to the TEAEs reported with greatest difference from placebo in the aducanumab 10 mg/kg for the entire study period. Similar results were observed in pooled Studies 301 and 302. The following table shows AEs in the follow-up period of Study 302 with incidence in the aducanumab 10 mg/kg arm of at least

2% and at least 1% higher than placebo.

Table 64. AEs in the Follow-up Period in the Aducanumab 10 mg/kg Group with Incidence of at Least 2% and at Least 1% Higher Than Placebo, by Preferred Term in Study 302

Preferred Term	ADU 3 mg/kg N=175 n (%)	ADU 6 mg/kg N=89 n (%)	ADU 10 mg/kg N=265 n (%)	ALL ADU N=529 n (%)	Placebo N=254 n (%)
Amyloid related imaging Abnormality-Edema/Effusion	29 (17)	10 (11)	52 (20)	91 (17)	2 (1)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	15 (9)	7 (8)	36 (14)	58 (11)	4 (2)
Superficial Siderosis Of Central Nervous System	12 (7)	1 (1)	25 (9)	38 (7)	1 (0)
Headache	8 (5)	3 (3)	10 (4)	21 (4)	0
Fatigue	0	0	6 (2)	6 (1)	0
Nasopharyngitis	6 (3)	1 (1)	8 (3)	15 (3)	2 (1)
Confusional state	3 (2)	0	7 (3)	10 (2)	2 (1)
Urinary tract infection	6 (3)	1 (1)	7 (3)	14 (3)	5 (2)
Dizziness	3 (2)	1 (1)	6 (2)	10 (2)	2 (1)

This table was created by the reviewer using ISS ADAE dataset, POOLC=POOLA1; Treatment Discontinuation Subject Level flag A1 = 1; Epoch= follow up; StudyID: 302; Group by USUBJID, AEDECOD, POOLTR3reassigned

I compared difference in incidences of AEs in the follow-up period compared to the entire study period for the aducanumab 10 mg/kg arm with comparison to placebo. I note that fatigue and nasopharyngitis were AEs that occurred most frequently in the follow up period compared to the entire trial period (comparison of difference from placebo). Overall, the maximum difference in incidence between the follow up period and the entire study period was small (no higher than 3%, occurring with fatigue).

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Aducanumab is a new molecular entity. It is not approved in other regions of the world.

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable.

8.9.3. Additional Safety Issues from Other Disciplines

The reader is referred to the clinical review by Dr. Brian Trummer for a review of events related to ARIA.

8.10. Integrated Assessment of Safety

Safety findings from BLA 761178 are summarized below.

Deaths. There were 25 deaths occurring in subjects who received aducanumab. There was not an excess of deaths in aducanumab-treated groups compared to placebo-treated groups. Most subjects had underlying risk factors for events with fatal outcome. No deaths were attributed to treatment with aducanumab.

SAE. The incidence of SAEs in the aducanumab 10 mg/kg arm was comparable to placebo. ARIA-E and superficial siderosis of the central nervous system were the most frequent SAEs reported in pooled Studies 301 and 302 in the aducanumab 10 mg/kg arm. ARIA-E was reported in 1.4% of the aducanumab 10 mg/kg arm compared to 0.1% of placebo. Superficial siderosis of the central nervous system was reported in 0.5% of the aducanumab 10 mg/kg arm compared to no subjects on placebo. The long-term extension periods of pooled Studies 103, 301, and 302 showed infection and ARIA-E to be the most frequently occurring SAEs in the aducanumab 10 mg/kg arm; however, none occurred with an incidence of greater than 3%.

AE leading to drug or study discontinuations. Adverse events leading to study withdrawal were reported at a low incidence in aducanumab-treated subjects in the placebo-controlled periods of pooled Studies 301 and 302 (4%). The most frequent adverse events leading to study withdrawal in the placebo-controlled period of pooled Studies 301 and 302 included superficial siderosis of the central nervous system and ARIA-microhemorrhages and hemosiderin deposits. Adverse events leading to treatment discontinuation were driven by protocol for ARIA events. Adverse events leading to treatment discontinuation occurred in approximately 9% of aducanumab-treated subjects in the placebo-controlled periods of pooled Studies 301 and 302. The most frequent adverse events leading to treatment discontinuation in pooled Studies 301 and 302 were superficial siderosis of the central nervous system, ARIA-microhemorrhages and hemosiderin deposits, and ARIA-E.

Significant AEs. Evaluation of severe AEs did not identify a new safety signal.

Most common AE. The most common TEAEs in pooled Studies 301 and 302 were ARIA-E, ARIA-microhemorrhages and hemosiderin deposits, and superficial siderosis. In pooled Studies 301 and 302, treatment emergent AEs with at least 2% risk (rounded) and at least 2% greater than placebo in the aducanumab 10 mg/kg arm were: ARIA-E (35% and 3% on aducanumab 10 mg/kg and placebo, respectively), superficial siderosis of central nervous system (15% and 2% on aducanumab 10 mg/kg and placebo, respectively), ARIA-microhemorrhages and hemosiderin deposits (19% and 7% on aducanumab 10 mg/kg and placebo, respectively), headache (21% and 16% on aducanumab 10 mg/kg and placebo, respectively), confusion/delirium/altered mental status/disorientation (8% and 4% on aducanumab 10 mg/kg

and placebo, respectively), fall (15% and 12% on aducanumab 10 mg/kg and placebo, respectively), and diarrhea (9% and 7% on aducanumab 10 mg/kg and placebo, respectively). Vital sign, laboratory and ECG evaluations in Study 302 and pooled Studies 301 and 302 did not identify a signal and quantitative ECG evaluations in Study 102 did not identify a signal.

Pre-specified AE of interest

- Hepatic Safety – There was no signal of hepatotoxicity identified.
- Immunogenicity – The number of aducanumab-treated subjects in Studies 301 and 302 with treatment emergent ADA responses was low at 0.6% (15/2689). The database was not sufficient in assessing immunogenicity with aducanumab because of the low number of subjects with treatment-emergent ADA responses.
- Intracranial Hemorrhage – The incidence of AEs related to intracranial hemorrhage in pooled Studies 301 and 302 was similar between aducanumab and placebo-treated subjects (0.4% and 0.5%, respectively). SAEs of intracranial hemorrhage occurred in fewer than 1% of subjects in pooled Studies 301 and 302. A review of the narratives of SAEs related to intracranial hemorrhage showed that a majority of events were related to ARIA.
- Adverse Events in Subjects Without ARIA – The most common AEs occurring in subjects without ARIA in the aducanumab 10 mg/kg arm of pooled Studies 301 and 302 included fall, hemorrhage, and diarrhea (difference from placebo no higher than 3%).
- Suicidality - There was no evidence of an increased risk of suicidality with aducanumab.
- Hypersensitivity Reactions – One subject reported the SAEs of angioedema and urticaria, which also led to treatment discontinuation and study withdrawal. A small increase in incidence in AEs belonging to the Hypersensitivity SMQ were noted in pooled Studies 301 and 302 for all-aducanumab treated subjects compared to placebo (9.2% versus 8.1%, respectively). Most AEs were mild to moderate in severity. The most frequently AEs related to hypersensitivity reported in pooled Studies 301 and 302 were eczema, allergic rhinitis, and rash.
- Infusion Site Reactions - There was no evidence of a safety signal with aducanumab and infusion site reactions.
- Evaluation of Injuries and Accidents –A slightly higher incidence of road traffic accident was seen in the aducanumab 10 mg/kg arm of pooled Studies 301 and 302 compared to placebo (1.6% versus 1.0%, respectively). A review of narratives of road traffic accident showed one subject with likely symptomatic ARIA as a contributory factor to the event.

9. Advisory Committee Meeting and Other External Consultations

A Peripheral and Central Nervous System Drugs Advisory Committee meeting was held on November 6, 2020 during which the efficacy and safety data of aducanumab for the treatment of Alzheimer's disease were presented to the Committee. The safety of aducanumab was not

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discussed at the meeting. For further discussion on the topic, please see the clinical review by Dr. Kevin Krudys.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

I recommend that Hypersensitivity Reactions be added as a Warnings and Precautions statement to the label.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

The applicant has proposed a communication plan REMS for the topic of ARIA. The reviewer is referred to the clinical review by Dr. Brian Trummer for a review of this topic.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. Adverse Events Occurring in Subjects Originally Assigned to Placebo Who Received One Dose of Aducanumab in the Placebo-Controlled Period of Studies 301 and 302

Table 65. Adverse Events Occurring in Subjects Reassigned to Placebo Arm in Studies 301 and 302

Subject ID	ADU Dose (mg/kg)	Study Day ADU dose	Adverse Event (Preferred Term)	AE Occurrence		Serious	AE Start Day	AE End Day
				Before ADU Dose	After ADU Dose			
(b) (6)	6	533	Fall		x	Y	551	551
			Headache		x	N	547	548
			Hypotension	x		N	418	474
(b) (6)	10	448	Psychomotor hyperactivity	x		N	425	not listed
(b) (6)	3	533	Anxiety	x		N	339	421
			Gait disturbance	x		N	87	87
			Hypotension	x		N	85	113
			Insomnia	x		N	43	196
			Vision blurred	x		N	57	57
(b) (6)	10	533	Atrial fibrillation	x		N	224	227
			Cardiac failure congestive	x		N	225	226
			Hemangioma of skin	x		N	454	not listed
			Headache	x		N	1	1
			Headache	x		N	177	630
			Irritability	x		N	108	110
			Irritability	x		N	479	not listed
			Memory impairment	x		N	108	110
			Normocytic anemia	x		N	224	334
			Pneumonia	x		Y	224	226

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Subject ID	ADU Dose (mg/kg)	Study Day ADU dose	Adverse Event (Preferred Term)	AE Occurrence		Serious	AE Start Day	AE End Day
				Before ADU Dose	After ADU Dose			
			Pulpitis dental	x		N	5	30
			Upper respiratory tract infection	x		N	222	226
			Urinary tract infection	x		N	503	509
(b) (6)	10	65	Acute sinusitis		x	N	185	191
			Acute sinusitis		x	N	281	290
			Blood testosterone decreased		x	N	234	not listed
			Headache	x		N	3	11
			Headache		x	N	185	191
			Influenza like illness		x	N	185	191
			Leukocytosis		x	N	185	194
			Nausea	x		N	3	11
			Pyrexia		x	N	185	190
			Tension headache	x		N	30	65
			Weight decreased		x	N	187	194
(b) (6)	3	534	Diverticulum	x		N	439	not listed

Y: Yes; N: No

13.2. Severity of TEAEs in the Placebo-Controlled Period of Pooled Studies 301 and 302 and in Study 103.

Table 66. Incidence of a Subject Experiencing a TEAE by Severity in Studies 301 and 302.

Severity	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 (%)
Mild	661 (87)	266 (80)	960 (87)	1887 (86)	890 (82)
Moderate	425 (56)	163 (49)	631 (57)	1219 (55)	476 (44)
Severe	120 (16)	35 (11)	163 (15)	318 (14)	92 (8)

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; Grouped by USUBJID, AESEV, POOLTR3 Reassigned A1; Tabulate by AESEV and POOLTR3 Reassigned A1

Table 67. Incidence of a Subject Experiencing a TEAE by Severity in Study 103.

Severity	ADU 1 mg/kg N=31 n (%)	ADU 3 mg/kg N=32 n (%)	ADU 6 mg/kg N=30 n (%)	ADU 10 mg/kg N=32 n (%)	ADU titration N=23 n (%)	ALL ADU N=148 n (%)	Placebo N=48 n (%)
Mild	25 (81)	24 (75)	27 (90)	29 (91)	21 (91)	126 (85)	44 (92)
Moderate	15 (48)	16 (50)	16 (53)	20 (63)	13 (57)	80 (54)	30 (63)
Severe	5 (16)	2 (6)	1 (3)	7 (22)	2 (9)	17 (11)	8 (17)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; APHASE: Placebo-controlled; Group by USUBJID, AESEV; TRT01P; tabulated on AESEV; TRT01P.

Table 68. Severe TEAEs with Incidence of at Least 0.4% Higher in Aducanumab 10 mg/kg Arm Compared to Placebo in Pooled Studies 301 and 302

Adverse Events	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 (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	21 (2.8)	4 (1.2)	49 (4.4)	74 (3.4)	0
Superficial Siderosis Of Central Nervous System	16 (2.1)	1 (0.3)	36 (3.3)	53 (2.4)	2 (0.2)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	27 (3.6)	2 (0.6)	29 (2.6)	58 (2.6)	0
Cardiac Arrest	1 (0.1)	0	4 (0.4)	5 (0.2)	0

Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	1 (0.1)	2 (0.6)	4 (0.4)	7 (0.3)	0

This table was created by the reviewer using ISS ADAE, POOLC=POOLA1; SAFFL=Y; TRTEMFL=Y; AESEV= severe; Grouped by USUBJID, AEDECOD, POOLTR3 Reassigned A1; Tabulate by AEDECOD and POOLTR3 Reassigned A1

Table 69. Severe TEAEs with Higher Incidence in Aducanumab 10 mg/kg Arm Compared to Placebo by Preferred Term in Study 103

Adverse Event	ADU 1 mg/kg N=31 n (%)	ADU 3 mg/kg N=32 n (%)	ADU 6 mg/kg N=30 n (%)	ADU 10 mg/kg N=32 n (%)	ADU titration N=23 n (%)	ALL ADU N=148 n (%)	Placebo N=48 n (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	0	0	1 (3.3)	3 (9.4)	1 (4.3)	5 (3.4)	0
Headache	0	1 (3.1)	0	1 (3.1)	0	2 (1.4)	0
Syncope	1 (3.2)	0	0	1 (3.1)	0	2 (1.4)	0
Arthritis	0	0	0	1 (3.1)	0	1 (0.7)	0
Cerebrovascular accident	0	0	0	1 (3.1)	0	1 (0.7)	0
Fall	0	0	0	1 (3.1)	0	1 (0.7)	0
Femur fracture	0	0	0	1 (3.1)	0	1 (0.7)	0
Migraine	0	0	0	1 (3.1)	0	1 (0.7)	0
Diverticular perforation	0	0	0	1 (3.1)	0	1 (0.7)	1 (2.1)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; APHASE: Placebo-controlled; AESEV: severe; Group by USUBJID, AEDECOD; TRT01P; tabulated on AEDECOD; TRT01P.

Table 70. Severe TEAEs Occurring in at Least 10 Subjects in the Aducanumab 10 mg/kg Arm in the Combined Placebo-Controlled and Long-Term Extension Periods of Pooled Studies 301 and 302

Adverse Event	ADU < 10 mg/kg N=1371 n (%)	ADU 10 mg/kg N=1386 n (%)
Amyloid Related Imaging Abnormality-Edema/Effusion	34 (2.5)	64 (4.6)
Superficial Siderosis Of Central Nervous System	20 (1.5)	48 (3.5)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	37 (2.7)	43 (3.1)
Infection, All MQG	11 (0.8)	18 (1.3)

Adverse Event	ADU < 10 mg/kg N=1371 n (%)	ADU 10 mg/kg N=1386 n (%)
Malignancy FDA B MQG	26 (1.9)	13 (0.9)
Acute Coronary Syndrome FDA B MQG	6 (0.4)	12 (0.9)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; AESEV= severe; StudyID: 301 and 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

13.3. TEAEs in Studies 103, 301, and 302

Table 71. TEAEs in the Aducanumab 10 mg/kg Arm with Incidence of at Least 5% Higher Than Placebo in Study 103

Adverse Event	ADU 1 mg/kg N=31 n (%)	ADU 3 mg/kg N=32 n (%)	ADU 6 mg/kg N=30 n (%)	ADU 10 mg/kg N=32 n (%)	ADU titratio n N=23 n (%)	ALL ADU N=148 n (%)	PBO N=48 n (%)
Total with at least one TEAE	29 (92)	27 (84)	28 (93)	29 (91)	21 (91)	134 (90)	47 (98)
Amyloid Related Imaging Abnormality-Edema/Effusion	1 (3)	2 (6)	11 (37)	13 (41)	8 (35)	35 (24)	0
Headache FDA B MQG	5 (16)	5 (16)	8 (27)	10 (31)	6 (26)	34 (23)	4 (8)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	1 (3)	3 (9)	5 (17)	7 (22)	4 (17)	20 (14)	3 (6)
Superficial Siderosis Of Central Nervous System	2 (7)	1 (3)	2 (7)	4 (13)	3 (13)	12 (8)	0
Anemia MQG	1 (3)	1 (3)	0	4 (13)	2 (9)	8 (5)	0
Constipation	3 (10)	1 (3)	1 (3)	3 (9)	1 (4)	9 (6)	0
Confusion, Delirium, Altered Mental Status, Disorientation, Coma MQG	3 (10)	2 (6)	2 (7)	3 (9)	1 (4)	11 (7)	1 (2)

Procedural pain	2 (7)	0	0	2 (6)	0	4 (3)	0
Paresthesia	1 (3)	0	0	2 (6)	0	3 (2)	0
Myopia	0	0	0	2 (6)	0	2 (1)	0
Dyspepsia FDA B MQG	3 (10)	0	1 (3)	2 (6)	2 (9)	8 (5)	0
Visual Disturbance MQG	1 (3)	0	1 (3)	2 (6)	0	4 (3)	0
Bronchospasm FDA N MQG	0	0	0	2 (6)	0	2 (1)	0
Abnormal Liver Function Tests MQG	3 (10)	0	1 (3)	3 (9)	1 (4)	8 (5)	2 (4)
Urinary tract infection	3 (10)	2 (6)	4 (13)	5 (16)	5 (22)	19 (13)	5 (10)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; APHASE: Placebo-controlled; Group by USUBJID, AEDECOD, TRT01P; tabulated on TRT01P. MQG: MedDRA query group.

Table 72. TEAEs With Incidence Greater than 10% in the Aducanumab 10 mg/kg Arm in the Combined Placebo-Controlled and Long-Term Extension Periods of Studies 301 and 302

Adverse Event	ADU < 10 mg/kg N=1371 n (%)	ADU 10 mg/kg N=1386 n (%)
Total with at least one TEAE	1210 (88)	1228 (89)
Infection, All MQG	570 (42)	563 (41)
Amyloid Related Imaging Abnormality-Edema/Effusion	348 (25)	472 (34)
Headache FDA B MQG	283 (21)	294 (21)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	237 (17)	264 (19)
Arrhythmia FDA B MQG	208 (15)	232 (17)
Fall	212 (15)	227 (16)
Superficial Siderosis Of Central Nervous System	141 (10)	209 (15)
Nasopharyngitis	175 (13)	191 (14)
Hemorrhage FDA N MQG	183 (13)	187 (13)
Arthritis FDA B MQG	161 (12)	178 (13)
Vertigo FDA B MQG	156 (11)	177 (13)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; StudyID: 301 and 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

Table 73. TEAEs With Incidence Greater than 10% in the Aducanumab 10mg/kg Group in the Combined Placebo-Controlled and Long-Term Extension Periods of Studies 103, 301, and 302

Adverse Event	ADU < 10 mg/kg N=1493 n (%)	ADU 10 mg/kg N=1449 n (%)
Total with at least one TEAE	1327 (89)	1287 (89)
Infection, All MQG	645 (43)	606 (42)
Amyloid Related Imaging Abnormality-Edema/Effusion	371 (25)	495 (34)
Headache FDA B MQG	317 (21)	318 (22)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	261 (17)	276 (19)
Fall	249 (17)	244 (17)
Arrhythmia FDA B MQG	242 (16)	246 (17)
Superficial Siderosis Of Central Nervous System	147 (10)	217 (15)
Nasopharyngitis	193 (13)	203 (14)
Hemorrhage FDA N MQG	220 (15)	199 (14)
Arthritis FDA B MQG	193 (13)	194 (13)
Vertigo FDA B MQG	172 (12)	194 (13)

This table was created by the reviewer using ISS ADAE, POOLC=POOLB; SAFFL=Y; TRTEMFL=Y; StudyID: 103, 301, and 302; Group by USUBJID, AEDECOD, POOLTR3 Reassigned B; tabulated on POOLTR3 Reassigned B. MQG: MedDRA query group.

Table 74. TEAEs in the 10 mg/kg Aducanumab Group with Incidence of at Least 2% and at Least 2% Higher Than Placebo, by Preferred Term, Maximum Dose Received in the Placebo-Controlled Period of Study 302

Preferred Term	1 mg/kg (N = 13)	3 mg/kg (N = 412)	6 mg/kg (N = 208)	10 mg/kg (N = 458)	All Aducanumab (N =1091)	Placebo (N = 547)
Total Subjects with any Adverse Events	9 (69.2%)	378 (91.7%)	181 (87.0%)	428 (93.4%)	996 (91.3%)	478 (87.4%)
Amyloid Related Imaging Abnormality-Edema/Effusion	0 (0.0%)	134 (32.5%)	52 (25.0%)	142 (31.0%)	328 (30.1%)	13 (2.4%)
Headache	1 (7.7%)	86 (20.9%)	34 (16.3%)	96 (21.0%)	217 (19.9%)	84 (15.4%)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	0 (0.0%)	86 (20.9%)	29 (13.9%)	80 (17.5%)	195 (17.9%)	37 (6.8%)
Superficial Siderosis Of Central Nervous System	0 (0.0%)	54 (13.1%)	17 (8.2%)	54 (11.8%)	125 (11.5%)	14 (2.6%)
Dizziness	1 (7.7%)	39 (9.5%)	12 (5.8%)	45 (9.8%)	97 (8.9%)	44 (8.0%)
Back pain	0 (0.0%)	31 (7.5%)	10 (4.8%)	40 (8.7%)	81 (7.4%)	36 (6.6%)

Preferred Term	1 mg/kg (N = 13)	3 mg/kg (N = 412)	6 mg/kg (N = 208)	10 mg/kg (N = 458)	All Aducanumab (N =1091)	Placebo (N = 547)
Diarrhea	1 (7.7%)	34 (8.3%)	8 (3.8%)	37 (8.1%)	80 (7.3%)	30 (5.5%)
Cough	0 (0.0%)	14 (3.4%)	11 (5.3%)	32 (7.0%)	57 (5.2%)	28 (5.1%)
Vomiting	1 (7.7%)	18 (4.4%)	6 (2.9%)	25 (5.5%)	50 (4.6%)	17 (3.1%)
Nasal congestion	0 (0.0%)	2 (0.5%)	4 (1.9%)	14 (3.1%)	20 (1.8%)	6 (1.1%)

This table was created by the reviewer using data from analyses by Senior Clinical Analyst Dr. Rui Li.

Table 75. TEAEs in the 10 mg/kg Aducanumab Group with Incidence of at Least 2% and at Least 2% Higher Than Placebo, by Preferred Term, Maximum Dose Received in Pooled Studies 301 and 302

Preferred Term	1 mg/kg (N = 29)	3 mg/kg (N = 844)	6 mg/kg (N = 403)	10 mg/kg (N = 922)	All Aducanumab (N =2198)	Placebo (N =1087)
Total Subjects with any Adverse Events	16 (55.2%)	781 (92.5%)	352 (87.3%)	844 (91.5%)	1993 (90.7%)	945 (86.9%)
Amyloid Related Imaging Abnormality- Edema/Effusion	1 (3.4%)	277 (32.8%)	103 (25.6%)	287 (31.1%)	668 (30.4%)	29 (2.7%)
Headache	2 (6.9%)	179 (21.2%)	64 (15.9%)	186 (20.2%)	431 (19.6%)	165 (15.2%)
Amyloid Related Imaging Abnormality- Microhemorrhages And Hemosiderin Deposits	0 (0.0%)	176 (20.9%)	59 (14.6%)	153 (16.6%)	388 (17.7%)	71 (6.5%)
Fall	1 (3.4%)	113 (13.4%)	57 (14.1%)	139 (15.1%)	310 (14.1%)	128 (11.8%)
Superficial Siderosis Of Central Nervous System	1 (3.4%)	112 (13.3%)	34 (8.4%)	118 (12.8%)	265 (12.1%)	24 (2.2%)
Diarrhea	1 (3.4%)	67 (7.9%)	27 (6.7%)	86 (9.3%)	181 (8.2%)	74 (6.8%)
Back pain	0 (0.0%)	49 (5.8%)	21 (5.2%)	81 (8.8%)	151 (6.9%)	78 (7.2%)
Confusional state	0 (0.0%)	40 (4.7%)	13 (3.2%)	35 (3.8%)	88 (4.0%)	26 (2.4%)

This table was created by the reviewer using data from analyses by Senior Clinical Analyst Dr. Rui Li.

Table 76. TEAEs with an Incidence Greater than 10% in the Aducanumab 10mg/kg Group by Preferred Term, Maximum Dose Received in the Combined Placebo-Controlled and Long-Term Extension Periods of Study 302.

Preferred Term	Aducanumab < 10 mg/kg (N = 822)	Aducanumab 10 mg/kg (N = 531)
Total Subjects with any Adverse Events	700 (85.2%)	494 (93.0%)
Amyloid Related Imaging Abnormality-Edema/Effusion	222 (27.0%)	170 (32.0%)
Headache	149 (18.1%)	106 (20.0%)
Fall	104 (12.7%)	98 (18.5%)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	145 (17.6%)	96 (18.1%)
Nasopharyngitis	99 (12.0%)	91 (17.1%)
Superficial Siderosis Of Central Nervous System	93 (11.3%)	70 (13.2%)
Dizziness	61 (7.4%)	57 (10.7%)

This table was created by the reviewer using data from analyses by Senior Clinical Analyst Dr. Rui Li.

Table 77. TEAEs with an Incidence Greater than 10% in the Aducanumab 10mg/kg Group by Preferred Term, Maximum Dose Received in the Combined Placebo-Controlled and Long-Term Extension Periods of Studies 103, 301, and 302.

Preferred Term	Aducanumab < 10 mg/kg (N =1787)	Aducanumab 10 mg/kg (N =1155)
Total Subjects with any Adverse Events	1549 (86.7%)	1065 (92.2%)
Amyloid Related Imaging Abnormality-Edema/Effusion	498 (27.9%)	368 (31.9%)
Headache	337 (18.9%)	241 (20.9%)
Fall	282 (15.8%)	210 (18.2%)
Amyloid Related Imaging Abnormality-Microhemorrhages And Hemosiderin Deposits	337 (18.9%)	200 (17.3%)
Nasopharyngitis	213 (11.9%)	183 (15.8%)
Superficial Siderosis Of Central Nervous System	203 (11.4%)	161 (13.9%)
Dizziness	142 (7.9%)	127 (11.0%)
Diarrhea	146 (8.2%)	122 (10.6%)
Upper respiratory tract infection	161 (9.0%)	115 (10.0%)

13.4. TEAEs Related to Contusion in Pooled Studies 301 and 302

The following list includes TEAEs by preferred term related to contusion in pooled Studies 301 and 302: Bone Contusion; Cardiac Contusion; Catheter Site Bruise; Contusion; Ecchymosis; Eye Contusion; Eyelid Contusion; Infusion Site Bruising; Oral Contusion; Post Procedural Contusion; Pulmonary Contusion; Vessel Puncture Site Bruise.

The following tables show the frequency of Hemorrhage FDA N MQG after TEAEs related to contusion were excluded and the frequency of TEAEs related to contusion in pooled Studies 301 and 302.

Table 78. Frequency of TEAEs Related to Hemorrhage FDA N MQG after Exclusion of TEAEs Related to Contusion in Pooled Studies 301 and 302.

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 (%)
7	9	8	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.

Table 79. Frequency of TEAEs Related to Contusion in Pooled Studies 301 and 302.

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 (%)
5	7	7	6	6

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.

13.5. Preferred Terms Related to Laboratory Findings Within the SOC Investigations

The following is a list of preferred terms within the SOC Investigations related to Laboratory Findings in Studies 301 and 302: 5-Hydroxyindolacetic Acid In Urine Decreased; Alanine Aminotransferase Abnormal; Alanine Aminotransferase Increased; Amylase Increased; Antinuclear Antibody Positive; Aspartate Aminotransferase Increased; Band Neutrophil Count Increased; Bilirubin Conjugated Increased; Biopsy Bone; Blood Alkaline Phosphatase Increased; Blood Bilirubin Increased; Blood Calcium Decreased; Blood Calcium Increased; Blood

Cholesterol Increased; Blood Creatine Phosphokinase Mb Increased; Blood Creatine Increased; Blood Creatinine Abnormal; Blood Creatinine Increased; Blood Culture Positive; Blood Folate Decreased; Blood Glucose Abnormal; Blood Glucose Decreased; Blood Glucose Increased; Blood Iron Decreased; Blood Ketone Body Increased; Blood Lactate Dehydrogenase Increased; Blood Lactic Acid Increased; Blood Parathyroid Hormone Increased; Blood Phosphorus Decreased; Blood Phosphorus Increased; Blood Potassium Decreased; Blood Potassium Increased; Blood Sodium Decreased; Blood Test Abnormal; Blood Testosterone Decreased; Blood Thyroid Stimulating Hormone Increased; Blood Urea Increased; Blood Uric Acid Increased; Blood Urine; Blood Urine Present; B-Lymphocyte Count Increased; Brain Natriuretic Peptide Increased; Cortisol Decreased; C-Reactive Protein Increased; Csf Cell Count Increased; Drug Level Increased; Eosinophil Count Abnormal; Eosinophil Count Increased; Eosinophil Percentage Abnormal; Fibrin D Dimer Increased; Gamma-Glutamyltransferase Increased; Gastric Ph Decreased; Glycosylated Hemoglobin Increased; Hematocrit Decreased; Hematocrit Increased; Hemoglobin Decreased; Hepatic Enzyme Increased; Influenza A Virus Test Positive; Liver Function Test Abnormal; Liver Function Test Increased; Low Density Lipoprotein Increased; Lymphocyte Count Decreased; Lymphocyte Morphology Abnormal; Mean Cell Volume Abnormal; Mean Cell Volume Increased; Monocyte Count Decreased; Neutrophil Count Decreased; Neutrophil Count Increased; Occult Blood; Occult Blood Positive; Platelet Count Decreased; Platelet Count Increased; Prostatic Specific Antigen Increased; Protein Total Decreased; Protein Urine; Protein Urine Present; Proteus Test Positive; Prothrombin Time Prolonged; Red Blood Cell Count Decreased; Red Blood Cell Count Increased; Red Blood Cell Sedimentation Rate Increased; Red Cell Distribution Width Increased; Renal Function Test Abnormal; Respiratory Syncytial Virus Test Positive; Rheumatoid Factor Increased; Serum Ferritin Decreased; Serum Ferritin Increased; Smooth Muscle Antibody Positive; Specific Gravity Urine Increased; Thyroid Hormones Decreased; Transaminases Increased; Troponin Increased; Tumor Marker Increased; Urine Analysis Abnormal; Vanillyl Mandelic Acid Urine Decreased; Vitamin B12 Decreased; Vitamin B12 Increased; Vitamin D Decreased; White Blood Cell Count Decreased; White Blood Cell Count Increased; White Blood Cells Urine; White Blood Cells Urine Positive.

13.6. TEAEs in Subjects without ARIA in Study 103

Table 80. TEAEs Reported in Subjects Without ARIA-E, ARIA-Microhemorrhages and Hemosiderin Deposits, or Superficial Siderosis in the 10 mg/kg Aducanumab Group with Incidence of at Least 9% Higher Than Placebo in Study 103

Adverse Event	ADU 1 mg/kg N=26 n (%)	ADU 3 mg/kg N=23 n (%)	ADU 6 mg/kg N=17 n (%)	ADU 10 mg/kg N=17 n (%)	ADU titration N=15 n (%)	All ADU N=98 n (%)	Placebo N=35 n (%)
Anemia MQG	1 (4)	1 (4)	0	4 (24)	2 (13)	8 (8)	0

Adverse Event	ADU 1 mg/kg N=26 n (%)	ADU 3 mg/kg N=23 n (%)	ADU 6 mg/kg N=17 n (%)	ADU 10 mg/kg N=17 n (%)	ADU titration N=15 n (%)	All ADU N=98 n (%)	Placebo N=35 n (%)
Headache FDA B MQG	5 (19)	2 (9)	2 (12)	4 (24)	3 (20)	16 (16)	1 (3)
Urinary tract infection	2 (8)	2 (9)	2 (12)	4 (24)	4 (27)	14 (14)	3 (9)
Constipation	1 (4)	1 (4)	1 (6)	2 (12)	1 (7)	6 (6)	0
Pain in extremity	0	1 (4)	1 (6)	2 (12)	0	4 (4)	0
Dyspepsia FDA B MQG	3 (12)	0	0	2 (12)	1 (7)	6 (6)	0
Arthritis FDA B MQG	2 (8)	6 (26)	1 (6)	3 (18)	3 (20)	15 (15)	3 (9)
Gastrointestinal Bleed MQG	0	0	0	2 (12)	0	2 (2)	1 (3)
Arthralgia FDA B MQG	2 (8)	6 (26)	1 (6)	2 (12)	2 (13)	13 (13)	1 (3)
Abnormal Liver Function Tests MQG	2 (8)	0	0	2 (12)	0	4 (4)	1 (3)
Pyrexia FDA B MQG	1 (4)	0	0	2 (12)	1 (7)	4 (4)	1 (3)

This table was created by the reviewer using Study 103 ADAE, TRTEMFL=Y; ARIA E, H, SS Subject Level Flag Placebo-controlled: Inversion of 1; APHASE: Placebo-controlled; Group by USUBJID, AEDECOD, TRT01P; tabulated on TRT01P. MQG: MedDRA query group.

13.7. Preferred Terms within the SOC Injury, Poisoning, and Procedural Complications with Potential Traumatic Etiology

The following is a list of preferred terms within the SOC Injury, poisoning, and procedural complications occurring within Studies 301 and 302 that had potential traumatic etiology: Accident; Accident at home; Accident at work; Ankle fracture; Aqueous humour leakage; Back injury; Bone contusion; Breast injury; Buttock injury; Cardiac contusion; Cartilage injury; Cervical vertebral fracture; Chest injury; Clavicle fracture; Compression fracture; Concussion; Contusion; Corneal abrasion; Craniocerebral injury; Crush injury; Deafness traumatic; Epicondylitis; Epiphyseal fracture; Eye contusion; Eye injury; Eyelid contusion; Face injury; Facial bones fracture; Fall; Femoral neck fracture; Femur fracture; Fibula fracture; Foot fracture; Forearm fracture; Fracture; Fractured coccyx; Fractured sacrum; Gingival injury; Hand fracture; Head injury; Hip fracture; Humerus fracture; Injury; Injury corneal; Jaw fracture; Joint capsule rupture; Joint dislocation; Joint injury; Ligament injury; Ligament rupture; Ligament sprain; Limb crushing injury; Limb injury; Lip injury; Lower limb fracture; Lumbar vertebral fracture; Mallet finger; Meniscus injury; Multiple fractures; Muscle rupture; Muscle strain; Nail injury; Nerve injury; Patella fracture; Pelvic fracture; Periorbital hematoma; Periorbital Hemorrhage; Peripheral nerve injury; Pubis fracture; Pulmonary contusion; Radius fracture; Rib fracture;

Road traffic accident; Scapula fracture; Scar; Scratch; Seroma; Skeletal injury; Skin abrasion; Skin injury; Skin laceration; Skin wound; Skull fracture; Soft tissue injury; Spinal compression fracture; Spinal fracture; Sports injury; Sternal fracture; Stress fracture; Subdural hematoma; Subdural Hemorrhage; Tendon injury; Tendon rupture; Thoracic vertebral fracture; Tibia fracture; Tooth avulsion; Tooth fracture; Tooth injury; Traumatic hematoma; Ulna fracture; Upper limb fracture; Wound; Wrist fracture.

13.8. MedDRA Query Groups

The following is a list of MedDRA query groups referenced in this review and the preferred terms that contribute to the group. All preferred terms that contribute to their respective groups are listed even though the preferred term may have not been reported within the clinical program.

Abnormal Liver Function Tests

Alanine aminotransferase; alanine aminotransferase abnormal; alanine aminotransferase increased; aspartate aminotransferase; aspartate aminotransferase abnormal; aspartate aminotransferase increased; drug-induced liver injury; gamma-glutamyltransferase; gamma-glutamyltransferase abnormal; gamma-glutamyltransferase increased; hepatic enzyme abnormal; hepatic enzyme increased; hepatic function abnormal; hepatocellular injury; hepatotoxicity; hypertransaminasaemia; liver function test abnormal; liver function test increased; liver injury; transaminases; transaminases abnormal; transaminases increased.

Acute Coronary Syndrome FDA B

Acute cardiac event; acute myocardial infarction; age indeterminate myocardial infarction; angina pectoris; angina unstable; aortic annulus rupture; aortic root compression; arteriosclerosis coronary artery; arteriospasm coronary; blood creatine phosphokinase increased; blood creatine phosphokinase mb abnormal; blood creatine phosphokinase mb increased; cardiac arrest; cardiac enzymes increased; cardiac troponin i increased; cardiac troponin t increased; coronary arterial stent insertion; coronary artery bypass; coronary artery compression; coronary artery disease; coronary artery occlusion; coronary artery stenosis; coronary artery thrombosis; ecg signs of myocardial infarction; ecg signs of myocardial ischaemia; elastic vessel recoil complication; electrocardiogram st segment abnormal; electrocardiogram st segment depression; electrocardiogram st segment elevation; electrocardiogram st-t change; electrocardiogram st-t segment elevation; myocardial hypoxia; myocardial infarction; myocardial infarction old; myocardial ischaemia; myocardial necrosis; myocardial necrosis marker increased; myocardial reinfarction; myocardial reperfusion injury; myocardial stunning; papillary muscle infarction; periprocedural myocardial infarction; post procedural myocardial infarction; silent myocardial infarction; troponin i increased; troponin increased; troponin t increased; wellens' syndrome.

Allergic Reaction, Hypersensitivity

Allergic bronchitis; allergic oedema; allergic pharyngitis; allergic sinusitis; allergic transfusion reaction; allergy to vaccine; alveolitis allergic; anaphylactic reaction; anaphylactic shock; anaphylactic transfusion reaction; anaphylactoid reaction; angioedema; angioneurotic oedema; auricular swelling; blepharitis allergic; bronchopulmonary aspergillosis allergic; circumoral oedema; conjunctivitis allergic; contrast media allergy; dermatitis allergic; dermatitis atopic; device allergy; drug eruption; drug hypersensitivity; drug rash with eosinophilia and systemic symptoms; ear swelling; epiglottic oedema; face oedema; fixed eruption; fuchs' syndrome; hypersensitivity; infusion related reaction; injection related reaction; injection site atrophy; injection site discomfort; injection site hypersensitivity; injection site hypertrophy; injection site irritation; injection site macule; injection site necrosis; injection site plaque; injection site scab; injection site scar; injection site vesicles; laryngeal oedema; laryngitis allergic; laryngospasm; lip oedema; lip swelling; multiple allergies; nephritis allergic; oropharyngeal spasm; palatal oedema; pharyngeal oedema; pharyngeal swelling; photosensitivity allergic reaction; swelling face; swollen tongue; tongue oedema; urticaria; urticaria cholinergic; urticaria chronic; urticaria generalised; urticaria localised; urticaria pigmentosa; vasculitic rash.

Anemia

Anaemia; anaemia folate deficiency; anaemia haemolytic autoimmune; anaemia heinz body; anaemia macrocytic; anaemia megaloblastic; anaemia neonatal; anaemia of chronic disease; anaemia of malignant disease; anaemia of pregnancy; anaemia postoperative; anaemia splenic; anaemia vitamin b12 deficiency; anaemia vitamin b6 deficiency; aplasia pure red cell; aplastic anaemia; autoimmune haemolytic anaemia; cold type haemolytic anaemia; deficiency anaemia; erythropenia; haematocrit decreased; haemoglobin decreased; haemolytic anaemia; haemorrhagic anaemia; hyperchromic anaemia; hypochromic anaemia; iron deficiency anaemia; microangiopathic haemolytic anaemia; microcytic anaemia; nephrogenic anaemia; normochromic normocytic anaemia; pernicious anaemia; red blood cell count decreased; refractory anaemia with an excess of blasts; sideroblastic anaemia; warm type haemolytic anaemia.

Arrhythmia FDA B

Accelerated idioventricular rhythm; agonal rhythm; anomalous atrioventricular excitation; arrhythmia; arrhythmia neonatal; arrhythmia nos; arrhythmia nos foetal; arrhythmia nos neonatal; arrhythmia supraventricular; atrial bigeminy; atrial fibrillation; atrial fibrillation aggravated; atrial flutter; atrial flutter with 1:1 atrioventricular conduction; atrial parasystole; atrial tachycardia; atrioventricular extrasystoles; bradyarrhythmia; bradycardia; bradycardia foetal; bradycardia neonatal; bradycardia nos; bradytachycardia; cardiac fibrillation; cardiac fibrillation nos; cardiac flutter; cardiac iron overload; cardiac pacemaker insertion; central bradycardia; chagas' cardiomyopathy; congenital supraventricular tachycardia; dizziness; emery-dreifuss muscular dystrophy; extrasystoles; extrasystoles nos; foetal arrhythmia; foetal tachyarrhythmia; heart rate decreased; heart rate increased; heart rate irregular; junctional ectopic tachycardia; long qt syndrome; long qt syndrome congenital; loss of consciousness;

neonatal bradyarrhythmia; neonatal sinus bradycardia; neonatal sinus tachycardia; neonatal tachyarrhythmia; neonatal tachycardia; nodal arrhythmia; ogden syndrome; orthostatic collapse; pacemaker generated arrhythmia; palpitations; palpitations aggravated; parasystole; parasystolia; paroxysmal arrhythmia; presyncope; pulsus bigeminus; rebound tachycardia; reperfusion arrhythmia; reperfusion arrhythmias; rhythm idioventricular; sick sinus syndrome; sinoatrial node dysfunction; sinus arrhythmia; sinus bradycardia; sinus node dysfunction; sinus tachycardia; sudden cardiac death; supraventricular arrhythmia nos; supraventricular extrasystoles; supraventricular tachyarrhythmia; supraventricular tachycardia; syncope; syncope aggravated; syncope vasovagal; tachyarrhythmia; tachycardia; tachycardia aggravated; tachycardia foetal; tachycardia irregular; tachycardia nos; tachycardia paroxysmal; tachycardia paroxysmal nos; tachycardia supraventricular aggr; torsade de pointes; trigeminy; vasovagal attack; ventricular arrhythmia; ventricular arrhythmia nos; ventricular bigeminy; ventricular extrasystoles; ventricular fibrillation; ventricular fibrillation and flutter; ventricular flutter; ventricular parasystole; ventricular quadrigeminy; ventricular tachyarrhythmia; ventricular tachycardia; ventricular trigeminy; wandering pacemaker; withdrawal arrhythmia; wolff-parkinson-white syndrome; wolff-parkinson-white syndrome congenital.

Arthralgia FDA B

Administration site joint discomfort; administration site joint effusion; administration site joint erythema; administration site joint movement impairment; administration site joint pain; administration site joint warmth; amyloid arthropathy; ankle arthroplasty; ankle impingement; application site joint discomfort; application site joint effusion; application site joint erythema; application site joint movement impairment; application site joint pain; application site joint swelling; application site joint warmth; arthralgia; arthralgia aggravated; arthrodesis; arthrofibrosis; arthropathy; arthroscopy abnormal; arthrotoxicity; articular calcification; articular disc disorder; aspiration joint abnormal; atlantoaxial instability; behcet's syndrome; carpal collapse; cervicobrachial syndrome; chondrocalcinosis; chondrocalcinosis pyrophosphate; chondromalacia; costochondral separation; craniocervical syndrome; crowned dens syndrome; crystal arthropathy; destructive spondyloarthropathy; diabetic arthropathy; diabetic cheiroarthropathy; facet joint syndrome; gouty tophus; haemarthrosis; haemophilic arthropathy; hip arthroplasty; hyper igd syndrome; infusion site joint discomfort; infusion site joint effusion; infusion site joint erythema; infusion site joint infection; infusion site joint movement impairment; infusion site joint pain; infusion site joint swelling; infusion site joint warmth; injection site joint discomfort; injection site joint effusion; injection site joint erythema; injection site joint infection; injection site joint movement impairment; injection site joint pain; injection site joint swelling; injection site joint warmth; intervertebral discitis; joint adhesion; joint ankylosis; joint arthroplasty; joint capsule rupture; joint contracture; joint crepitation; joint debridement; joint deposit; joint destruction; joint dislocation pathological; joint effusion; joint fluid drainage; joint lock; joint microhaemorrhage; joint range of motion decreased; joint stiffness; joint swelling; joint warmth; knee arthroplasty; knee impingement syndrome; lateral patellar compression syndrome; medical device site joint discomfort; medical

device site joint effusion; medical device site joint erythema; medical device site joint movement impairment; medical device site joint pain; medical device site joint swelling; medical device site joint warmth; multicentric reticulohistiocytosis; musculoskeletal stiffness; neck pain; neuropathic arthropathy; osteoarthritis; periarticular disorder; plica syndrome; pogosta disease; polyarthralgia; psoriatic arthropathy; rheumatic disorder; rheumatic fever; rheumatoid lung; rheumatoid neutrophilic dermatosis; rheumatoid nodule; rheumatoid nodule removal; rheumatoid scleritis; rheumatoid vasculitis; schnitzler's syndrome; senile ankylosing vertebral hyperostosis; shoulder arthroplasty; spinal fusion acquired; spinal pain; spondylitis; spondyloarthropathy; spondylopathy traumatic; spondylosis; swollen joint count increased; synovectomy; synovial fluid analysis abnormal; synovial fluid crystal present; synovial fluid protein present; synovial fluid red blood cells positive; synovial fluid white ; lood cells positive; synoviorthesis; tender joint count increased; traumatic arthropathy; traumatic arthrosis; ulnocarpal abutment syndrome; vaccination site joint discomfort; vaccination site joint effusion; vaccination site joint erythema; vaccination site joint movement impairment; vaccination site joint pain; vaccination site joint swelling; vaccination site joint warmth; vertebral osteophyte.

Arthritis FDA B

Administration site joint discomfort; administration site joint effusion; administration site joint erythema; administration site joint infection; administration site joint inflammation; administration site joint movement impairment; administration site joint pain; administration site joint warmth; amyloid arthropathy; ankle arthroplasty; ankle impingement; ankylosing spondylitis; antithyroid arthritis syndrome; application site joint discomfort; application site joint effusion; application site joint erythema; application site joint inflammation; application site joint movement impairment; application site joint pain; application site joint swelling; application site joint warmth; arthralgia; arthralgia aggravated; arthritis; arthritis allergic; arthritis bacterial; arthritis climacteric; arthritis enteropathic; arthritis fungal; arthritis gonococcal; arthritis helminthic; arthritis infective; arthritis reactive; arthritis rubella; arthritis salmonella; arthritis viral; arthrodesis; arthrofibrosis; arthropathy; arthroscopy abnormal; arthrotoxicity; articular calcification; articular disc disorder; aspiration joint abnormal; atlantoaxial instability; autoimmune arthritis; axial spondyloarthritis; behcet's syndrome; blau syndrome; caplan's syndrome; carcinomatous polyarthritis; carpal collapse; cervicobrachial syndrome; chondrocalcinosis; chondrocalcinosis pyrophosphate; chondromalacia; costochondral separation; craniocervical syndrome; crowned dens syndrome; crystal arthropathy; destructive spondyloarthropathy; diabetic arthropathy; diabetic cheiroarthropathy; enteropathic spondylitis; epidemic polyarthritis; facet joint syndrome; felty's syndrome; femoroacetabular impingement; gout; gouty arthritis; gouty tophus; haemarthrosis; haemophilic arthropathy; hip arthroplasty; hyper igd syndrome; infective spondylitis; infrapatellar fat pad inflammation; infusion site joint discomfort; infusion site joint effusion; infusion site joint erythema; infusion site joint infection; infusion site joint inflammation; infusion site joint movement impairment; infusion site joint pain; infusion site joint swelling;

infusion site joint warmth; injection site joint discomfort; injection site joint effusion; injection site joint erythema; injection site joint infection; injection site joint inflammation; injection site joint movement impairment; injection site joint pain; injection site joint swelling; injection site joint warmth; interspinous osteoarthritis; intervertebral discitis; joint abscess; joint adhesion; joint ankylosis; joint arthroplasty; joint capsule rupture; joint contracture; joint crepitation; joint debridement; joint deposit; joint destruction; joint dislocation pathological; joint effusion; joint fluid drainage; joint lock; joint microhaemorrhage; joint range of motion decreased; joint stiffness; joint swelling; joint warmth; juvenile arthritis; juvenile idiopathic arthritis; juvenile psoriatic arthritis; juvenile spondyloarthritis; knee arthroplasty; knee impingement syndrome; laryngeal rheumatoid arthritis; lateral patellar compression syndrome; localized osteoarthritis; medical device site joint discomfort; medical device site joint effusion; medical device site joint erythema; medical device site joint infection; medical device site joint inflammation; medical device site joint movement impairment; medical device site joint pain; medical device site joint swelling; medical device site joint warmth; monoarthritis; multicentric reticulohistiocytosis; musculoskeletal stiffness; neck pain; neuropathic arthropathy; nodal osteoarthritis; osteoarthritis; osteoarthropathy; palindromic rheumatism; paraneoplastic arthritis; peri-arthritis; peri-arthritis calcarea; periarticular disorder; plica syndrome; pogosta disease; polyarthralgia; polyarthritis; poncet's disease; psoriatic arthropathy; pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome; rapidly progressive osteoarthritis; reiter's syndrome; rheumatic disorder; rheumatic fever; rheumatoid arthritis; rheumatoid lung; rheumatoid neutrophilic dermatosis; rheumatoid nodule; rheumatoid nodule removal; rheumatoid scleritis; rheumatoid vasculitis; sacroiliitis; schnitzler's syndrome; senile ankylosing vertebral hyperostosis; septic arthritis gonococcal; septic arthritis haemophilus; septic arthritis neisserial; septic arthritis staphylococcal; septic arthritis streptobacillus; septic arthritis streptococcal; seronegative arthritis; shoulder arthroplasty; sle arthritis; spinal fusion acquired; spinal osteoarthritis; spinal pain; spondylitis; spondyloarthropathy; spondylopathy traumatic; spondylosis; still's disease; still's disease adult onset; swollen joint count increased; synovectomy; synovial fluid analysis abnormal; synovial fluid crystal present; synovial fluid protein present; synovial fluid red blood cells positive; synovial fluid white blood cells positive; synoviorthesis; synovitis; tender joint count increased; traumatic arthritis; traumatic arthropathy; traumatic arthrosis; ulnocarpal abutment syndrome; vaccination site joint discomfort; vaccination site joint effusion; vaccination site joint erythema; vaccination site joint infection; vaccination site joint inflammation; vaccination site joint movement impairment; vaccination site joint pain; vaccination site joint swelling; vaccination site joint warmth; vertebral osteophyte.

Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis

Allergic bronchitis; alveolitis; bacterial tracheitis; bronchial infection; bronchiectasis; bronchiolitis; bronchitis; bronchitis acute; bronchitis acute viral; bronchitis bacterial; bronchitis chemical; bronchitis chronic; bronchitis fungal; bronchitis pneumococcal; bronchitis viral; bronchopneumopathy; bronchopulmonary aspergillosis allergic; fungal tracheitis; infective

exacerbation of bronchiectasis; lower respiratory tract infection; lower respiratory tract infection bacterial; lower respiratory tract infection fungal; lower respiratory tract infection viral; lung infection; lung infection pseudomonal; obstructive chronic bronchitis with acute exacerbation; pseudomonas bronchitis; pulmonary mycosis; rhinotracheitis; sinobronchitis; tracheitis; tracheobronchitis; tracheobronchitis viral.

Bronchospasm FDA N

Analgesic asthma syndrome; aspirin-exacerbated respiratory disease; asthma; asthma aggravated; asthma aspirin-sensitive; asthma exercise induced; asthma late onset; asthma nos; asthma-chronic obstructive pulmonary disease overlap syndrome; asthmatic crisis; bronchial hyperactivity; bronchial hyperreactivity; bronchospasm; bronchospasm aggravated; bronchospasm nos; bronchospasm paradoxical; childhood asthma; infantile asthma; occupational asthma; reactive airways dysfunction syndrome; reversible airways obstruction; reversible airways obstruction nos; severe asthma with fungal sensitisation; small airways disease; status asthmaticus.

Celullitis, Erysipelas

Administration site cellulitis; breast cellulitis; cellulitis; cellulitis gangrenous; cellulitis of male external genital organ; cellulitis orbital; cellulitis staphylococcal; cellulitis streptococcal; erysipelas; external ear cellulitis; incision site cellulitis; injection site cellulitis; periorbital cellulitis; post procedural cellulitis; vulval cellulitis.

Conduction Disturbance

Adams-stokes syndrome; atrioventricular block; atrioventricular block complete; atrioventricular block first degree; atrioventricular block second degree; atrioventricular block third degree; atrioventricular dissociation; bifascicular block; bundle branch block; bundle branch block bilateral; bundle branch block left; bundle branch block right; conduction disorder; defect conduction intraventricular; electrocardiogram pr prolongation; electrocardiogram qrs complex prolonged; sinoatrial block; sinus arrest; trifascicular block; wolff-parkinson-white syndrome.

Confusion, Delirium, Altered Mental Status, Disorientation, Coma

Altered state of consciousness; apallic syndrome; catatonia; cerebral circulatory failure; coma; coma hepatic; confusion postoperative; confusional state; decerebration; delirium; depressed level of consciousness; diabetic hyperosmolar coma; disorientation; dissociative fugue; disturbance in attention; hypercapnic coma; hypoglycaemic coma; hypoglycaemic unconsciousness; hypoxic-ischaemic encephalopathy; incoherent; lethargy; mental impairment; mental status changes; shock hypoglycaemic; somnolence; stupor; transient global amnesia; traumatic coma; unresponsive to stimuli; vascular dementia.

Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Difficile Colitis

Acute haemorrhagic ulcerative colitis; amoebic dysentery; campylobacter gastroenteritis; campylobacter infection; campylobacter intestinal infection; clostridial infection; clostridium colitis; clostridium difficile colitis; clostridium test positive; colitis; colitis erosive; colitis ischaemic; colitis microscopic; colitis psychogenic; colitis ulcerative; colon dysplasia; colonic obstruction; crohn's disease; cytomegalovirus colitis; diarrhoea; diarrhoea haemorrhagic; diarrhoea infectious; dysentery; enteritis; enteritis infectious; enteritis; ecroticans; enterocele; enterocolitis; enterocolitis bacterial; enterocolitis fungal; enterocolitis haemorrhagic; enterocolitis infectious; enterocolitis viral; gastroenteritis; gastroenteritis adenovirus; gastroenteritis aeromonas; gastroenteritis bacterial; gastroenteritis clostridial; gastroenteritis cryptosporidial; gastroenteritis enteroviral; gastroenteritis escherichia coli; gastroenteritis norovirus; gastroenteritis norwalk virus; gastroenteritis rotavirus; gastroenteritis salmonella; gastroenteritis viral; gastrointestinal candidiasis; gastrointestinal infection; gastrointestinal inflammation; gastrointestinal viral infection; inflammatory bowel disease; intestinal ischaemia; intestinal perforation; large intestinal ulcer; large intestine perforation; mechanical ileus; necrotising colitis; parasitic infection intestinal; post procedural diarrhoea; pseudomembranous colitis; sigmoiditis viral diarrhea.

Diarrhoea FDA N

Allergic gastroenteritis; amoebic dysentery; antidiarrheal supportive care; antidiarrhoeal supportive care; autoimmune enteropathy; bacterial diarrhoea; cholera; diarrhoea; diarrhoea aggravated; diarrhoea haemorrhagic; diarrhoea infectious; diarrhoea neonatal; diarrhoea nos; diarrhoea postoperative; dysentery; dysentery nos; loose stools; post procedural diarrhoea; sprue-like enteropathy; stools watery; viral diarrhea.

Diverticular Disease

Acute diverticulitis; diverticular perforation; diverticulitis; diverticulitis intestinal haemorrhagic; diverticulum; diverticulum duodenal; diverticulum intestinal; diverticulum intestinal haemorrhagic; diverticulum oesophageal.

Dyspepsia FDA B

Abdominal discomfort; abdominal distension; abdominal pain upper; acid peptic disease; biliary dyspepsia; burn oesophageal; burning sensation; chest discomfort; chest pain; distension nos; dyspepsia; dyspepsia aggravated; early satiety; epigastric discomfort; eructation; gastric disorder; gastric irritation; gastritis; gastroesophagitis; gastrointestinal pain; gastrooesophageal reflux disease; gastrooesophagitis; non-cardiac chest pain; oesophageal discomfort; oesophageal irritation; oesophageal pain; oesophageal reflux; oesophageal reflux aggravated; oesophagitis; oesophagitis aggravated; oesophagitis nos; reflux gastritis; reflux oesophagitis; ulcer type pain.

Elevated Blood Urea Nitrogen or Creatinine, Anuria, Acute Renal Failure, Chronic Renal Failure, Oliguria

Acute kidney injury; acute prerenal failure; anuria; azotaemia; blood creatine increased; blood creatinine abnormal; blood creatinine increased; blood urea increased; blood urea nitrogen/creatinine ratio increased; cardiorenal syndrome; creatinine renal clearance abnormal; creatinine renal clearance decreased; glomerular filtration rate abnormal; glomerular filtration rate decreased; hepatorenal failure; hypercreatinaemia; hypercreatininaemia; nephropathy toxic; oliguria; postoperative renal failure; postrenal failure; prerenal failure; renal disorder; renal failure; renal failure acute; renal failure chronic; renal function test abnormal; renal impairment; renal insufficiency; renal ischaemia; uraemic encephalopathy; urate nephropathy; urine output decreased.

Encephalitis, Encephalopathy

Acute disseminated encephalomyelitis; acute encephalitis with refractory, repetitive partial seizures; acute haemorrhagic leukoencephalitis; brain damage; encephalitis; encephalomyelitis; encephalopathy; hypercapnic encephalopathy; hypertensive encephalopathy; hyponatraemic encephalopathy; hypoxic encephalopathy; hypoxic-ischaemic encephalopathy; leukoencephalopathy; metabolic encephalopathy; noninfective encephalitis; septic encephalopathy; tick-borne viral encephalitis; toxic encephalopathy; uraemic encephalopathy; vascular encephalopathy.

Fracture

Acetabulum fracture; ankle fracture; avulsion fracture; cervical vertebral fracture; clavicle fracture; comminuted fracture; compression fracture; epiphyseal fracture; external fixation of fracture; facial bones fracture; femoral neck fracture; femur fracture; fibula fracture; foot fracture; forearm fracture; fracture; fracture displacement; fracture malunion; fractured coccyx; fractured ischium; fractured sacrum; hand fracture; hip fracture; humerus fracture; internal fixation of fracture; jaw fracture; lower limb fracture; lumbar vertebral fracture; multiple fractures; open fracture; osteoporotic fracture; patella fracture; pathological fracture; pelvic fracture; periprosthetic fracture; pubis fracture; radius fracture; rib fracture; scapula fracture; skull fracture; skull fractured base; spinal compression fracture; spinal fracture; sternal fracture; stress fracture; thoracic vertebral fracture; tibia fracture; traumatic fracture; ulna fracture; upper limb fracture; wrist fracture.

Gastrointestinal Bleed

Chronic gastrointestinal bleeding; colonic haematoma; colonic haemorrhage; diarrhoea haemorrhagic; diverticulitis intestinal haemorrhagic; diverticulum intestinal haemorrhagic; duodenal ulcer haemorrhage; duodenitis haemorrhagic; dysentery; enterocolitis haemorrhagic; gastric haemorrhage; gastric occult blood positive; gastric ulcer haemorrhage; gastric varices haemorrhage; gastritis haemorrhagic; gastroduodenitis haemorrhagic; gastrointestinal angiodysplasia haemorrhagic; gastrointestinal haemorrhage; gastrointestinal polyp haemorrhage; gastrointestinal ulcer haemorrhage; haematemesis; haematochezia; haemorrhagic erosive gastritis; intestinal haemorrhage; intestinal polyp haemorrhage; large

intestinal haemorrhage; large intestinal ulcer haemorrhage; lower gastrointestinal haemorrhage; melaena; occult blood; occult blood positive; oesophageal haemorrhage; oesophageal ulcer haemorrhage; oesophageal varices haemorrhage; oesophagitis haemorrhagic; peptic ulcer haemorrhage; proctitis haemorrhagic; rectal haemorrhage; rectal ulcer haemorrhage; small intestinal haemorrhage; upper gastrointestinal haemorrhage.

Headache FDA B

Basilar migraine; cervicogenic headache; chronic paroxysmal hemicrania; cluster headache; cluster headaches; cold-stimulus headache; complicated migraine; drug withdrawal headache; exertional headache; external compression headache; familial hemiplegic migraine; familiar hemiplegic migraine; frequent headaches; head discomfort; headache; headache histamine; headache nos; headache nos aggravated; headache postoperative; hemicephalgia; hemiplegic migraine; lumbar puncture headache; medication overuse headache; migraine; migraine aggravated; migraine hemiplegic; migraine nos; migraine prophylaxis; migraine with aura; migraine without aura; new daily persistent headache; occipital neuralgia; ophthalmoplegic migraine; post lumbar puncture syndrome; post myelography headache; post procedural headache; post-traumatic headache; premenstrual headache; primary cough headache; primary headache associated with sexual activity; procedural headache; reaction to spinal or lumbar puncture; retinal migraine; sinus headache; status migrainosus; sunct syndrome; tension headache; tension headaches; thunderclap headache; vascular headache; vestibular migraine; vogt-koyanagi-harada disease.

Hemorrhage FDA N

Abdominal aortic aneurysm haemorrhage; abdominal haematoma; abdominal wall haematoma; abdominal wall haemorrhage; acute haemorrhagic leukoencephalitis; acute haemorrhagic ulcerative colitis; administration site bruise; administration site haematoma; administration site haemorrhage; adrenal haematoma; adrenal haemorrhage; anal fissure haemorrhage; anal haemorrhage; anal ulcer haemorrhage; anastomotic haemorrhage; anastomotic ulcer haemorrhage; anastomotic ulcer haemorrhage, obstructive; aneurysm ruptured; anorectal varices haemorrhage; antepartum haemorrhage; aortic aneurysm rupture; aortic annulus rupture; aortic dissection rupture; aortic intramural haematoma; aortic perforation; aortic rupture; aortoenteric fistula; aponeurosis contusion; application site bleeding; application site bruise; application site bruising; application site haematoma; application site haemorrhage; application site purpura; arterial haemorrhage; arterial haemorrhage nos; arterial intramural haematoma; arterial perforation; arterial rupture; arterial rupture nos; arteriovenous fistula site haematoma; arteriovenous fistula site haemorrhage; arteriovenous graft site haematoma; arteriovenous graft site haemorrhage; atrial rupture; auricular haematoma; basal ganglia haematoma; basal ganglia haemorrhage; basilar artery perforation; battle's sign; benign familial haematuria; biliary-vascular fistula; bladder tamponade; bladder thrombotic tamponade; bleeding peripartum; bleeding tendency; bleeding varicose vein; blood blister; blood in stool; blood loss anaemia; blood urine; blood urine

present; bloody airway discharge; bloody discharge; bloody drainage; bloody peritoneal effluent; bone contusion; bone marrow haemorrhage; brain contusion; brain stem haematoma; brain stem haemorrhage; brain stem microhaemorrhage; breast haematoma; breast haemorrhage; broad ligament haematoma; bronchial haemorrhage; bronchial varices haemorrhage; bursal haematoma; cardiac contusion; carotid aneurysm rupture; carotid artery perforation; catheter site bruise; catheter site ecchymosis; catheter site haematoma; catheter site haemorrhage; central nervous system haemorrhage; cephalhaematoma; cerebellar haematoma; cerebellar haematoma nos; cerebellar haemorrhage; cerebellar microhaemorrhage; cerebral aneurysm perforation; cerebral aneurysm ruptured syphilitic; cerebral arteriovenous malformation haemorrhagic; cerebral artery perforation; cerebral cyst haemorrhage; cerebral haematoma; cerebral haemorrhage; cerebral haemorrhage foetal; cerebral haemorrhage neonatal; cerebral microhaemorrhage; cervix haematoma uterine; cervix haemorrhage uterine; chest wall haematoma; choroidal haematoma; choroidal haemorrhage; chronic gastrointestinal bleeding; chronic pigmented purpura; ciliary body haemorrhage; clotted haemothorax; coital bleeding; colitis haemorrhagic; colonic haematoma; colonic haemorrhage; conjunctival haemorrhage; contusion; contusion pulmonary; corneal bleeding; coronary artery atheroma haemorrhage; cullen's sign; cystitis haemorrhagic; deep dissecting haematoma; diarrhoea haemorrhagic; diverticulitis intestinal haemorrhagic; diverticulum intestinal haemorrhagic; duodenal haemorrhage; duodenal ulcer haemorrhage; duodenal ulcer haemorrhage, obstructive; duodenitis haemorrhagic; dysfunctional uterine bleeding; ear haemorrhage; ecchymosis; encephalitis haemorrhagic; enteritis haemorrhagic; enterocolitis haemorrhagic; epidural haemorrhage; epistaxis; exsanguination; extra-axial haemorrhage; extradural haematoma; extraischaemic cerebral haematoma; extravasation blood; eye contusion; eye haematoma; eye haemorrhage; eye haemorrhage nos; eyelid bleeding; eyelid contusion; eyelid haematoma; eyelid haemorrhage; femoral artery perforation; femoral vein perforation; gardner-diamond syndrome; gastric haemorrhage; gastric mucosal hypertrophy, haemorrhagic; gastric ulcer haemorrhage; gastric ulcer haemorrhage, obstructive; gastric varices haemorrhage; gastritis alcoholic haemorrhagic; gastritis atrophic haemorrhagic; gastritis haemorrhagic; gastritis haemorrhagic aggravated; gastroduodenal haemorrhage; gastroduodenitis haemorrhagic; gastrointestinal angiodysplasia haemorrhagic; gastrointestinal haemorrhage; gastrointestinal haemorrhage nos; gastrointestinal organ contusion; gastrointestinal polyp haemorrhage; gastrointestinal ulcer haemorrhage; gastrointestinal vascular malformation haemorrhagic; genital contusion; genital haemorrhage; genital haemorrhage nos; gingival bleeding; graft haemorrhage; grey turner's sign; haemarthrosis; haematemesis; haematidrosis; haematochezia; haematocoele; haematoma; haematoma infection; haematoma nos; haematomyelia; haematosalpinx; haematospermia; haematotympanum; haematuria; haematuria aggravated; haematuria traumatic; haemobilia; haemopericardium; haemoperitoneum; haemophilic pseudotumour; haemoptysis; haemorrhage; haemorrhage coronary artery; haemorrhage foetal; haemorrhage in pregnancy; haemorrhage into ovarian cyst; haemorrhage intracranial; haemorrhage neonatal; haemorrhage nos; haemorrhage nos aggravated; haemorrhage nos foetal; haemorrhage nos

neonatal; haemorrhage subcutaneous; haemorrhage subepidermal; haemorrhage urinary tract; haemorrhagic adrenal infarction; haemorrhagic anaemia; haemorrhagic arteriovenous malformation; haemorrhagic ascites; haemorrhagic breast cyst; haemorrhagic cerebral infarction; haemorrhagic cholecystitis; haemorrhagic cyst; haemorrhagic diathesis; haemorrhagic disease of newborn; haemorrhagic disorder; haemorrhagic erosive gastritis; haemorrhagic hepatic cyst; haemorrhagic infarction; haemorrhagic necrotic pancreatitis; haemorrhagic ovarian cyst; haemorrhagic pneumonia; haemorrhagic stroke; haemorrhagic thyroid cyst; haemorrhagic transformation stroke; haemorrhagic tumour necrosis; haemorrhagic urticaria; haemorrhagic varicella syndrome; haemorrhagic vasculitis; haemorrhoidal haemorrhage; haemothorax; hemorrhagic tumour necrosis; hemorrhoidal bleeding; henoch-schonlein purpura; henoch-schonlein purpura nephritis; hepatic haemangioma rupture; hepatic haematoma; hepatic haemorrhage; hereditary haemorrhagic telangiectasia; hereditary renal microhaematuria; hyperfibrinolysis; hyphaema; idiopathic purpura; ileal haemorrhage; iliac artery perforation; iliac artery rupture; iliac vein perforation; implant site bruising; implant site haematoma; implant site haemorrhage; incision site haematoma; incision site haemorrhage; induced abortion haemorrhage; inferior vena cava perforation; infusion site bruising; infusion site haematoma; infusion site haemorrhage; injection site bruising; injection site haematoma; injection site haemorrhage; instillation site bruise; instillation site haematoma; instillation site haemorrhage; intermenstrual bleeding; internal haemorrhage; intestinal haematoma; intestinal haemorrhage; intestinal polyp haemorrhage; intestinal stoma site bleeding; intestinal varices haemorrhage; intra-abdominal haematoma; intra-abdominal haemorrhage; intra-abdominal haemorrhage nos; intracerebral haematoma evacuation; intracerebral haematoma evacuation nos; intracranial epidural haematoma; intracranial haematoma; intracranial haemorrhage nos; intracranial tumour haemorrhage; intraocular haematoma; intraoperative haemorrhage; intrapartum haemorrhage; intraventricular haemorrhage; intraventricular haemorrhage neonatal; intraventricular haemorrhage nos; iris haemorrhage; jejunal haemorrhage; joint microhaemorrhage; kidney contusion; lacrimal haemorrhage; large intestinal haemorrhage; large intestinal ulcer haemorrhage; large intestinal ulcer nos haemorrhage; laryngeal haematoma; laryngeal haemorrhage; lip haematoma; lip haemorrhage; liver contusion; loin pain haematuria syndrome; lower gastrointestinal haemorrhage; lower limb artery perforation; lymph node haemorrhage; majocchi's purpura; mallory-weiss syndrome; maxillary sinus haematoma; mediastinal haematoma; mediastinal haemorrhage; medical device site bruise; medical device site haematoma; medical device site haemorrhage; melaena; melaena neonatal; meningorrhagia; menometrorrhagia; menorrhagia; mesenteric haematoma; mesenteric haemorrhage; metrorrhagia; mouth haemorrhage; mucocutaneous haemorrhage; mucosal haemorrhage; mucosal haemorrhage nos; muscle contusion; muscle haemorrhage; myocardial haemorrhage; myocardial rupture; naevus haemorrhage; nail bed bleeding; nasal septum haematoma; neonatal gastrointestinal haemorrhage; nephritis haemorrhagic; nipple exudate bloody; ocular retrobulbar haemorrhage; oesophageal haemorrhage; oesophageal intramural haematoma; oesophageal ulcer haemorrhage; oesophageal varices haemorrhage; oesophagitis

haemorrhagic; operative haemorrhage; optic disc haemorrhage; optic nerve sheath haemorrhage; oral contusion; oral mucosa haematoma; oral mucosal petechiae; osteorrhagia; ovarian haematoma; ovarian haemorrhage; palpable purpura; pancreatic contusion; pancreatic haemorrhage; pancreatitis haemorrhagic; papillary muscle haemorrhage; paranasal sinus haematoma; paranasal sinus haemorrhage; parathyroid haemorrhage; parotid gland haemorrhage; pelvic haematoma; pelvic haematoma obstetric; pelvic haemorrhage; penile contusion; penile haematoma; penile haemorrhage; peptic ulcer haemorrhage; peptic ulcer haemorrhage, obstructive; perforation of great vessels; pericardial haemorrhage; perineal haematoma; periorbital contusion; periorbital haematoma; periorbital haemorrhage; periosteal haematoma; peripartum haemorrhage; peripheral artery aneurysm rupture; peripheral artery haematoma; perirenal haematoma; peritoneal effusion bloody; peritoneal haematoma; peritoneal haemorrhage; periventricular haemorrhage neonatal; petechiae; pharyngeal haematoma; pharyngeal haemorrhage; pituitary haemorrhage; placenta praevia haemorrhage; pleural haemorrhage; polymenorrhagia; post abortion haemorrhage; post coital bleeding; post procedural contusion; post procedural haematoma; post procedural haematuria; post procedural haemorrhage; post transfusion purpura; post-menopausal bleeding; postmenopausal haemorrhage; postoperative bruise; postoperative haematoma; post-operative haemorrhage; postpartum haemorrhage; post-partum haemorrhage; post-traumatic punctate intraepidermal haemorrhage; premature separation of placenta; procedural haemorrhage; proctitis haemorrhagic; prostatic haemorrhage; pulmonary alveolar haemorrhage; pulmonary contusion; pulmonary haematoma; pulmonary haemorrhage; pulmonary haemorrhage neonatal; puncture site bruise; puncture site haematoma; puncture site haemorrhage; purpura; purpura cerebri; purpura fulminans; purpura neonatal; purpura nonthrombocytopenic; purpura non-thrombocytopenic; purpura nos; purpura senile; putamen haemorrhage; radiation associated haemorrhage; rectal bleeding; rectal haemorrhage; rectal ulcer haemorrhage; renal artery perforation; renal cyst haemorrhage; renal haematoma; renal haemorrhage; respiratory tract haemorrhage; respiratory tract haemorrhage neonatal; respiratory tract haemorrhage nos; retinal aneurysm rupture; retinal bleeding; retinal haemorrhage; retinopathy haemorrhagic; retroperitoneal haematoma; retroperitoneal haemorrhage; retroplacental haematoma; ruptured cerebral aneurysm; schamberg's disease; scleral haemorrhage; scrotal haematocoele; scrotal haematoma; shock haemorrhagic; skin bleeding; skin haemorrhage; skin neoplasm bleeding; skin ulcer haemorrhage; small intestinal haemorrhage; small intestinal ulcer haemorrhage; small intestinal ulcer nos haemorrhage; soft tissue haemorrhage; spermatic cord haemorrhage; spinal cord haematoma; spinal cord haemorrhage; spinal epidural haematoma; spinal epidural haemorrhage; spinal haematoma; spinal subarachnoid haemorrhage; spinal subdural haematoma; spinal subdural haemorrhage; spleen contusion; splenic artery perforation; splenic haematoma; splenic haemorrhage; splenic varices haemorrhage; splinter haemorrhages; spontaneous haematoma; spontaneous haemorrhage; spontaneous hyphaema; stoma site haemorrhage; stomatitis haemorrhagic; subarachnoid haematoma; subarachnoid haemorrhage; subarachnoid haemorrhage nos; subchorionic haematoma; subchorionic haemorrhage; subcutaneous haematoma; subdural

haematoma; subendocardial haemorrhage; subgaleal haematoma; subgaleal haemorrhage; subretinal haematoma; thrombocytopenic purpura; thrombotic thrombocytopenic purpura; tongue haematoma; tooth pulp haemorrhage; traumatic haematoma; traumatic intracranial haematoma; umbilical haematoma; urinary occult blood positive; urticaria haemorrhagica; uterine haematoma; vaccination site bruising; vaccination site haematoma; vaccination site haemorrhage; vaginal haematoma; vaginal haemorrhage; vascular access site bruising; vascular access site contusion; vascular access site haematoma; vascular access site haemorrhage; vascular graft haemorrhage; vascular purpura; vessel puncture site bruise; vessel puncture site haematoma; vitreous haematoma; vulval haematoma; withdrawal bleeding irregular; wound haematoma.

Hernia

Abdominal hernia; abdominal hernia gangrenous; abdominal hernia infection; abdominal hernia obstructive; abdominal hernia perforation; abdominal incarcerated hernia; colpocele; diaphragmatic hernia; femoral hernia; femoral hernia, obstructive
hernia; hernia obstructive; hernia pain; hernia repair; hernial eventration; incarcerated inguinal hernia; incarcerated umbilical hernia; incisional hernia; incisional hernia repair; ; nguinal hernia; inguinal hernia gangrenous; inguinal hernia repair; inguinal hernia strangulated; inguinal hernia, obstructive; internal hernia; lumbar hernia; pancreatitis relapsing; postoperative hernia; umbilical hernia; umbilical hernia obstructive.

Hypertension, Blood Pressure Increased

Accelerated hypertension; blood pressure ambulatory increased; blood pressure diastolic increased; blood pressure inadequately controlled; blood pressure increased; blood pressure systolic increased; diastolic hypertension; eclampsia; endocrine hypertension; essential hypertension; gestational hypertension; hypertension; hypertension neonatal; hypertensive angiopathy; hypertensive crisis; hypertensive emergency; hypertensive encephalopathy; labile blood pressure; labile hypertension; malignant hypertension; maternal hypertension affecting foetus; mean arterial pressure increased; neurogenic hypertension; pre-eclampsia; procedural hypertension; renal hypertension; renovascular hypertension; scleroderma renal crisis; secondary hypertension; supine hypertension; systolic hypertension; withdrawal hypertension.

Infection, All

Abdominal abscess; abdominal hernia infection; abdominal infection; abdominal wall abscess; abdominal wall infection; abortion infected; abscess; abscess bacterial; abscess drainage; abscess fungal; abscess intestinal; abscess jaw; abscess limb; abscess neck; abscess of external auditory meatus; abscess of eyelid; abscess of salivary gland; abscess oral; abscess rupture; abscess soft tissue; abscess sweat gland; acanthamoeba infection; acanthamoeba keratitis; acarasis; acid fast bacilli infection; acinetobacter bacteraemia; acinetobacter infection; acquired immunodeficiency syndrome; actinomycosis; actinomycotic abdominal infection; actinomycotic pulmonary infection; actinomycotic skin infection; acute diverticulitis; acute

endocarditis; acute hepatitis b; acute hepatitis c; acute postoperative sialadenitis; acute pulmonary histoplasmosis; acute sinusitis; acute tonsillitis; adenoiditis; adenoviral conjunctivitis; adenoviral haemorrhagic cystitis; adenoviral hepatitis; adenoviral upper respiratory infection; adenovirus infection; administration site cellulitis; administration site infection; administration site joint infection; adrenal gland tuberculosis; aeromonas infection; african trypanosomiasis; alcaligenes infection; american trypanosomiasis; amoebiasis; anal abscess; anal candidiasis; anal fistula infection; anal fungal infection; anorectal human papilloma virus infection; anorectal infection; appendiceal abscess; appendicitis; appendicitis perforated; application site infection; arteriovenous fistula site infection; arteriovenous graft site abscess; arteriovenous graft site infection; arthritis bacterial; arthritis fungal; arthritis infective; ascariasis; ascites infection; aspergilloma; aspergillosis; atypical mycobacterial infection; atypical mycobacterial lymphadenitis; atypical mycobacterial pneumonia; atypical pneumonia; avian influenza; axillary candidiasis; babesiosis; bacteraemia; bacterial diarrhoea; bacterial infection; bacterial prostatitis; bacterial pyelonephritis; bacterial rhinitis; bacterial sepsis; bacterial tracheitis; bacterial vaginosis; bacteroides bacteraemia; balanitis candida; bartholin's abscess; beta haemolytic streptococcal infection; biliary sepsis; biliary tract infection fungal; bladder candidiasis; blastocystis infection; blister infected; blood culture positive; body tinea; borrelia infection; brain abscess; breast abscess; breast cellulitis; bronchial infection; bronchiolitis; bronchitis; bronchitis acute; bronchitis acute viral; bronchitis bacterial; bronchitis fungal; bronchitis pneumococcal; bronchitis viral; bronchopneumonia; bronchopulmonary aspergillosis; bronchopulmonary aspergillosis allergic; bullous impetigo; burn infection; bursitis infective; bursitis infective staphylococcal; campylobacter gastroenteritis; campylobacter infection; campylobacter intestinal infection; candida infection; candida pneumonia; candida sepsis; candidiasis; candiduria; carbuncle; cardiac infection; catheter related infection; catheter site abscess; catheter site infection; cellulitis; cellulitis gangrenous; cellulitis laryngeal; cellulitis of male external genital organ; cellulitis orbital; cellulitis staphylococcal; cellulitis streptococcal central line infection; central nervous system fungal infection; central nervous system infection; cerebral fungal infection; cerebral toxoplasmosis; cervicitis; cervicitis streptococcal; ; chest wall abscess; chikungunya virus infection; chlamydial infection; cholangitis cholangitis acute; cholangitis suppurative; cholecystitis; cholecystitis acute; cholecystitis chronic; cholecystitis infective; cholecystocholangitis; chronic sinusitis; chronic tonsillitis; citrobacter infection; citrobacter sepsis; clostridial infection; clostridium colitis; clostridium difficile colitis; clostridium difficile infection; clostridium difficile sepsis; coccidioidomycosis; colonic abscess; community acquired infection; conjunctivitis bacterial; conjunctivitis infective; conjunctivitis viral; coxsackie viral infection; creutzfeldt-jakob disease; croup infectious; culture urine positive; culture wound positive; cutaneous tuberculosis; cystitis; cystitis bacterial; cystitis escherichia; cystitis klebsiella; cystitis pseudomonal; cystitis viral; cytomegalovirus colitis; cytomegalovirus hepatitis; cytomegalovirus infection; cytomegalovirus test positive; dacryocystitis; dacryocystitis infective; dengue fever; dental gangrene; dermatitis infected; dermatophytosis; dermatophytosis of nail; device related infection; device related sepsis; diabetic foot infection; diabetic gangrene; diarrhoea infectious; disseminated tuberculosis;

diverticulitis; diverticulitis intestinal haemorrhagic; douglas' abscess; ear infection; ear infection bacterial; ear infection fungal; ear infection viral; ear lobe infection; echinococcosis; ecthyma; eczema impetiginous; eczema infected; emphysematous cholecystitis; empyema; encephalitis fungal; encephalitis herpes; encephalitis viral; endocarditis; endocarditis bacterial; endocarditis enterococcal; endocarditis gonococcal; endocarditis haemophilus; endocarditis helminthic; endocarditis histoplasma; endocarditis meningococcal; endocarditis pseudomonas; endocarditis staphylococcal; endocarditis syphilitic; endocarditis viral; endophthalmitis; enteritis infectious; enterobacter bacteraemia; enterobacter infection; enterobacter sepsis; enterobiasis; enterococcal bacteraemia; enterococcal infection; enterococcal sepsis; enterocolitis bacterial; enterocolitis fungal; enterocolitis haemorrhagic; enterocolitis infectious; enterocolitis viral; enterovirus infection; epidemic nephropathy; epidemic polyarthritis; epiglottitis; epstein-barr virus infection; erysipelas; erythrasma; escherichia bacteraemia; escherichia infection; escherichia pyelonephritis; escherichia sepsis; escherichia urinary tract infection; external ear cellulitis; extradural abscess; eye abscess; eye infection; eye infection bacterial; eye infection fungal; eye infection staphylococcal; eye infection viral; eyelid boil; eyelid infection; fasciolopsiasis; febrile infection; folliculitis; fungaemia; fungal abscess central nervous system; fungal balanitis; fungal cystitis; fungal endocarditis; fungal infection; fungal labyrinthitis; fungal oesophagitis; fungal paronychia; fungal peritonitis; fungal pharyngitis; fungal rash; fungal retinitis; fungal rhinitis; fungal sepsis; fungal skin infection; fungal tracheitis; furuncle gallbladder empyema; gangrene; gardnerella infection; gas gangrene; gastric infection; gastric ulcer helicobacter; gastritis bacterial; gastritis fungal; gastritis viral; gastroenteritis; gastroenteritis adenovirus; gastroenteritis aeromonas; gastroenteritis bacterial; gastroenteritis clostridial; gastroenteritis cryptosporidial; gastroenteritis enteroviral; gastroenteritis escherichia coli; gastroenteritis norovirus; gastroenteritis norwalk virus; gastroenteritis rotavirus; gastroenteritis salmonella; gastroenteritis viral; gastrointestinal bacterial infection; gastrointestinal candidiasis; gastrointestinal fungal infection; gastrointestinal infection; gastrointestinal viral infection; genital abscess; genital candidiasis; genital herpes; genital infection; genital infection bacterial; genital infection female; genital infection fungal; genital infection male; genitourinary chlamydia infection; genitourinary tract infection; giardiasis; gingival abscess; gingival infection; gonorrhoea; graft infection; groin abscess; groin infection; h1n1 influenza; haematoma infection; haemophilus infection; haemorrhoid infection; helicobacter gastritis; helicobacter infection; helminthic infection; hepatic cyst infection; hepatic infection fungal; hepatitis a, hepatitis b; hepatitis c; hepatitis chronic active; hepatitis chronic persistent; hepatitis infectious; hepatitis viral; herpangina; herpes dermatitis; herpes oesophagitis; herpes ophthalmic; herpes simplex; herpes simplex meningoencephalitis; herpes simplex ophthalmic; herpes virus infection; herpes zoster; herpes zoster ophthalmic; herpes zoster oticus; herpetic stomatitis; hiv infection; hookworm infection; hordeolum; hydrocele male infected; impetigo; implant site abscess; implant site infection; incision site abscess; incision site cellulitis; incision site infection; infected bite; infected bites; infected cyst; infected dermal cyst; infected epidermal cyst; infected fistula; infected naevus; infected sebaceous cyst; infected seroma; infected skin ulcer; infected varicose vein; infection; infection parasitic;

infectious colitis; infectious mononucleosis; infectious peritonitis; infectious pleural effusion; infective exacerbation of bronchiectasis; infective exacerbation of chronic obstructive airways disease; infective glossitis; infective myositis; infective tenosynovitis; infective thrombosis; infective uveitis; influenza; influenza like illness; infusion site cellulitis; infusion site infection; injection site abscess; injection site cellulitis; injection site infection; intertrigo candida; intervertebral discitis; joint abscess; kaposi's varicelliform eruption; keratitis fungal; keratitis herpetic; keratitis viral; kidney infection; klebsiella bacteraemia; klebsiella infection; klebsiella sepsis; labyrinthitis; laryngitis; laryngitis bacterial; laryngitis fungal; laryngitis viral; latent tuberculosis; legionella infection; leishmaniasis; lice infestation; lip infection; listeria sepsis; liver abscess; lobar pneumonia; localised infection; loeffler's syndrome; lower respiratory tract infection; lower respiratory tract infection bacterial; lower respiratory tract infection fungal; lower respiratory tract infection viral; lung abscess; lung infection; lung infection pseudomonal; lyme disease; lymph gland infection; lymph node abscess; lymph node tuberculosis; lymphadenitis fungal; lymphangitis; malaria; malarial myocarditis; mastitis; mastitis bacterial; mastitis fungal; mastoiditis; mediastinitis; meningitis; meningitis aseptic; meningitis bacterial; meningitis fungal; meningitis herpes; meningitis listeria; meningitis meningococcal; meningitis pneumococcal; meningitis streptococcal; meningitis tuberculous; meningitis viral; meningococcal carditis; metapneumovirus infection; microsporidia infection; mollusum contagiosum; mononucleosis syndrome; moraxella infection; morganella infection; mucosal infection; mumps; murine typhus; muscle abscess; mycetoma mycotic; mycobacterial infection; mycobacterium abscessus infection; mycobacterium avium complex infection; mycoplasma infection; myocarditis meningococcal; myocarditis syphilitic; myocarditis toxoplasmal; myringitis; nail bed infection bacterial; nail bed infection fungal; nail infection; nail tinea; nasal abscess; nasopharyngitis; necrotising fasciitis; necrotising fasciitis fungal; nematodiasis; neuroborreliosis; neurocysticercosis; neutropenic sepsis; nipple infection; nosocomial infection; oesophageal candidiasis; oesophageal infection; omphalitis; onychomycosis; oophoritis; ophthalmic herpes simplex; ophthalmic herpes zoster; opisthorchiasis; oral bacterial infection; oral candidiasis; oral fungal infection; oral herpes; oral infection; oral viral infection; orchitis; organising pneumonia; oropharyngeal candidiasis; oropharyngitis fungal; osteomyelitis; osteomyelitis acute; osteomyelitis chronic; osteomyelitis fungal; otitis externa; otitis externa fungal; otitis media; otitis media acute; otitis media bacterial; otitis media chronic; otitis media fungal; otitis media viral; overgrowth bacterial; overgrowth fungal; pancreatic abscess; pancreatitis fungal; papilloma viral infection; parainfluenzae virus infection; paraoesophageal abscess; parasitic gastroenteritis; parasitic infection intestinal; paraspinal abscess; paronychia; parotid abscess; parotitis; pasteurella infection; pelvic abscess; pelvic infection; pelvic inflammatory disease; penile abscess; penile infection; peptic ulcer helicobacter; perianal abscess; perianal fungal infection; pericarditis fungal; pericarditis gonococcal; pericarditis infective; pericarditis meningococcal; pericarditis mycoplasmal; pericarditis syphilitic; pericarditis tuberculous; perichondritis; peridiverticular abscess; perineal abscess; perineal infection; perinephric abscess; periodontal infection; periorbital cellulitis; perirectal abscess; peritoneal abscess; peritoneal infection; peritoneal tuberculosis; peritonitis; peritonitis

bacterial; peritonsillar abscess; peritonsillitis; periumbilical abscess; pertussis; pharyngeal abscess; pharyngitis; pharyngitis bacterial; pharyngitis mycoplasmal; pharyngitis streptococcal; pharyngotonsillitis; phlebitis infective; pilonidal cyst; plasmodium falciparum infection; pneumococcal bacteraemia; pneumococcal sepsis; pneumocystis jiroveci pneumonia; pneumocystis jirovecii pneumonia; pneumonia; pneumonia aspiration; pneumonia bacterial; pneumonia chlamydial; pneumonia cryptococcal; pneumonia cytomegaloviral; pneumonia fungal; pneumonia haemophilus; pneumonia herpes viral; pneumonia influenzal; pneumonia klebsiella; pneumonia legionella; pneumonia moraxella; pneumonia mycoplasmal; pneumonia necrotising; pneumonia pneumococcal; pneumonia primary atypical; pneumonia pseudomonal; pneumonia staphylococcal; pneumonia streptococcal; pneumonia viral; post procedural cellulitis; post procedural infection; post procedural pneumonia; post procedural sepsis; postoperative abscess; postoperative infection; postoperative wound infection; proctitis fungal; proctitis infectious; propionibacterium infection; prostate infection; proteus infection; pseudomembranous colitis; pseudomonal bacteraemia; pseudomonal sepsis; pseudomonas bronchitis; pseudomonas infection; psittacosis; psoas abscess; pulmonary mycosis; pulmonary sepsis; pulmonary tuberculoma; pulmonary tuberculosis; pulpitis dental; puncture site infection; pyelocystitis; pyelonephritis; pyelonephritis acute; pyelonephritis chronic; pyelonephritis fungal; pyoderma; pyoderma streptococcal; pyometra; pyonephrosis; pyopneumothorax; q fever; rash pustular; rectal abscess; renal cyst infection; renal tuberculosis; respiratory moniliasis; respiratory tract infection; respiratory tract infection bacterial; respiratory tract infection fungal; respiratory tract infection viral; retroperitoneal abscess; retroviral infection; rhinitis; rhinovirus infection; rocky mountain spotted fever; root canal infection; roseola; rotavirus infection; rubella; salmonella sepsis; salmonellosis; salpingitis; salpingo-oophoritis; scrotal abscess; scrotal infection; scrub typhus; sebaceous gland infection; sepsis; sepsis syndrome; septic arthritis staphylococcal; septic arthritis streptococcal; septic embolus; septic encephalopathy; septic necrosis; septic rash; septic shock; serratia infection; serratia sepsis; sexually transmitted disease; shigella infection; shunt infection; sialoadenitis; sinobronchitis; sinusitis; sinusitis bacterial; sinusitis fungal; skin bacterial infection; skin candida; skin infection; soft tissue infection; splenic abscess; splenic infection fungal; staphylococcal abscess; staphylococcal bacteraemia; staphylococcal infection; staphylococcal osteomyelitis; staphylococcal pharyngitis; staphylococcal sepsis; staphylococcal skin infection; stenotrophomonas infection; stitch abscess; stoma site abscess; streptobacillus infection; streptococcal abscess; streptococcal bacteraemia; streptococcal endocarditis; streptococcal infection; streptococcal sepsis; streptococcal urinary tract infection; strongyloidiasis; subacute endocarditis; subcutaneous abscess; subdiaphragmatic abscess; superinfection; superinfection fungal; superinfection lung; sycosis barbae; syphilis; syphilitic endocarditis of heart valve; systemic candida; systemic mycosis; taeniasis; testicular abscess; tick-borne viral encephalitis; tinea capitis; tinea cruris; tinea faciei; tinea infection; tinea manuum; tinea pedis; tinea versicolour; tongue abscess; tongue fungal infection; tonsillitis; tonsillitis bacterial; tonsillitis fungal; tonsillitis streptococcal; tooth abscess; tooth infection; toxic shock syndrome; toxoplasmosis; tracheitis; tracheobronchitis; tracheobronchitis viral;

trachoma; trichophyton infection; trichophytosis; tropical eosinophilia; tuberculosis; tuberculosis of central nervous system; tuberculosis of genitourinary system; tuberculous pleurisy; typhoid fever; typhus; upper respiratory fungal infection; upper respiratory tract infection; upper respiratory tract infection bacterial; ureaplasma infection; ureteritis; urethritis; urethritis gonococcal; urinary bladder abscess; urinary tract infection; urinary tract infection bacterial; urinary tract infection enterococcal; urinary tract infection fungal; urinary tract infection pseudomonal; urinary tract infection staphylococcal; urinary tract infection viral; urogenital infection bacterial; urogenital infection fungal; urosepsis; uterine infection; vaginal abscess; vaginal candidiasis; vaginal infection; vaginal mycosis; vaginitis bacterial; vaginitis gardnerella; vancomycin-resistant enterococcal infection; varicella; viraemia; viral cardiomyopathy; viral diarrhoea; viral infection; viral labyrinthitis; viral myocarditis; viral pericarditis; viral pharyngitis; viral rash; viral rhinitis; viral sinusitis; viral skin infection; viral tracheitis; viral upper respiratory tract infection; vulval abscess; vulval cellulitis; vulvitis; vulvovaginal candidiasis; vulvovaginal mycotic infection; vulvovaginitis; vulvovaginitis gonococcal; vulvovaginitis trichomonal; west nile viral infection; wound abscess; wound infection; wound infection bacterial; wound infection fungal; wound infection pseudomonas; wound infection staphylococcal; wound sepsis; yersinia infection.

Intracranial Hemorrhage

Cerebral haematoma; cerebral haemorrhage; haemorrhage intracranial; subarachnoid haemorrhage.

Malignancy FDA B

Abdominal neoplasm; abdominal neoplasm nos; abdominal wall neoplasm; abdominal wall neoplasm malignant; abdominal wall neoplasm nos; acinar cell carcinoma of pancreas; acinic cell carcinoma of salivary gland; acral lentiginous melanoma; acral lentiginous melanoma stage ii; acral lentiginous melanoma stage iii; acral lentiginous melanoma stage iv; acral lentiginous melanoma stage i; acth-producing pituitary tumour; acute bilineal leukaemia; acute biphenotypic leukaemia; acute leukaemia; acute lymphocytic leukaemia; acute lymphocytic leukaemia recurrent; acute lymphocytic leukaemia refractory; acute megakaryocytic leukaemia; acute monocytic leukaemia; acute myeloid leukaemia; acute myeloid leukaemia recurrent; acute myeloid leukaemia refractory; acute myelomonocytic leukaemia; acute oesophageal mucosal lesion; acute promyelocytic leukaemia; acute undifferentiated leukaemia; adenocarcinoma; adenocarcinoma gastric; adenocarcinoma of appendix; adenocarcinoma of colon; adenocarcinoma of salivary gland; adenocarcinoma of the cervix; adenocarcinoma pancreas; adenoid cystic carcinoma; adenoid cystic carcinoma of external auditory canal; adenoid cystic carcinoma of salivary gland; adenolymphoma; adenosquamous carcinoma of the cervix; adenosquamous carcinoma of vagina; adenosquamous cell carcinoma; adenosquamous cell lung cancer; adenosquamous cell lung cancer recurrent; adenosquamous cell lung cancer stage 0; adenosquamous cell lung cancer stage i; adenosquamous cell lung cancer stage ii; adenosquamous cell lung cancer stage iii; adenosquamous cell lung cancer stage iv; adrenal

carcinoma; adrenal gland cancer; adrenal gland cancer metastatic; adrenal neoplasm; adrenal neoplasm nos; adrenocortical carcinoma; adult t-cell lymphoma/leukaemia; adult t-cell lymphoma/leukaemia recurrent; adult t-cell lymphoma/leukaemia refractory; adult t-cell lymphoma/leukaemia stage i; adult t-cell lymphoma/leukaemia stage ii; adult t-cell lymphoma/leukaemia stage iii; adult t-cell lymphoma/leukaemia stage iv; aesthesioneuroblastoma; aleukaemic leukaemia; anaemia of malignant disease; anal cancer; anal cancer metastatic; anal cancer recurrent; anal cancer stage 0; anal cancer stage i; anal cancer stage ii; anal cancer stage iii; anal cancer stage iv; anal neoplasm; anal neoplasm nos; anal squamous cell carcinoma; anaplastic large cell lymphoma t- and null-cell types; anaplastic large cell lymphoma t- and null-cell types recurrent; anaplastic large cell lymphoma t- and null-cell types refractory; anaplastic large cell lymphoma t- and null-cell types stage i; anaplastic large cell lymphoma t- and null-cell types stage ii; anaplastic large cell lymphoma t- and null-cell types stage iii; anaplastic large cell lymphoma t- and null-cell types stage iv; anaplastic large-cell lymphoma; anaplastic thyroid cancer; angiocentric lymphoma; angiocentric lymphoma recurrent; angiocentric lymphoma refractory; angiocentric lymphoma stage i; angiocentric lymphoma stage ii; angiocentric lymphoma stage iii; angiocentric lymphoma stage iv; angioimmunoblastic t-cell lymphoma; angioimmunoblastic t-cell lymphoma recurrent; angioimmunoblastic t-cell lymphoma refractory; angioimmunoblastic t-cell lymphoma stage i; angioimmunoblastic t-cell lymphoma stage ii; angioimmunoblastic t-cell lymphoma stage iii; angioimmunoblastic t-cell lymphoma stage iv; angiosarcoma; angiosarcoma metastatic; apocrine breast carcinoma; appendix cancer; astrocytoma malignant; atypical teratoid/rhabdoid tumour of cns; b precursor type acute leukaemia; basal cell carcinoma; basosquamous carcinoma; basosquamous carcinoma of skin; b-cell lymphoma; b-cell lymphoma recurrent; b-cell lymphoma refractory; b-cell lymphoma stage i; b-cell lymphoma stage ii; b-cell lymphoma stage iii; b-cell lymphoma stage iv; b-cell prolymphocytic leukaemia; b-cell small lymphocytic lymphoma; b-cell small lymphocytic lymphoma recurrent; b-cell small lymphocytic lymphoma refractory; b-cell small lymphocytic lymphoma stage i; b-cell small lymphocytic lymphoma stage ii; b-cell small lymphocytic lymphoma stage iii; b-cell small lymphocytic lymphoma stage iv; b-cell type acute leukaemia; b-cell unclassifiable lymphoma high grade; b-cell unclassifiable lymphoma low grade; bile duct adenocarcinoma; bile duct adenosquamous carcinoma; bile duct cancer; bile duct cancer recurrent; bile duct cancer stage 0; bile duct cancer stage i; bile duct cancer stage ii; bile duct cancer stage iii; bile duct cancer stage iv; bile duct squamous cell carcinoma; biliary cancer metastatic; biliary neoplasm; biliary neoplasm nos; bing-neel syndrome; bladder adenocarcinoma stage ii; bladder adenocarcinoma stage iii; bladder adenocarcinoma stage iv; bladder adenocarcinoma recurrent; bladder adenocarcinoma stage 0; bladder adenocarcinoma stage i; bladder adenocarcinoma stage unspecified; bladder cancer; bladder cancer recurrent; bladder cancer stage 0, with cancer in situ; bladder cancer stage 0, without cancer in situ; bladder cancer stage i, with cancer in situ; bladder cancer stage i, without cancer in situ; bladder cancer stage ii; bladder cancer stage iii; bladder cancer stage iv; bladder neoplasm; bladder neoplasm nos; bladder squamous cell carcinoma stage ii; bladder squamous cell carcinoma stage iii; bladder squamous cell

carcinoma stage iv; bladder squamous cell carcinoma recurrent; bladder squamous cell carcinoma stage 0; bladder squamous cell carcinoma stage i; bladder squamous cell carcinoma stage unspecified; bladder transitional cell carcinoma; bladder transitional cell carcinoma stage ii; bladder transitional cell carcinoma stage iii; bladder transitional cell carcinoma stage iv; bladder transitional cell carcinoma metastatic; bladder transitional cell carcinoma recurrent; bladder transitional cell carcinoma stage 0; bladder transitional cell carcinoma stage i; blast crisis in myelogenous leukaemia; bone cancer; bone cancer metastatic; bone giant cell tumour; bone giant cell tumour malignant; bone marrow leukaemic cell infiltration; bone marrow tumour cell infiltration; bone neoplasm; bone neoplasm malignant; bone neoplasm nos; bone sarcoma; borderline mucinous tumour of ovary; borderline ovarian tumour; borderline serous tumour of ovary; brain cancer metastatic; brain neoplasm; brain neoplasm malignant; brain neoplasm nos; brain tumour operation; breast cancer; breast cancer female; breast cancer in situ; breast cancer male; breast cancer metastatic; breast cancer recurrent; breast cancer stage i; breast cancer stage ii; breast cancer stage iii; breast cancer stage iv; breast implant-associated anaplastic large cell lymphoma; breast neoplasm; breast neoplasm male; breast neoplasm nos male; breast tumour excision; brenner tumour; bronchial carcinoma; bronchial neoplasm; bronchioloalveolar carcinoma; buccal cavity neoplasm nos; burkitt's leukaemia; burkitt's lymphoma; burkitt's lymphoma recurrent; burkitt's lymphoma refractory; burkitt's lymphoma stage i; burkitt's lymphoma stage ii; burkitt's lymphoma stage iii; burkitt's lymphoma stage iv; cancer fatigue; cancer pain; cancer staging; cancer surgery; carbohydrate antigen 72-4 increased; carcinoembryonic antigen increased; carcinoid crisis; carcinoid heart disease; carcinoid syndrome; carcinoid tumour; carcinoid tumour of the appendix; carcinoid tumour of the caecum; carcinoid tumour of the duodenum; carcinoid tumour of the gastrointestinal tract; carcinoid tumour of the liver; carcinoid tumour of the ovary; carcinoid tumour of the pancreas; carcinoid tumour of the prostate; carcinoid tumour of the small bowel; carcinoid tumour of the stomach; carcinoid tumour pulmonary; carcinoma; carcinoma ex-pleomorphic adenoma; carcinoma in situ; carcinoma in situ of eye; carcinoma in situ of penis; carcinoma in situ of skin; carcinoma in situ of trachea; carcinomatous polyarthritis; cardiac neoplasm malignant; cardiac neoplasm malignant nos; cardiac neoplasm unspecified; carotid body tumour; cartilage neoplasm; cartilage neoplasm nos; central nervous system leukaemia; central nervous system lymphoma; central nervous system neoplasm; central nervous system neoplasm nos; cerebellar tumour; cerebellopontine angle tumour; cervical neoplasm nos; cervix cancer metastatic; cervix carcinoma; cervix carcinoma recurrent; cervix carcinoma stage 0; cervix carcinoma stage i; cervix carcinoma stage ii; cervix carcinoma stage iii; cervix carcinoma stage iv; cervix neoplasm; cervix neoplasm recurrent; cervix neoplasm stage i; cervix neoplasm stage ii; cervix neoplasm stage iii; cervix neoplasm stage iv; chest wall tumour; cholangiocarcinoma; chondrosarcoma metastatic; choriocarcinoma; choroid neoplasm; choroid plexus carcinoma; chromophobe renal cell carcinoma; chronic eosinophilic leukaemia; chronic leukaemia; chronic lymphocytic leukaemia; chronic lymphocytic leukaemia recurrent; chronic lymphocytic leukaemia refractory; chronic lymphocytic leukaemia stage 0; chronic lymphocytic leukaemia stage 1; chronic lymphocytic leukaemia stage 2; chronic lymphocytic leukaemia stage 3; chronic lymphocytic

leukaemia stage 4; chronic lymphocytic leukaemia transformation; chronic myeloid leukaemia; chronic myeloid leukaemia recurrent; chronic myeloid leukaemia transformation; chronic myelomonocytic leukaemia; ciliary body melanoma; clear cell carcinoma of cervix; clear cell carcinoma of the kidney; clear cell endometrial carcinoma; clear cell renal cell carcinoma; colon cancer; colon cancer metastatic; colon cancer recurrent; colon cancer stage 0; colon cancer stage i; colon cancer stage ii; colon cancer stage iii; colon cancer stage iv; colon neoplasm; colorectal adenocarcinoma; colorectal cancer; colorectal cancer metastatic; colorectal cancer recurrent; colorectal cancer stage i; colorectal cancer stage ii; colorectal cancer stage iii; colorectal cancer stage iv; colorectal carcinoma stage 0; composite lymphoma; congenital malignant neoplasm; congenital neoplasm; conjunctival neoplasm; connective tissue neoplasm; cutaneous lymphoma; cystadenocarcinoma ovary; desmoid tumour; desmoplastic small round cell tumour; diaphragm neoplasm; differentiation syndrome; diffuse large b-cell lymphoma; diffuse large b-cell lymphoma recurrent; diffuse large b-cell lymphoma refractory; diffuse large b-cell lymphoma stage i; diffuse large b-cell lymphoma stage ii; diffuse large b-cell lymphoma stage iii; diffuse large b-cell lymphoma stage iv; disseminated large cell lymphoma; double hit lymphoma; ductal adenocarcinoma of pancreas; duodenal neoplasm; ear neoplasm; ear neoplasm malignant; eccrine carcinoma; endocrine neoplasm; endocrine neoplasm malignant; endometrial adenocarcinoma; endometrial cancer; endometrial cancer metastatic; endometrial cancer recurrent; endometrial cancer stage 0; endometrial cancer stage i; endometrial cancer stage ii; endometrial cancer stage iii; endometrial cancer stage iv; endometrial neoplasm; enteropathy-associated t-cell lymphoma; eosinophilic leukaemia; epididymal cancer; epididymal neoplasm; epiglottic carcinoma; epstein-barr virus associated lymphoma; erythroleukaemia; ewing-like sarcoma; external ear neoplasm malignant; extradural neoplasm; extragonadal primary embryonal carcinoma; extragonadal primary germ cell tumour; extragonadal primary germ cell tumour mixed; extragonadal primary germ cell tumour mixed stage i; extragonadal primary germ cell tumour mixed stage ii; extragonadal primary germ cell tumour mixed stage iii; extragonadal primary malignant teratoma; extranodal marginal zone b-cell lymphoma (balt type); extranodal marginal zone b-cell lymphoma (malt type); extranodal marginal zone b-cell lymphoma (malt type) recurrent; extranodal marginal zone b-cell lymphoma (malt type) refractory; extranodal marginal zone b-cell lymphoma (malt type) stage i; extranodal marginal zone b-cell lymphoma (malt type) stage ii; extranodal marginal zone b-cell lymphoma (malt type) stage iii; extranodal marginal zone b-cell lymphoma (malt type) stage iv; eyelid tumour; fallopian tube cancer; fallopian tube cancer metastatic; fallopian tube cancer stage i; fallopian tube cancer stage ii; fallopian tube cancer stage iii; fallopian tube cancer stage iv; fallopian tube neoplasm; familial medullary thyroid cancer; female reproductive neoplasm; female reproductive tract carcinoma in situ; follicle centre lymphoma diffuse small cell lymphoma; follicle centre lymphoma diffuse small cell lymphoma recurrent; follicle centre lymphoma diffuse small cell lymphoma refractory; follicle centre lymphoma diffuse small cell lymphoma stage i; follicle centre lymphoma diffuse small cell lymphoma stage ii; follicle centre lymphoma diffuse small cell lymphoma stage iii; follicle centre lymphoma diffuse small cell lymphoma stage iv; follicle centre lymphoma, follicular grade i, ii, iii; follicle centre lymphoma,

follicular grade i, ii, iii recurrent; follicle centre lymphoma, follicular grade i, ii, iii refractory; follicle centre lymphoma, follicular grade i, ii, iii stage i; follicle centre lymphoma, follicular grade i, ii, iii stage ii; follicle centre lymphoma, follicular grade i, ii, iii stage iii; follicle centre lymphoma, follicular grade i, ii, iii stage iv; follicular thyroid cancer; gallbladder adenocarcinoma; gallbladder adenosquamous carcinoma; gallbladder cancer; gallbladder cancer metastatic; gallbladder cancer recurrent; gallbladder cancer stage 0; gallbladder cancer stage i; gallbladder cancer stage ii; gallbladder cancer stage iii; gallbladder cancer stage iv; gallbladder neoplasm; gallbladder squamous cell carcinoma; gastric cancer; gastric cancer stage iv with metastases; gastric cancer recurrent; gastric cancer stage 0; gastric cancer stage i; gastric cancer stage ii; gastric cancer stage iii; gastric cancer stage iv; gastric neoplasm; gastrinoma malignant; gastroenteropancreatic neuroendocrine tumour disease; gastrointestinal adenocarcinoma; gastrointestinal cancer metastatic; gastrointestinal carcinoma; gastrointestinal carcinoma in situ; gastrointestinal lymphoma; gastrointestinal neoplasm; gastrointestinal stromal cancer; gastrointestinal stromal tumour; gastrointestinal submucosal tumour; gastroesophageal cancer; gastroesophageal cancer recurrent; genital cancer male; genital cancer male in situ; genital neoplasm malignant female; genitourinary tract neoplasm; germ cell cancer; germ cell cancer metastatic; germ cell neoplasm; gestational trophoblastic tumour; gingival cancer; glioblastoma multiforme; glioma; glioneuronal tumour; glomus jugulare tumour; glomus tumour; glomus tympanicum tumour; glottis carcinoma; granular cell tumour; granulosa cell tumour of the testis; growth hormone-producing pituitary tumour; haematological malignancy; haematopoietic neoplasm; haemorrhagic tumour necrosis; hairy cell leukaemia; hairy cell leukaemia recurrent; head and neck cancer; head and neck cancer metastatic; head and neck cancer stage i; head and neck cancer stage ii; head and neck cancer stage iii; head and neck cancer stage iv; hepatic cancer; hepatic cancer metastatic; hepatic cancer recurrent; hepatic cancer stage i; hepatic cancer stage ii; hepatic cancer stage iii; hepatic cancer stage iv; hepatic neoplasm; hepatic neoplasm malignant; hepatic neoplasm malignant recurrent; hepatobiliary cancer; hepatobiliary cancer in situ; hepatobiliary neoplasm; hepatocellular carcinoma; hepatosplenic t-cell lymphoma; her-2 positive breast cancer; her-2 positive gastric cancer; hereditary leiomyomatosis renal cell carcinoma; hereditary non-polyposis colorectal cancer syndrome; hereditary papillary renal carcinoma; hidradenocarcinoma; high grade b-cell lymphoma burkitt-like lymphoma; high grade b-cell lymphoma burkitt-like lymphoma recurrent; high grade b-cell lymphoma burkitt-like lymphoma refractory; high grade b-cell lymphoma burkitt-like lymphoma stage i; high grade b-cell lymphoma burkitt-like lymphoma stage ii; high grade b-cell lymphoma burkitt-like lymphoma stage iii; high grade b-cell lymphoma burkitt-like lymphoma stage iv; high-grade b-cell lymphoma; hormone refractory breast cancer; hormone-dependent prostate cancer; hormone-refractory prostate cancer; hormone-secreting ovarian tumour; huerthle cell carcinoma; hypercalcaemia of malignancy; hypopharyngeal cancer; hypopharyngeal cancer recurrent; hypopharyngeal cancer stage 0; hypopharyngeal cancer stage i; hypopharyngeal cancer stage ii; hypopharyngeal cancer stage iii; hypopharyngeal cancer stage iv; hypopharyngeal neoplasm; iatrogenic metastasis; immunoblastic lymphoma; infected neoplasm; inflammatory carcinoma

of breast stage iii; inflammatory carcinoma of breast stage iv; inflammatory carcinoma of breast recurrent; inflammatory carcinoma of the breast; inflammatory malignant fibrous histiocytoma; inflammatory myofibroblastic tumour; intestinal adenocarcinoma; intestinal metastasis; intestinal t-cell lymphoma recurrent; intestinal t-cell lymphoma refractory; intestinal t-cell lymphoma stage i; intestinal t-cell lymphoma stage ii; intestinal t-cell lymphoma stage iii; intestinal t-cell lymphoma stage iv; intracranial germ cell tumour; intracranial meningioma malignant; intracranial tumour haemorrhage; intraductal papillary breast neoplasm; intraductal papillary mucinous neoplasm; intraductal papillary-mucinous carcinoma of pancreas; intraocular melanoma; intratumoural aneurysm; invasive breast carcinoma; invasive ductal breast carcinoma; invasive lobular breast carcinoma; invasive papillary breast carcinoma; iris neoplasm; iritic melanoma; joint neoplasm; juvenile chronic myelomonocytic leukaemia; keratinising squamous cell carcinoma of nasopharynx; lacrimal duct neoplasm; large cell carcinoma of the respiratory tract stage unspecified; large cell lung cancer; large cell lung cancer metastatic; large cell lung cancer recurrent; large cell lung cancer stage 0; large cell lung cancer stage i; large cell lung cancer stage ii; large cell lung cancer stage iii; large cell lung cancer stage iv; large intestine carcinoma; laryngeal cancer; laryngeal cancer metastatic; laryngeal cancer recurrent; laryngeal cancer stage 0; laryngeal cancer stage i; laryngeal cancer stage ii; laryngeal cancer stage iii; laryngeal cancer stage iv; laryngeal neoplasm; laryngeal squamous cell carcinoma; leiomyosarcoma; leiomyosarcoma metastatic; lentigo maligna; lentigo maligna recurrent; lentigo maligna stage i; lentigo maligna stage ii; lentigo maligna stage iii; lentigo maligna stage iv; leptomeningeal myelomatosis; leukaemia; leukaemia basophilic; leukaemia cutis; leukaemia granulocytic; leukaemia monocytic; leukaemia recurrent; leukaemic cardiac infiltration; leukaemic infiltration; leukaemic infiltration extramedullary; leukaemic infiltration gingiva; leukaemic infiltration hepatic; leukaemic infiltration ovary; leukaemic infiltration pulmonary; leukaemic infiltration renal; leukaemic lymphoma; leukaemic retinopathy; leydig cell tumour of the testis; lip and/or oral cavity cancer; lip and/or oral cavity cancer recurrent; lip and/or oral cavity cancer stage 0; lip and/or oral cavity cancer stage i; lip and/or oral cavity cancer stage ii; lip and/or oral cavity cancer stage iii; lip and/or oral cavity cancer stage iv; lip neoplasm; lip neoplasm malignant stage unspecified; lip squamous cell carcinoma; lipodermoid tumour; liposarcoma; liver carcinoma ruptured; lobular breast carcinoma in situ; lung adenocarcinoma; lung adenocarcinoma stage ii; lung adenocarcinoma stage iii; lung adenocarcinoma stage iv; lung adenocarcinoma metastatic; lung adenocarcinoma recurrent; lung adenocarcinoma stage 0; lung adenocarcinoma stage i; lung cancer metastatic; lung carcinoma cell type unspecified stage ii; lung carcinoma cell type unspecified stage iii; lung carcinoma cell type unspecified stage iv; lung carcinoma cell type unspecified recurrent; lung carcinoma cell type unspecified stage 0; lung carcinoma cell type unspecified stage i; lung infiltration malignant; lung neoplasm; lung neoplasm malignant; lung neoplasm surgery; lung squamous cell carcinoma stage ii; lung squamous cell carcinoma stage iii; lung squamous cell carcinoma stage iv; lung squamous cell carcinoma metastatic; lung squamous cell carcinoma recurrent; lung squamous cell carcinoma stage 0; lung squamous cell carcinoma stage i; lung squamous cell carcinoma stage unspecified; lymphangiosis carcinomatosa; lymphatic system

neoplasm; lymphocytic leukaemia; lymphocytic lymphoma; lymphoma; lymphoma aids related; lymphoma operation; lymphomatoid papulosis; lymphoplasmacytoid lymphoma/immunocytoma; lymphoplasmacytoid lymphoma/immunocytoma recurrent; lymphoplasmacytoid lymphoma/immunocytoma refractory; lymphoplasmacytoid lymphoma/immunocytoma stage i; lymphoplasmacytoid lymphoma/immunocytoma stage ii; lymphoplasmacytoid lymphoma/immunocytoma stage iii; lymphoplasmacytoid lymphoma/immunocytoma stage iv; male reproductive tract neoplasm; malignant anorectal neoplasm; malignant ascites; malignant biliary obstruction; malignant connective tissue neoplasm; malignant cranial nerve neoplasm; malignant fibrous histiocytoma; malignant gastrointestinal obstruction; malignant genitourinary tract neoplasm; malignant glioma; malignant joint neoplasm; malignant lymphoid neoplasm; malignant lymphoma unclassifiable high grade; malignant lymphoma unclassifiable low grade; malignant mast cell neoplasm; malignant mediastinal neoplasm; malignant melanoma; malignant melanoma in situ; malignant melanoma of eyelid; malignant melanoma of sites other than skin; malignant melanoma stage i; malignant melanoma stage ii; malignant melanoma stage iii; malignant melanoma stage iv; malignant meningioma metastatic; malignant mesenchymoma; malignant mesenchymoma metastatic; malignant mesenchymoma recurrent; malignant mesenteric neoplasm; malignant middle ear neoplasm; malignant muscle neoplasm; malignant neoplasm of ampulla of vater; malignant neoplasm of auricular cartilage; malignant neoplasm of choroid; malignant neoplasm of conjunctiva; malignant neoplasm of cornea; malignant neoplasm of eye; malignant neoplasm of eyelid; malignant neoplasm of islets of langerhans; malignant neoplasm of lacrimal duct; malignant neoplasm of lacrimal gland; malignant neoplasm of orbit; malignant neoplasm of paraurethral glands; malignant neoplasm of placenta; malignant neoplasm of pleura; malignant neoplasm of pleura metastatic; malignant neoplasm of renal pelvis; malignant neoplasm of retina; malignant neoplasm of seminal vesicle; malignant neoplasm of spermatic cord; malignant neoplasm of spinal cord; malignant neoplasm of thorax; malignant neoplasm of thymus; malignant neoplasm of unknown primary site; malignant neoplasm of uterine adnexa; malignant neoplasm papilla of vater; malignant neoplasm progression; malignant nervous system neoplasm; malignant nipple neoplasm; malignant nipple neoplasm female; malignant nipple neoplasm male; malignant oligodendroglioma; malignant ovarian cyst; malignant palate neoplasm; malignant pericardial neoplasm; malignant peritoneal neoplasm; malignant pituitary tumour; malignant pleural effusion; malignant polyp; malignant respiratory tract neoplasm; malignant splenic neoplasm; malignant sweat gland neoplasm; malignant transformation; malignant tumour excision; malignant urinary tract neoplasm; mandibular mass; mantle cell lymphoma; mantle cell lymphoma recurrent; mantle cell lymphoma refractory; mantle cell lymphoma stage i; mantle cell lymphoma stage ii; mantle cell lymphoma stage iii; mantle cell lymphoma stage iv; marginal zone lymphoma; marginal zone lymphoma recurrent; marginal zone lymphoma refractory; marginal zone lymphoma stage i; marginal zone lymphoma stage ii; marginal zone lymphoma stage iii; marginal zone lymphoma stage iv; mastocytic leukaemia; maternal cancer in pregnancy; mature b-cell type acute leukaemia; maxillofacial sinus neoplasm; mediastinum neoplasm; medullary carcinoma of breast; medullary thyroid cancer;

meningeal neoplasm; meningioma malignant; mesenteric neoplasm; mesothelioma malignant; metaplastic breast carcinoma; metastases to bone; metastases to central nervous system; metastases to eye; metastases to gallbladder; metastases to heart; metastases to large intestine; metastases to liver; metastases to lung; metastases to lymph nodes; metastases to pancreas; metastases to peritoneum; metastases to pleura; metastases to spine; metastasis; metastatic bronchial carcinoma; metastatic carcinoid tumour; metastatic carcinoma of the bladder; metastatic choriocarcinoma; metastatic gastric cancer; metastatic lymphoma; metastatic malignant melanoma; metastatic neoplasm; metastatic nervous system neoplasm; metastatic pain; metastatic renal cell carcinoma; metastatic salivary gland cancer; metastatic squamous cell carcinoma; metastatic uterine cancer; microsatellite instability cancer; minimal residual disease; mismatch repair cancer syndrome; mixed adenoneuroendocrine carcinoma; mixed hepatocellular cholangiocarcinoma; mucinous adenocarcinoma of appendix; mucinous breast carcinoma; mucinous cystadenocarcinoma of pancreas; mucinous cystadenocarcinoma ovary; mucinous endometrial carcinoma; mucoepidermoid carcinoma; mucoepidermoid carcinoma of salivary gland; mueller's mixed tumour; muscle neoplasm; musculoskeletal cancer; myeloid leukaemia; myeloma cast nephropathy; myelomalacia; myeloproliferative neoplasm; nasal cavity cancer; nasal neoplasm; nasal sinus cancer; nasopharyngeal cancer; nasopharyngeal cancer metastatic; nasopharyngeal cancer recurrent; nasopharyngeal cancer stage 0; nasopharyngeal cancer stage i; nasopharyngeal cancer stage ii; nasopharyngeal cancer stage iii; nasopharyngeal cancer stage iv; natural killer-cell leukaemia; natural killer-cell lymphoblastic lymphoma; neoplasm; neoplasm malignant; neoplasm of appendix; neoplasm of cornea unspecified malignancy; neoplasm of orbit; neoplasm of thymus; neoplasm progression; neoplasm prostate; neoplasm recurrence; neoplasm skin; neoplasm swelling; nephroblastoma; nervous system neoplasm; nervous system neoplasm surgery; neuroectodermal neoplasm; neuroendocrine breast tumour; neuroendocrine carcinoma; neuroendocrine carcinoma metastatic; neuroendocrine carcinoma of the bladder; neuroendocrine carcinoma of the skin; neuroendocrine tumour; neuroendocrine tumour of the lung; neuroendocrine tumour of the lung metastatic; neurogenic tumour; nipple neoplasm; nodal marginal zone b-cell lymphoma; nodal marginal zone b-cell lymphoma recurrent; nodal marginal zone b-cell lymphoma refractory; nodal marginal zone b-cell lymphoma stage i; nodal marginal zone b-cell lymphoma stage ii; nodal marginal zone b-cell lymphoma stage iii; nodal marginal zone b-cell lymphoma stage iv; nodular lymphocyte predominant hodgkin lymphoma; nongerminomatous germ cell tumour of the cns; non-hodgkin's lymphoma; non-hodgkin's lymphoma metastatic; non-hodgkin's lymphoma recurrent; non-hodgkin's lymphoma refractory; non-hodgkin's lymphoma stage i; non-hodgkin's lymphoma stage ii; non-hodgkin's lymphoma stage iii; non-hodgkin's lymphoma stage iv; non-hodgkin's lymphoma transformed recurrent; non-hodgkin's lymphoma unspecified histology aggressive; non-hodgkin's lymphoma unspecified histology aggressive recurrent; non-hodgkin's lymphoma unspecified histology aggressive refractory; non-hodgkin's lymphoma unspecified histology aggressive stage i; non-hodgkin's lymphoma unspecified histology aggressive stage ii; non-hodgkin's lymphoma unspecified histology aggressive stage iii; non-hodgkin's lymphoma unspecified histology aggressive stage iv; non-hodgkin's lymphoma

unspecified histology indolent; non-hodgkin's lymphoma unspecified histology indolent stage i; non-hodgkin's lymphoma unspecified histology indolent stage ii; non-hodgkin's lymphoma unspecified histology indolent stage iii; non-hodgkin's lymphoma unspecified histology indolent stage iv; nonkeratinising carcinoma of nasopharynx; non-renal cell carcinoma of kidney; non-small cell lung cancer; non-small cell lung cancer metastatic; non-small cell lung cancer recurrent; non-small cell lung cancer stage 0; non-small cell lung cancer stage i; non-small cell lung cancer stage ii; non-small cell lung cancer stage iii; non-small cell lung cancer stage iiia; non-small cell lung cancer stage iiib; non-small cell lung cancer stage iv; nut midline carcinoma; ocular cancer metastatic; ocular lymphoma; ocular neoplasm; ocular surface squamous neoplasia; oesophageal adenocarcinoma; oesophageal adenocarcinoma stage ii; oesophageal adenocarcinoma stage iii; oesophageal adenocarcinoma stage iv; oesophageal adenocarcinoma metastatic; oesophageal adenocarcinoma recurrent; oesophageal adenocarcinoma stage 0; oesophageal adenocarcinoma stage i; oesophageal cancer metastatic; oesophageal carcinoma; oesophageal carcinoma recurrent; oesophageal carcinoma stage 0; oesophageal neoplasm; oesophageal squamous cell carcinoma; oesophageal squamous cell carcinoma stage ii; oesophageal squamous cell carcinoma stage iii; oesophageal squamous cell carcinoma stage iv; oesophageal squamous cell carcinoma metastatic; oesophageal squamous cell carcinoma recurrent; oesophageal squamous cell carcinoma stage 0; oesophageal squamous cell carcinoma stage i; oestrogen receptor positive breast cancer; optic nerve neoplasm; oral cavity cancer metastatic; oral neoplasm; oropharyngeal cancer; oropharyngeal cancer recurrent; oropharyngeal cancer stage 0; oropharyngeal cancer stage i; oropharyngeal cancer stage ii; oropharyngeal cancer stage iii; oropharyngeal cancer stage iv; oropharyngeal cancer stage unspecified; oropharyngeal neoplasm; oropharyngeal squamous cell carcinoma; osteosarcoma metastatic; otic cancer metastatic; ovarian cancer; ovarian cancer metastatic; ovarian cancer recurrent; ovarian cancer stage i; ovarian cancer stage ii; ovarian cancer stage iii; ovarian cancer stage iv; ovarian clear cell carcinoma; ovarian embryonal carcinoma; ovarian endometrioid carcinoma; ovarian epithelial cancer; ovarian epithelial cancer metastatic; ovarian epithelial cancer recurrent; ovarian epithelial cancer stage i; ovarian epithelial cancer stage ii; ovarian epithelial cancer stage iii; ovarian epithelial cancer stage iv; ovarian germ cell cancer; ovarian germ cell cancer stage i; ovarian germ cell cancer stage ii; ovarian germ cell cancer stage iii; ovarian germ cell cancer stage iv; ovarian germ cell choriocarcinoma; ovarian germ cell choriocarcinoma stage ii; ovarian germ cell choriocarcinoma stage iii; ovarian germ cell choriocarcinoma stage iv; ovarian germ cell choriocarcinoma stage i; ovarian germ cell embryonal carcinoma stage ii; ovarian germ cell embryonal carcinoma stage iii; ovarian germ cell embryonal carcinoma stage iv; ovarian germ cell embryonal carcinoma stage i; ovarian germ cell endodermal sinus tumour; ovarian germ cell endodermal sinus tumour stage i; ovarian germ cell endodermal sinus tumour stage ii; ovarian germ cell endodermal sinus tumour stage iii; ovarian germ cell endodermal sinus tumour stage iv; ovarian germ cell tumour; ovarian germ cell tumour mixed; ovarian granulosa cell tumour; ovarian granulosa-theca cell tumour; ovarian low malignant potential tumour; ovarian melanoma; ovarian neoplasm; ovarian sertoli-leydig cell tumour; ovarian stromal cancer; ovarian theca cell tumour; paget's

disease of nipple; pancoast's tumour; pancreatic carcinoma; pancreatic carcinoma stage ii; pancreatic carcinoma stage iii; pancreatic carcinoma stage iv; pancreatic carcinoma metastatic; pancreatic carcinoma recurrent; pancreatic carcinoma stage 0; pancreatic carcinoma stage i; pancreatic neoplasm; pancreatic neuroendocrine tumour; pancreatic neuroendocrine tumour metastatic; papillary cystadenoma lymphomatosum; papillary renal cell carcinoma; papillary serous endometrial carcinoma; papillary thyroid cancer; papillary tumour of renal pelvis; paracancerous pneumonia; paraganglion neoplasm; paraganglion neoplasm malignant; paranasal sinus and nasal cavity malignant neoplasm; paranasal sinus and nasal cavity malignant neoplasm recurrent; paranasal sinus and nasal cavity malignant neoplasm stage 0; paranasal sinus and nasal cavity malignant neoplasm stage i; paranasal sinus and nasal cavity malignant neoplasm stage ii; paranasal sinus and nasal cavity malignant neoplasm stage iii; paranasal sinus and nasal cavity malignant neoplasm stage iv; paranasal sinus neoplasm; paraneoplastic arthritis; paraneoplastic dermatomyositis; paraneoplastic dermatosis; paraneoplastic encephalomyelitis; paraneoplastic glomerulonephritis; paraneoplastic hypoglycaemia; paraneoplastic myelopathy; paraneoplastic nephrotic syndrome; paraneoplastic neurological syndrome; paraneoplastic pemphigus; paraneoplastic pleural effusion; paraneoplastic rash; paraneoplastic retinopathy; paraneoplastic syndrome; paraneoplastic thrombosis; parathyroid tumour; parathyroid tumour malignant; pelvic neoplasm; penile cancer; penile neoplasm; penile squamous cell carcinoma; penis carcinoma; penis carcinoma stage ii; penis carcinoma stage iii; penis carcinoma stage iv; penis carcinoma metastatic; penis carcinoma recurrent; penis carcinoma stage i; pericardial effusion malignant; pericardial mesothelioma malignant; pericardial mesothelioma malignant recurrent; pericardial neoplasm; pericarditis malignant; peripheral nervous system neoplasm; peripheral primitive neuroectodermal bone tumour; peripheral primitive neuroectodermal tumour of soft tissue; peripheral t-cell lymphoma unspecified; peripheral t-cell lymphoma unspecified recurrent; peripheral t-cell lymphoma unspecified refractory; peripheral t-cell lymphoma unspecified stage i; peripheral t-cell lymphoma unspecified stage ii; peripheral t-cell lymphoma unspecified stage iii; peripheral t-cell lymphoma unspecified stage iv; peritoneal carcinoma metastatic; peritoneal mesothelioma malignant; peritoneal mesothelioma malignant recurrent; peritoneal neoplasm; peritumoural oedema; phaeochromocytoma malignant; pharyngeal cancer; pharyngeal cancer metastatic; pharyngeal cancer recurrent; pharyngeal cancer stage 0; pharyngeal cancer stage i; pharyngeal cancer stage ii; pharyngeal cancer stage iii; pharyngeal cancer stage iv; pharyngeal neoplasm; phosphaturic mesenchymal tumour; phyllodes tumour pilomatrix carcinoma; pineal neoplasm; pineal parenchymal neoplasm malignant; pituitary cancer metastatic; pituitary neoplasm malignant recurrent; pituitary tumour; pituitary tumour recurrent; pituitary tumour removal; placental neoplasm; plasma cell leukaemia; plasma cell myeloma; plasma cell myeloma recurrent; plasma cell myeloma refractory; plasmablastic lymphoma; plasmacytoma; pleomorphic leiomyosarcoma; pleomorphic malignant fibrous histiocytoma; pleura carcinoma; pleural mass; pleural mesothelioma; pleural mesothelioma malignant; pleural mesothelioma malignant recurrent; pleural neoplasm; pleuropulmonary blastoma; polyneuropathy in malignant disease; poorly differentiated thyroid carcinoma;

porocarcinoma; postcricoid cancer; precancerous cells present; precancerous lesion excision; precancerous mucosal lesion; precancerous skin lesion; precursor b-lymphoblastic lymphoma; precursor b-lymphoblastic lymphoma recurrent; precursor b-lymphoblastic lymphoma refractory; precursor b-lymphoblastic lymphoma stage i; precursor b-lymphoblastic lymphoma stage ii; precursor b-lymphoblastic lymphoma stage iii; precursor b-lymphoblastic lymphoma stage iv; precursor t-lymphoblastic leukaemia acute; precursor t-lymphoblastic lymphoma/leukaemia; precursor t-lymphoblastic lymphoma/leukaemia recurrent; precursor t-lymphoblastic lymphoma/leukaemia refractory; precursor t-lymphoblastic lymphoma/leukaemia stage i; precursor t-lymphoblastic lymphoma/leukaemia stage ii; precursor t-lymphoblastic lymphoma/leukaemia stage iii; precursor t-lymphoblastic lymphoma/leukaemia stage iv; primary breast lymphoma; primary cardiac lymphoma; primary gastrointestinal follicular lymphoma; primary mediastinal large b-cell lymphoma; primary mediastinal large b-cell lymphoma recurrent; primary mediastinal large b-cell lymphoma refractory; primary mediastinal large b-cell lymphoma stage i; primary mediastinal large b-cell lymphoma stage ii; primary mediastinal large b-cell lymphoma stage iii; primary mediastinal large b-cell lymphoma stage iv; primary pulmonary melanoma; primitive neuroectodermal tumour; primitive neuroectodermal tumour metastatic; prolactin-producing pituitary tumour; polymphocytic leukaemia; prostate cancer; prostate cancer metastatic; prostate cancer recurrent; prostate cancer stage 0; prostate cancer stage i; prostate cancer stage ii; prostate cancer stage iii; prostate cancer stage iv; pulmonary tumour thrombotic microangiopathy; rectal adenocarcinoma; rectal cancer; rectal cancer metastatic; rectal cancer recurrent; rectal cancer stage 0; rectal cancer stage i; rectal cancer stage ii; rectal cancer stage iii; rectal cancer stage iv; rectal neoplasm; rectosigmoid cancer; rectosigmoid cancer metastatic; rectosigmoid cancer recurrent; rectosigmoid cancer stage 0; rectosigmoid cancer stage i; rectosigmoid cancer stage ii; rectosigmoid cancer stage iii; rectosigmoid cancer stage iv; recurrent cancer; refractory cancer; renal cancer; renal cancer metastatic; renal cancer recurrent; renal cancer stage i; renal cancer stage ii; renal cancer stage iii; renal cancer stage iv; renal cell carcinoma; renal cell carcinoma stage ii; renal cell carcinoma stage iii; renal cell carcinoma stage iv; renal cell carcinoma recurrent; renal cell carcinoma stage i; renal cell carcinoma stage unspecified; renal neoplasm; renal tumour excision; respiratory tract carcinoma in situ; respiratory tract neoplasm; retinal neoplasm; retro-orbital neoplasm; retroperitoneal cancer; retroperitoneal neoplasm; retroperitoneal neoplasm metastatic; rhabdoid tumour; rhabdoid tumour of the kidney; salivary gland cancer; salivary gland cancer recurrent; salivary gland cancer stage 0; salivary gland cancer stage i; salivary gland cancer stage ii; salivary gland cancer stage iii; salivary gland cancer stage iv; salivary gland neoplasm; sarcoma; sarcoma of skin; sarcoma uterus; sarcomatoid carcinoma; sarcomatoid carcinoma of the lung; sarcomatoid mesothelioma; scrotal cancer; sebaceous carcinoma; second primary malignancy; serous cystadenocarcinoma of pancreas; serous cystadenocarcinoma ovary; sertoli cell testicular tumour; signet-ring cell carcinoma; sinus cancer metastatic; skin cancer; skin cancer metastatic; skin carcinoma; skin neoplasm bleeding; skin neoplasm excision; skin squamous cell carcinoma metastatic; skin squamous cell carcinoma recurrent; small cell carcinoma; small cell carcinoma

of the cervix; small cell lung cancer; small cell lung cancer extensive stage; small cell lung cancer limited stage; small cell lung cancer metastatic; small cell lung cancer recurrent; small cell lung cancer stage unspecified; small intestine adenocarcinoma; small intestine carcinoma; small intestine carcinoma stage ii; small intestine carcinoma stage iii; small intestine carcinoma stage iv; small intestine carcinoma metastatic; small intestine carcinoma recurrent; small intestine carcinoma stage 0; small intestine carcinoma stage i; smooth muscle cell neoplasm; soft tissue neoplasm; solid pseudopapillary tumour of the pancreas; spinal cord neoplasm; spinal meningioma malignant; splenic marginal zone lymphoma; splenic marginal zone lymphoma recurrent; splenic marginal zone lymphoma refractory; splenic marginal zone lymphoma stage i; splenic marginal zone lymphoma stage ii; splenic marginal zone lymphoma stage iii; splenic marginal zone lymphoma stage iv; splenic neoplasm malignancy unspecified; squamous cell breast carcinoma; squamous cell carcinoma; squamous cell carcinoma of head and neck; squamous cell carcinoma of lung; squamous cell carcinoma of pharynx; squamous cell carcinoma of skin; squamous cell carcinoma of the cervix; squamous cell carcinoma of the hypopharynx; squamous cell carcinoma of the oral cavity; squamous cell carcinoma of the parotid gland; squamous cell carcinoma of the tongue; squamous cell carcinoma of the vagina; squamous cell carcinoma of the vulva; squamous endometrial carcinoma; superficial spreading melanoma stage unspecified; sweat gland tumour; targeted cancer therapy; t-cell chronic lymphocytic leukaemia; t-cell lymphoma; t-cell lymphoma recurrent; t-cell lymphoma refractory; t-cell lymphoma stage i; t-cell lymphoma stage ii; t-cell lymphoma stage iii; t-cell lymphoma stage iv; t-cell prolymphocytic leukaemia; t-cell type acute leukaemia; t-cell unclassifiable lymphoma high grade; t-cell unclassifiable lymphoma low grade tendon neoplasm; testicular cancer metastatic; testicular choriocarcinoma; testicular choriocarcinoma stage ii; testicular choriocarcinoma stage iii; testicular choriocarcinoma recurrent; testicular choriocarcinoma stage i; testicular embryonal carcinoma; testicular embryonal carcinoma stage ii; testicular embryonal carcinoma stage iii; testicular embryonal carcinoma stage i; testicular germ cell cancer; testicular germ cell cancer metastatic; testicular germ cell tumour; testicular germ cell tumour mixed; testicular germ cell tumour mixed incl choriocarcinoma stage i; testicular germ cell tumour mixed incl choriocarcinoma stage ii; testicular germ cell tumour mixed incl choriocarcinoma stage iii; testicular germ cell tumour mixed incl yolk sac tumour stage i; testicular germ cell tumour mixed incl yolk sac tumour stage ii; testicular germ cell tumour mixed stage i; testicular germ cell tumour mixed stage ii; testicular germ cell tumour mixed stage iii; testicular malignant teratoma; testicular malignant teratoma stage i; testicular malignant teratoma stage ii; testicular malignant teratoma stage iii; testicular neoplasm; testicular yolk sac tumour; testicular yolk sac tumour stage i; testicular yolk sac tumour stage ii; testicular yolk sac tumour stage iii; testis cancer; testis cancer recurrent; throat cancer; thymic cancer metastatic; thymoma malignant; thymoma malignant recurrent; thyroid b-cell lymphoma; thyroid cancer; thyroid cancer metastatic; thyroid cancer recurrent; thyroid cancer stage 0; thyroid cancer stage i; thyroid cancer stage ii; thyroid cancer stage iii; thyroid cancer stage iv; thyroid neoplasm; thyroid stimulating hormone-producing pituitary tumour; tongue cancer metastatic; tongue cancer recurrent; tongue carcinoma stage ii; tongue

carcinoma stage iii; tongue carcinoma stage iv; tongue carcinoma stage 0; tongue carcinoma stage i; tongue neoplasm; tongue neoplasm malignant stage unspecified; tonsil cancer; tonsil cancer metastatic; tonsillar neoplasm; tracheal cancer; tracheal neoplasm; transdifferentiation of neoplasm; transformation to acute myeloid leukaemia; transitional cell cancer of renal pelvis and ureter metastatic; transitional cell cancer of the renal pelvis and ureter; transitional cell cancer of the renal pelvis and ureter localised; transitional cell cancer of the renal pelvis and ureter recurrent; transitional cell cancer of the renal pelvis and ureter regional; transitional cell carcinoma; transitional cell carcinoma metastatic; transitional cell carcinoma recurrent; transitional cell carcinoma urethra; trichoblastic carcinoma; triple hit lymphoma; triple negative breast cancer; tubular breast carcinoma; tumour associated fever; tumour budding; tumour cavitation; tumour cell mobilisation; tumour compression; tumour embolism; tumour excision; tumour exudation; tumour fistulisation; tumour flare; tumour haemorrhage; tumour hyperprogression; tumour inflammation; tumour invasion; tumour local invasion; tumour lysis syndrome; tumour marker abnormal; tumour marker increased; tumour necrosis; tumour obstruction; tumour of ampulla of vater; tumour pain; tumour perforation; tumour pruritus; tumour pseudoprogression; tumour rupture; tumour thrombosis; tumour ulceration; undifferentiated carcinoma of colon; undifferentiated nasopharyngeal carcinoma; undifferentiated sarcoma; ureteral neoplasm; ureteric cancer; ureteric cancer local; ureteric cancer metastatic; ureteric cancer recurrent; ureteric cancer regional; urethral cancer; urethral cancer metastatic; urethral cancer recurrent; urethral neoplasm; urinary tract carcinoma in situ; urinary tract neoplasm; uterine cancer; uterine carcinoma in situ; uterine leiomyosarcoma; uterine neoplasm; uterine tumour excision; uveal melanoma; vaginal adenocarcinoma; vaginal cancer; vaginal cancer metastatic; vaginal cancer recurrent; vaginal cancer stage 0; vaginal cancer stage i; vaginal cancer stage ii; vaginal cancer stage iii; vaginal cancer stage iva; vaginal cancer stage ivb; vaginal neoplasm; vascular neoplasm; vocal cord neoplasm; vulval cancer; vulval cancer metastatic; vulval cancer recurrent; vulval cancer stage 0; vulval cancer stage i; vulval cancer stage ii; vulval cancer stage iii; vulval cancer stage iv; vulval neoplasm; vulvar adenocarcinoma; yolk sac tumour site unspecified.

Nausea, Vomiting

Nausea; procedural nausea; procedural vomiting; vomiting; vomiting projectile.

Pancreatitis FDA N

Alcoholic pancreatitis; alcoholic pancreopathy; autoimmune pancreatitis; cytomegalovirus pancreatitis; haemorrhagic necrotic pancreatitis; ischaemic pancreatitis; lupus pancreatitis; obstructive pancreatitis; oedematous pancreatitis; pancreas infection; pancreatic abscess; pancreatic haemorrhage; pancreatic necrosis; pancreatic phlegmon; pancreatic pseudocyst; pancreatic pseudocyst drainage; pancreatitis; pancreatitis acute; pancreatitis bacterial; pancreatitis chronic; pancreatitis due to biliary obstruction; pancreatitis fungal; pancreatitis haemorrhagic; pancreatitis helminthic; pancreatitis necrotising; pancreatitis relapsing; pancreatitis viral; pancreatorenal syndrome; traumatic pancreatitis.

Clinical Review
Natalie Branagan, MD
BLA761178
Aduhelm/aducanumab

Pre-syncope or Syncope
Drop attacks; presyncope.

Psychosis, Delusions, Hallucinations

Acute psychosis; alcoholic psychosis; brief psychotic disorder with marked stressors; brief psychotic disorder without marked stressors; brief psychotic disorder, with postpartum onset; childhood psychosis; delusion; epileptic psychosis; hallucination; hallucination auditory; hallucination, gustatory; hallucination, olfactory; hallucination, synaesthetic; hallucination, tactile; hallucination, visual; hallucinations, mixed; hysterical psychosis; paranoia; parkinson's disease psychosis; persecutory delusion; postictal psychosis; psychotic behaviour; psychotic disorder; psychotic disorder due to a general medical condition; psychotic symptom; reactive psychosis; rebound psychosis; schizoaffective disorder; schizoaffective disorder bipolar type; schizophrenia; schizophrenia simple; schizophrenia, paranoid type; schizophreniform disorder; senile psychosis; shared psychotic disorder; somatic delusion; somatic hallucination; substance-induced psychotic disorder; transient psychosis.

Pulmonary Embolism

Administration site phlebitis; administration site thrombosis; adrenal thrombosis; aortic thrombosis; arterial occlusive disease; arteriovenous graft thrombosis; axillary vein thrombosis; cavernous sinus thrombosis; cerebral thrombosis; cerebral venous thrombosis; coeliac artery occlusion; femoral artery occlusion; graft thrombosis; hepatic vein thrombosis; iliac vein thrombosis; infective thrombosis; infusion site thrombosis; jugular vein thrombosis; mesenteric artery stenosis; mesenteric artery thrombosis; mesenteric occlusion; mesenteric vascular occlusion; mesenteric vein thrombosis; pelvic venous thrombosis; peripheral arterial reocclusion; peripheral artery stenosis; peripheral artery thrombosis; phlebitis deep; phlebitis infective; portal vein thrombosis; pulmonary artery thrombosis; pulmonary embolism; pulmonary microemboli; retinal artery occlusion; retinal artery thrombosis; retinal infarction; spinal cord infarction; splenic infarction; splenic vein thrombosis; stent occlusion; subclavian vein thrombosis; superior vena cava syndrome; superior vena caval occlusion; thalamic infarction; thrombotic cerebral infarction; transverse sinus thrombosis; vascular bypass dysfunction; vascular graft thrombosis; vena cava thrombosis; venous thrombosis; venous thrombosis limb; vertebral artery occlusion; vertebral artery stenosis.

Pyrexia FDA B

Acute febrile neutrophilic dermatosis; body temperature increased; brazilian purpuric fever; chills; delirium febrile; febrile bone marrow aplasia; febrile convulsion; febrile infection; febrile infection-related epilepsy syndrome; febrile neutropenia; febrile nonhaemolytic transfusion reaction; feeling hot; fever; fever neonatal; hyperpyrexia; hyperpyrexia malignant; hyperthermia; hyperthermia malignant; intermittent pyrexia; masked fever; o'nyong-nyong fever; oropouche fever; parkinsonism hyperpyrexia syndrome; pharyngoconjunctival fever of

children; poikilothermia; post procedural fever; postoperative fever; postpartum pyrexia; puerperal pyrexia; pyrexia; rigors; sweating fever; tumour associated fever.

Rash FDA B

Acantholysis; acne; acquired blaschkoid dermatitis; acquired porokeratosis; administration site rash; application site bullae; application site rash; application site vesicles; blister; boston exanthema; brazilian purpuric fever; butterfly rash; candida nappy rash; catheter site dermatitis; catheter site rash; cutaneous blastomycosis; cutaneous listeriosis; cutaneous nocardiosis; cytophagic histiocytic panniculitis; dermatitis; dyschromatosis; eczema coxsackium; epidermal necrolysis; epidermolysis; epidermolysis bullosa; erythema; erythema migrans; erythema multiforme; exanthem; exfoliative rash; eyelid rash; fat embolism syndrome; fixed drug eruption; fixed eruption; fungal rash; genital rash; granuloma gluteale infantum; heat rash; heliotrope rash; implant site rash; implant site vesicles; incision site blister; incision site rash; incision site vesicles; infusion site rash; infusion site vesicles; injection site rash; injection site vesicles; instillation site rash; ipex syndrome; lyell syndrome; medical device site rash; mucocutaneous rash; nodular rash; paraneoplastic rash; paroxysmal extreme pain disorder; pemphigoid; perineal rash; photosensitive rash; rash; rash erythematous; rash erythematous aggravated; rash follicular; rash generalised; rash macular; rash maculo-papular; rash maculovesicular; rash morbilliform; rash neonatal; rash nos; rash papular; rash papulosquamous; rash pruritic; rash pustular; rash rubelliform; rash scaly; rash scarlatiniform; rash varicelliform; rash vesicular; saddan syndrome; septic rash; shagreen skin; skin disorder; skin eruption; skin exfoliation; skin irritation; skin lesion inflammation; skin reaction; skin weeping; southern tick-associated rash illness; stevens johnson syndrome; stevens-johnson syndrome; stoma site rash; systemic lupus erythematosus rash; target skin lesion; toxic epidermal necrolysis; toxic skin eruption; toxicoderma; urticaria; urticarial dermatitis; vaccination site rash; vascular access site rash; vasculitic rash; venipuncture site rash; vessel puncture site rash; viral rash; vulvovaginal rash.

Respiratory Depression FDA B

Acute respiratory failure; adaptive servo-ventilation; anoxia; apnoea; apnoeic attack; asphyxia; blood ph decreased; bradypnoea; breath sounds absent; breathing-related sleep disorder; capnogram abnormal; carbon dioxide abnormal; carbon dioxide increased; cardiopulmonary failure; cardio-respiratory arrest; cardio-respiratory arrest neonatal; central-alveolar hypoventilation; cheyne-stokes respiration; congenital central hypoventilation syndrome; cyanosis; cyanosis central; cyanosis neonatal; dependence on respirator; endotracheal intubation; endotracheal intubation complication; fat embolism syndrome; hypercapnia; hypercapnic coma; hypopnoea; hypoventilation; hypoventilation neonatal; hypoxia; infantile apnoea; infantile apnoeic attack; life support; lung hypoinflation; mechanical ventilation; mechanical ventilation complication; neonatal anoxia; neonatal asphyxia; neonatal hypoxia; neonatal respiratory acidosis; neonatal respiratory arrest; neonatal respiratory depression; neonatal respiratory failure; oxygen saturation abnormal; oxygen saturation decreased; oxygen

saturation immeasurable; oxygen therapy; pao2/fio2 ratio decreased; pco2 abnormal; pco2 increased; perry syndrome; pickwickian syndrome; po2 abnormal; po2 decreased; postoperative respiratory failure; prolonged expiration; respiration abnormal; respiratory acidosis; respiratory arrest; respiratory depression; respiratory depth decreased; respiratory failure; respiratory fatigue; respiratory paralysis; respiratory rate decreased; rohhad syndrome; sleep apnoea syndrome; weaning failure.

Sepsis

Abdominal sepsis; bacterial sepsis; biliary sepsis; candida sepsis; citrobacter sepsis; clostridium difficile sepsis; device related sepsis; enterobacter sepsis; enterococcal sepsis; escherichia sepsis; fungal sepsis; klebsiella sepsis; listeria sepsis; neutropenic sepsis; pneumococcal sepsis; post procedural sepsis; pseudomonas sepsis; pulmonary sepsis; salmonella sepsis; ; sepsis; sepsis syndrome; septic encephalopathy; septic rash; septic shock; serratia sepsis; staphylococcal sepsis; streptococcal sepsis; urosepsis; wound sepsis.

Solid Neoplasia, All (Benign, Malignant, Unknown)

Abdominal neoplasm; abdominal wall neoplasm; abdominal wall neoplasm benign; abdominal wall neoplasm malignant; acinar cell carcinoma of pancreas; acinic cell carcinoma of salivary gland; acoustic neuroma; acral lentiginous melanoma; acral lentiginous melanoma stage i; acral lentiginous melanoma stage ii; acral lentiginous melanoma stage iii; acral lentiginous melanoma stage iv; adenocarcinoma; adenocarcinoma gastric; adenocarcinoma of appendix; adenocarcinoma of colon; adenocarcinoma of salivary gland; adenocarcinoma of the cervix; adenocarcinoma pancreas; adenoid cystic carcinoma; adenoid cystic carcinoma of external auditory canal; adenoid cystic carcinoma of salivary gland; adenolipoma; adenolymphoma; adenoma benign; adenomatous polyposis coli; adenosquamous carcinoma of the cervix; adenosquamous carcinoma of vagina; adenosquamous cell carcinoma; adenosquamous cell lung cancer; adenosquamous cell lung cancer recurrent; adenosquamous cell lung cancer stage 0; adenosquamous cell lung cancer stage i; adenosquamous cell lung cancer stage ii; adenosquamous cell lung cancer stage iii; adenosquamous cell lung cancer stage iv; adrenal adenoma; adrenal carcinoma; adrenal gland cancer; adrenal gland cancer metastatic; adrenal neoplasm; adrenocortical carcinoma; aesthesioneuroblastoma; ameloblastoma; anal cancer; anal cancer metastatic; anal cancer recurrent; anal cancer stage 0; anal cancer stage i; anal cancer stage ii; anal cancer stage iii; anal cancer stage iv; anal neoplasm; anal squamous cell carcinoma; anaplastic thyroid cancer; angioliipoma; angiolymphoma; angiosarcoma; angiosarcoma metastatic; apocrine breast carcinoma; appendix cancer; astrocytoma malignant; basal cell carcinoma; basosquamous carcinoma; basosquamous carcinoma of skin; benign biliary neoplasm; benign bone neoplasm; benign breast neoplasm; benign cardiac neoplasm; benign colonic neoplasm; benign duodenal neoplasm; benign ear neoplasm; benign gastric neoplasm; benign gastrointestinal neoplasm; benign hepatic neoplasm; benign laryngeal neoplasm; benign lung neoplasm; benign lymph node neoplasm; benign neoplasm; benign neoplasm of adrenal gland; benign neoplasm of bladder; benign neoplasm of cervix uteri;

benign neoplasm of eye; benign neoplasm of eyelid; benign neoplasm of prostate; benign neoplasm of skin; benign neoplasm of thyroid gland; benign neoplasm of ureter; benign neoplasm of urethra; benign oesophageal neoplasm; benign ovarian tumour; benign pancreatic neoplasm; benign penile neoplasm; benign pleural neoplasm; benign renal neoplasm; benign salivary gland neoplasm; benign small intestinal neoplasm; benign soft tissue neoplasm; benign urinary tract neoplasm; benign vaginal neoplasm; bile duct adenocarcinoma; bile duct adenosquamous carcinoma; bile duct cancer; bile duct cancer recurrent; bile duct cancer stage 0; bile duct cancer stage i; bile duct cancer stage ii; bile duct cancer stage iii; bile duct cancer stage iv; bile duct squamous cell carcinoma; biliary cancer metastatic; biliary neoplasm; bladder adenocarcinoma recurrent; bladder adenocarcinoma stage 0; bladder adenocarcinoma stage i; bladder adenocarcinoma stage ii; bladder adenocarcinoma stage iii; bladder adenocarcinoma stage iv; bladder adenocarcinoma stage unspecified; bladder cancer; bladder cancer recurrent; bladder cancer stage 0, with cancer in situ; bladder cancer stage 0, without cancer in situ; bladder cancer stage i, with cancer in situ; bladder cancer stage i, without cancer in situ; bladder cancer stage ii; bladder cancer stage iii; bladder cancer stage iv; bladder neoplasm; bladder papilloma; bladder squamous cell carcinoma recurrent; bladder squamous cell carcinoma stage 0; bladder squamous cell carcinoma stage i; bladder squamous cell carcinoma stage ii; bladder squamous cell carcinoma stage iii; bladder squamous cell carcinoma stage iv; bladder squamous cell carcinoma stage unspecified; bladder transitional cell carcinoma; bladder transitional cell carcinoma metastatic; bladder transitional cell carcinoma recurrent; bladder transitional cell carcinoma stage 0; bladder transitional cell carcinoma stage i; bladder transitional cell carcinoma stage ii; bladder transitional cell carcinoma stage iii; bladder transitional cell carcinoma stage iv; bone cancer; bone cancer metastatic; bone giant cell tumour benign; bone neoplasm; bone neoplasm malignant; bone sarcoma; brain cancer metastatic; brain neoplasm; brain neoplasm benign; brain neoplasm malignant; breast adenoma; breast cancer; breast cancer female; breast cancer in situ; breast cancer male; breast cancer metastatic; breast cancer recurrent; breast cancer stage i; breast cancer stage ii; breast cancer stage iii; breast cancer stage iv; breast fibroma; breast neoplasm; brenner tumour; bronchial carcinoma; bronchial neoplasm; bronchioloalveolar carcinoma; carcinoid tumour of the duodenum; carcinoid; tumour pulmonary; carcinoma; carcinoma ex-pleomorphic adenoma; carcinoma in situ; carcinoma in situ of eye; carcinoma in situ of penis; carcinoma in situ of skin; carcinoma in situ of trachea; carcinomatous polyarthritis; cardiac fibroma; cardiac myxoma; cardiac neoplasm malignant; cardiac neoplasm unspecified; cardiac neurofibroma; cardiac teratoma; cerebellar tumour; cervix cancer metastatic; cervix carcinoma; cervix carcinoma recurrent; cervix carcinoma stage 0; cervix carcinoma stage i; cervix carcinoma stage ii; cervix carcinoma stage iii; cervix carcinoma stage iv; cholangiocarcinoma; cholesteatoma; chondroma; chondrosarcoma metastatic; choriocarcinoma; choroid melanoma; choroid plexus carcinoma; clear cell carcinoma of cervix; clear cell carcinoma of the kidney; clear cell endometrial carcinoma; clear cell renal cell carcinoma; colon adenoma; colon cancer; colon cancer metastatic; colon cancer recurrent; colon cancer stage 0; colon cancer stage i; colon cancer stage ii; colon cancer stage iii; colon cancer stage iv; colon neoplasm; colorectal

adenocarcinoma; colorectal cancer; colorectal cancer metastatic; colorectal cancer recurrent; colorectal cancer stage i; colorectal cancer stage ii; colorectal cancer stage iii; colorectal cancer stage iv; colorectal carcinoma stage 0; conjunctival neoplasm; connective tissue neoplasm; cystadenocarcinoma ovary; ductal adenocarcinoma of pancreas; duodenal neoplasm; ear neoplasm; ear neoplasm malignant; eccrine carcinoma; endometrial adenocarcinoma; endometrial cancer; endometrial cancer metastatic; endometrial cancer recurrent; endometrial cancer stage 0; endometrial cancer stage i; endometrial cancer stage ii; endometrial cancer stage iii; endometrial cancer stage iv; epididymal cancer; epididymal neoplasm; epiglottic carcinoma; epithelioid mesothelioma; extragonadal primary embryonal carcinoma; eye haemangioma; eyelid tumour; fallopian tube cancer; fallopian tube cancer metastatic; fallopian tube cancer stage i; fallopian tube cancer stage ii; fallopian tube cancer stage iii; fallopian tube cancer stage iv; familial medullary thyroid cancer; female reproductive tract carcinoma in situ; fibroadenoma of breast; fibroma; focal nodular hyperplasia; follicular thyroid cancer; gallbladder adenocarcinoma; gallbladder adenosquamous carcinoma; gallbladder cancer; gallbladder cancer metastatic; gallbladder cancer recurrent; gallbladder cancer stage 0; gallbladder cancer stage i; gallbladder cancer stage ii; gallbladder cancer stage iii; gallbladder cancer stage iv; gallbladder neoplasm; gallbladder squamous cell carcinoma; ganglioneuroma; gastric adenoma; gastric cancer; gastric cancer recurrent; gastric cancer stage 0; gastric cancer stage i; gastric cancer stage ii; gastric cancer stage iii; gastric cancer stage iv; gastric cancer stage iv with metastases; gastric neoplasm; gastrointestinal cancer metastatic; gastrointestinal carcinoma; gastrointestinal carcinoma in situ; gastrointestinal stromal cancer; gastrointestinal stromal tumour; gastrointestinal tract adenoma; gastroesophageal cancer; genital cancer male; genital cancer male in situ; genitourinary tract neoplasm; germ cell cancer; germ cell cancer metastatic; giant cell tumour of tendon sheath; gingival cancer; glioblastoma; glioblastoma multiforme; glioma; glomus jugulare tumour; glomus tumour; glottis carcinoma; granular cell tumour; haemangioma; haemangioma of liver; haemangioma of skin; haemangioma of spleen; hair follicle tumour benign; hamartoma; head and neck cancer; head and neck cancer metastatic; head and neck cancer stage i; head and neck cancer stage ii; head and neck cancer stage iii; head and neck cancer stage iv; hepatic cancer; hepatic cancer metastatic; hepatic cancer recurrent; hepatic cancer stage i; hepatic cancer stage ii; hepatic cancer stage iii; hepatic cancer stage iv; hepatic neoplasm; hepatic neoplasm malignant; hepatic neoplasm malignant recurrent; hepatobiliary cancer; hepatobiliary cancer in situ; hepatocellular carcinoma; her-2 positive breast cancer; her-2 positive gastric cancer; hidradenocarcinoma; hormone refractory breast cancer; hormone-dependent prostate cancer; hormone-refractory prostate cancer; huerthle cell carcinoma; hypercalcaemia of malignancy; hypopharyngeal cancer; hypopharyngeal cancer recurrent; hypopharyngeal cancer stage 0; hypopharyngeal cancer stage i; hypopharyngeal cancer stage ii; hypopharyngeal cancer stage iii; hypopharyngeal cancer stage iv; infected neoplasm; inflammatory carcinoma of breast recurrent; inflammatory carcinoma of breast stage iii; inflammatory carcinoma of breast stage iv; inflammatory carcinoma of the breast; intestinal adenocarcinoma; intraductal papillary mucinous neoplasm; intraductal papillary-mucinous carcinoma of pancreas; intraductal papilloma of breast;

intraductal proliferative breast lesion; intraocular melanoma; invasive breast carcinoma; invasive ductal breast carcinoma; invasive lobular breast carcinoma; invasive papillary breast carcinoma; iritic melanoma; juvenile melanoma benign; keratinising squamous cell carcinoma of nasopharynx; large cell carcinoma of the respiratory tract stage unspecified; large cell lung cancer; large cell lung cancer metastatic; large cell lung cancer recurrent; large cell lung cancer stage 0; large cell lung cancer stage i; large cell lung cancer stage ii; large cell lung cancer stage iii; large cell lung cancer stage iv; large intestine benign neoplasm; large intestine carcinoma; laryngeal cancer; laryngeal cancer metastatic; laryngeal cancer recurrent; laryngeal cancer stage 0; laryngeal cancer stage i; laryngeal cancer stage ii; laryngeal cancer stage iii; laryngeal cancer stage iv; laryngeal neoplasm; laryngeal papilloma; laryngeal squamous cell carcinoma; leiomyoma; leiomyosarcoma; leiomyosarcoma metastatic; lip and/or oral cavity cancer; lip and/or oral cavity cancer recurrent; lip and/or oral cavity cancer stage 0; lip and/or oral cavity cancer stage i; lip and/or oral cavity cancer stage ii; lip and/or oral cavity cancer stage iii; lip and/or oral cavity cancer stage iv; lip neoplasm; lip neoplasm benign; lip neoplasm malignant stage unspecified; lip squamous cell carcinoma; lipofibroma; lipoma; lipoma of breast; liposarcoma; liver carcinoma ruptured; lobular breast carcinoma in situ; lung adenocarcinoma; lung adenocarcinoma metastatic; lung adenocarcinoma recurrent; lung adenocarcinoma stage 0; lung adenocarcinoma stage i; lung adenocarcinoma stage ii; lung adenocarcinoma stage iii; lung adenocarcinoma stage iv; lung cancer metastatic; lung carcinoma cell type unspecified recurrent; lung carcinoma cell type unspecified stage 0; lung carcinoma cell type unspecified stage i; lung carcinoma cell type unspecified stage ii; lung carcinoma cell type unspecified stage iii; lung carcinoma cell type unspecified stage iv; lung infiltration malignant; lung neoplasm; lung neoplasm malignant; lung squamous cell carcinoma metastatic; lung squamous cell carcinoma recurrent; lung squamous cell carcinoma stage 0; lung squamous cell carcinoma stage i; lung squamous cell carcinoma stage ii; lung squamous cell carcinoma stage iii; lung squamous cell carcinoma stage iv; lung squamous cell carcinoma stage unspecified; lymphangioma; malignant anorectal neoplasm; malignant ascites; malignant fibrous histiocytoma; malignant glioma; malignant mediastinal neoplasm; malignant melanoma; malignant melanoma in situ; malignant melanoma stage i; malignant mesenchymoma; malignant muscle neoplasm; malignant neoplasm of ampulla of vater; malignant neoplasm of eye; malignant neoplasm of pleura; malignant neoplasm of renal pelvis; malignant neoplasm of unknown primary site; malignant palate neoplasm; malignant peritoneal neoplasm; malignant pleural effusion; malignant sweat gland neoplasm; malignant tumour excision; mediastinum neoplasm; medullary carcinoma of breast; medullary thyroid cancer; meningioma; meningioma benign; mesothelioma; mesothelioma malignant; metaplastic breast carcinoma; metastases to bone; metastases to central nervous system; metastases to eye; metastases to gallbladder; metastases to heart; metastases to large intestine; metastases to liver; metastases to lung; metastases to lymph nodes; metastases to pancreas; metastases to peritoneum; metastases to pleura; metastases to spine; metastasis; metastatic bronchial carcinoma; metastatic carcinoma of the bladder; metastatic choriocarcinoma; metastatic gastric cancer; metastatic lymphoma; metastatic malignant melanoma; metastatic neoplasm; metastatic pain; metastatic renal cell carcinoma;

metastatic salivary gland cancer; metastatic squamous cell carcinoma; metastatic uterine cancer; mixed adenoneuroendocrine carcinoma; mixed hepatocellular cholangiocarcinoma; mucinous adenocarcinoma of appendix; mucinous breast carcinoma; mucinous cystadenocarcinoma of pancreas; mucinous cystadenocarcinoma ovary; mucinous endometrial carcinoma; mucoepidermoid carcinoma; mucoepidermoid carcinoma of salivary gland; muscle neoplasm; musculoskeletal cancer; nasal cavity cancer; nasal neoplasm; nasal neoplasm benign; nasal sinus cancer; nasopharyngeal cancer; nasopharyngeal cancer metastatic; nasopharyngeal cancer recurrent; nasopharyngeal cancer stage 0; nasopharyngeal cancer stage i; nasopharyngeal cancer stage ii; nasopharyngeal cancer stage iii; nasopharyngeal cancer stage iv; neoplasm; neoplasm malignant; neoplasm of appendix; neoplasm prostate; neoplasm skin; neuroendocrine carcinoma; neuroendocrine carcinoma metastatic; neuroendocrine carcinoma of the bladder; neuroendocrine carcinoma of the skin; neuroendocrine tumour; neurofibroma; nonkeratinising carcinoma of nasopharynx; non-renal cell carcinoma of kidney; non-small cell lung cancer; non-small cell lung cancer metastatic; non-small cell lung cancer recurrent; non-small cell lung cancer stage 0; non-small cell lung cancer stage i; non-small cell lung cancer stage ii; non-small cell lung cancer stage iii; non-small cell lung cancer stage iiia; non-small cell lung cancer stage iiib; non-small cell lung cancer stage iv; nut midline carcinoma; ocular cancer metastatic; ocular neoplasm; oesophageal adenocarcinoma; oesophageal adenocarcinoma metastatic; oesophageal adenocarcinoma recurrent; oesophageal adenocarcinoma stage 0; oesophageal adenocarcinoma stage i; oesophageal adenocarcinoma stage ii; oesophageal adenocarcinoma stage iii; oesophageal adenocarcinoma stage iv; oesophageal cancer metastatic; oesophageal carcinoma; oesophageal carcinoma recurrent; oesophageal carcinoma stage 0; oesophageal neoplasm; oesophageal papilloma; oesophageal squamous; cell carcinoma; oesophageal squamous cell carcinoma metastatic; oesophageal squamous cell carcinoma recurrent; oesophageal squamous cell carcinoma stage 0; oesophageal squamous cell carcinoma stage i; oesophageal squamous cell carcinoma stage ii; oesophageal squamous cell carcinoma stage iii; oesophageal squamous cell carcinoma stage iv; oestrogen receptor positive breast cancer; oncocytoma; oral cavity cancer metastatic; oral neoplasm; oral neoplasm benign; oropharyngeal cancer; oropharyngeal cancer recurrent; oropharyngeal cancer stage 0; oropharyngeal cancer stage i; oropharyngeal cancer stage ii; oropharyngeal cancer stage iii; oropharyngeal cancer stage iv; oropharyngeal cancer stage unspecified; oropharyngeal neoplasm benign; oropharyngeal squamous cell carcinoma; osteochondroma; osteoma; osteosarcoma metastatic; otic cancer metastatic; ovarian adenoma; ovarian cancer; ovarian cancer metastatic; ovarian cancer recurrent; ovarian cancer stage i; ovarian cancer stage ii; ovarian cancer stage iii; ovarian cancer stage iv; ovarian clear cell carcinoma; ovarian embryonal carcinoma; ovarian endometrioid carcinoma; ovarian epithelial cancer; ovarian epithelial cancer metastatic; ovarian epithelial cancer recurrent; ovarian epithelial cancer stage i; ovarian epithelial cancer stage ii; ovarian epithelial cancer stage iii; ovarian epithelial cancer stage iv; ovarian germ cell cancer; ovarian germ cell cancer stage i; ovarian germ cell cancer stage ii; ovarian germ cell cancer stage iii; ovarian germ cell cancer stage iv; ovarian germ cell choriocarcinoma; ovarian germ cell choriocarcinoma stage i; ovarian germ cell choriocarcinoma

stage ii; ovarian germ cell choriocarcinoma stage iii; ovarian germ cell choriocarcinoma stage iv; ovarian germ cell embryonal carcinoma stage i; ovarian germ cell embryonal carcinoma stage ii; ovarian germ cell embryonal carcinoma stage iii; ovarian germ cell embryonal carcinoma stage iv; ovarian germ cell teratoma benign; ovarian neoplasm; ovarian stromal cancer; paget's disease of nipple; pancoast's tumour; pancreatic carcinoma; pancreatic carcinoma metastatic; pancreatic carcinoma recurrent; pancreatic carcinoma stage 0; pancreatic carcinoma stage i; pancreatic carcinoma stage ii; pancreatic carcinoma stage iii; pancreatic carcinoma stage iv; pancreatic neoplasm; pancreatic neuroendocrine tumour; papillary renal cell carcinoma; papillary serous endometrial carcinoma; papillary thyroid cancer; papilloma; paranasal sinus neoplasm; parathyroid tumour; parathyroid tumour benign; parathyroid tumour malignant; pelvic neoplasm; penile cancer; penile squamous cell carcinoma; penis carcinoma; penis carcinoma metastatic; penis carcinoma recurrent; penis carcinoma stage i; penis carcinoma stage ii; penis carcinoma stage iii; penis carcinoma stage iv; pericardial mesothelioma malignant; pericardial mesothelioma malignant recurrent; pericarditis malignant; peritoneal carcinoma metastatic; peritoneal neoplasm; pheochromocytoma; pharyngeal cancer; pharyngeal cancer metastatic; pharyngeal cancer recurrent; pharyngeal cancer stage 0; pharyngeal cancer stage i; pharyngeal cancer stage ii; pharyngeal cancer stage iii; pharyngeal cancer stage iv; pharyngeal neoplasm; pharyngeal neoplasm benign; pilomatrix carcinoma; pituitary cancer metastatic; pituitary tumour; pituitary tumour benign; plasmacytoma; pleomorphic adenoma; pleura carcinoma; pleural mesothelioma; pleural mesothelioma malignant; pleural neoplasm; poorly differentiated thyroid carcinoma; porocarcinoma; postcricoid cancer; prostate cancer; prostate cancer metastatic; prostate cancer recurrent; prostate cancer stage 0; prostate cancer stage i; prostate cancer stage ii; prostate cancer stage iii; prostate cancer stage iv; prostatic adenoma; rectal adenocarcinoma; rectal adenoma; rectal cancer; rectal cancer metastatic; rectal cancer recurrent; rectal cancer stage 0; rectal cancer stage i; rectal cancer stage ii; rectal cancer stage iii; rectal cancer stage iv; rectal neoplasm; rectosigmoid cancer; rectosigmoid cancer metastatic; rectosigmoid cancer recurrent; rectosigmoid cancer stage 0; rectosigmoid cancer stage i; rectosigmoid cancer stage ii; rectosigmoid cancer stage iii; rectosigmoid cancer stage iv; recurrent cancer; refractory cancer; renal adenoma; renal cancer; renal cancer metastatic; renal cancer recurrent; renal cancer stage i; renal cancer stage ii; renal cancer stage iii; renal cancer stage iv; renal cell carcinoma; renal cell carcinoma recurrent; renal cell carcinoma stage i; renal cell carcinoma stage ii; renal cell carcinoma stage iii; renal cell carcinoma stage iv; renal cell carcinoma stage unspecified; renal haemangioma; renal neoplasm; renal oncocytoma; renal tumour excision; respiratory tract carcinoma in situ; respiratory tract neoplasm; retroperitoneal cancer; salivary gland adenoma; salivary gland cancer; salivary gland cancer recurrent; salivary gland cancer stage 0; salivary gland cancer stage i; salivary gland cancer stage ii; salivary gland cancer stage iii; salivary gland cancer stage iv; salivary gland neoplasm; sarcoma; sarcoma of skin; sarcomatoid mesothelioma; scrotal cancer; sebaceous adenoma; sebaceous carcinoma; serous cystadenocarcinoma of pancreas; serous cystadenocarcinoma ovary; signet-ring cell carcinoma; sinonasal papilloma; sinus cancer metastatic; skin cancer; skin cancer metastatic; skin neoplasm

bleeding; skin neoplasm excision; skin squamous cell carcinoma metastatic; small cell carcinoma; small cell carcinoma of the cervix; small cell lung cancer; small cell lung cancer extensive stage; small cell lung cancer limited stage; small cell lung cancer metastatic; small cell lung cancer recurrent; small cell lung cancer stage unspecified; small intestine adenocarcinoma; small intestine carcinoma; small intestine carcinoma metastatic; small intestine carcinoma recurrent; small intestine carcinoma stage 0; small intestine carcinoma stage i; small intestine carcinoma stage ii; small intestine carcinoma stage iii; small intestine carcinoma stage iv; spinal cord neoplasm; spinal haemangioma; squamous cell breast carcinoma; squamous cell carcinoma; squamous cell carcinoma of head and neck; squamous cell carcinoma of lung; squamous cell carcinoma of pharynx; squamous cell carcinoma of skin; squamous cell carcinoma of the cervix; squamous cell carcinoma of the hypopharynx; squamous cell carcinoma of the oral cavity; squamous cell carcinoma of the tongue; squamous cell carcinoma of the vagina; squamous cell carcinoma of the vulva; squamous endometrial carcinoma; superficial spreading melanoma stage unspecified; sweat gland tumour; targeted cancer therapy; tendon neoplasm; testicular cancer metastatic; testicular choriocarcinoma; testicular choriocarcinoma recurrent; testicular choriocarcinoma stage i; testicular choriocarcinoma stage ii; testicular choriocarcinoma stage iii; testicular embryonal carcinoma; testicular embryonal carcinoma stage i; testicular embryonal carcinoma stage ii; testicular embryonal carcinoma stage iii; testicular germ cell cancer; testicular germ cell cancer metastatic; testicular neoplasm; testis cancer; testis cancer recurrent; throat cancer; thymic cancer metastatic; thymoma; thymoma malignant; thyroid adenoma; thyroid cancer; thyroid cancer metastatic; thyroid cancer recurrent; thyroid cancer stage 0; thyroid cancer stage i; thyroid cancer stage ii; thyroid cancer stage iii; thyroid cancer stage iv; thyroid neoplasm; tongue cancer metastatic; tongue cancer recurrent; tongue carcinoma stage 0; tongue carcinoma stage i; tongue carcinoma stage ii; tongue carcinoma stage iii; tongue carcinoma stage iv; tongue neoplasm; tongue neoplasm benign; tongue neoplasm malignant stage unspecified; tonsil cancer; tonsil cancer metastatic; tonsillar neoplasm; tracheal cancer; tracheal neoplasm; tracheobroncheopathia osteoclastica; transitional cell cancer of renal pelvis and ureter metastatic; transitional cell cancer of the renal pelvis and ureter; transitional cell cancer of the renal pelvis and ureter localised; transitional cell cancer of the renal pelvis and ureter recurrent; transitional cell cancer of the renal pelvis and ureter regional; transitional cell carcinoma; transitional cell carcinoma metastatic; transitional cell carcinoma recurrent; transitional cell carcinoma urethra; triple negative breast cancer; tubular breast carcinoma; tumour excision; tumour perforation; undifferentiated carcinoma of colon; undifferentiated nasopharyngeal carcinoma; undifferentiated sarcoma; ureteral neoplasm; ureteric cancer; ureteric cancer local; ureteric cancer metastatic; ureteric cancer recurrent; ureteric cancer regional; urethral adenoma; urethral cancer; urethral cancer metastatic; urethral cancer recurrent; urethral neoplasm; urinary bladder adenoma; urinary tract carcinoma in situ; urinary tract neoplasm; uterine cancer; uterine carcinoma in situ; uterine leiomyoma; uterine leiomyosarcoma; uterine neoplasm; vaginal adenocarcinoma; vaginal cancer; vaginal cancer metastatic; vaginal cancer recurrent; vaginal cancer stage 0; vaginal cancer stage i; vaginal cancer stage ii; vaginal cancer stage iii; vaginal cancer stage iva;

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vaginal cancer stage ivb; vascular neoplasm; vocal cord neoplasm; vulval cancer; vulval cancer metastatic; vulval cancer recurrent; vulval cancer stage 0; vulval cancer stage i; vulval cancer stage ii; vulval cancer stage iii; vulval cancer stage iv; vulvar adenocarcinoma.

Stroke, Transient Ischemic Attack

Brain stem haemorrhage; brain stem infarction; cerebellar haemorrhage; cerebellar infarction; cerebral infarction; cerebrovascular accident; embolic cerebral infarction; embolic stroke; haemorrhagic cerebral infarction; haemorrhagic stroke; haemorrhagic transformation stroke; ischaemic cerebral infarction; ischaemic stroke; lacunar infarction; thalamic infarction; thrombotic cerebral infarction; thrombotic stroke; transient ischaemic attack.

Vertigo FDA B

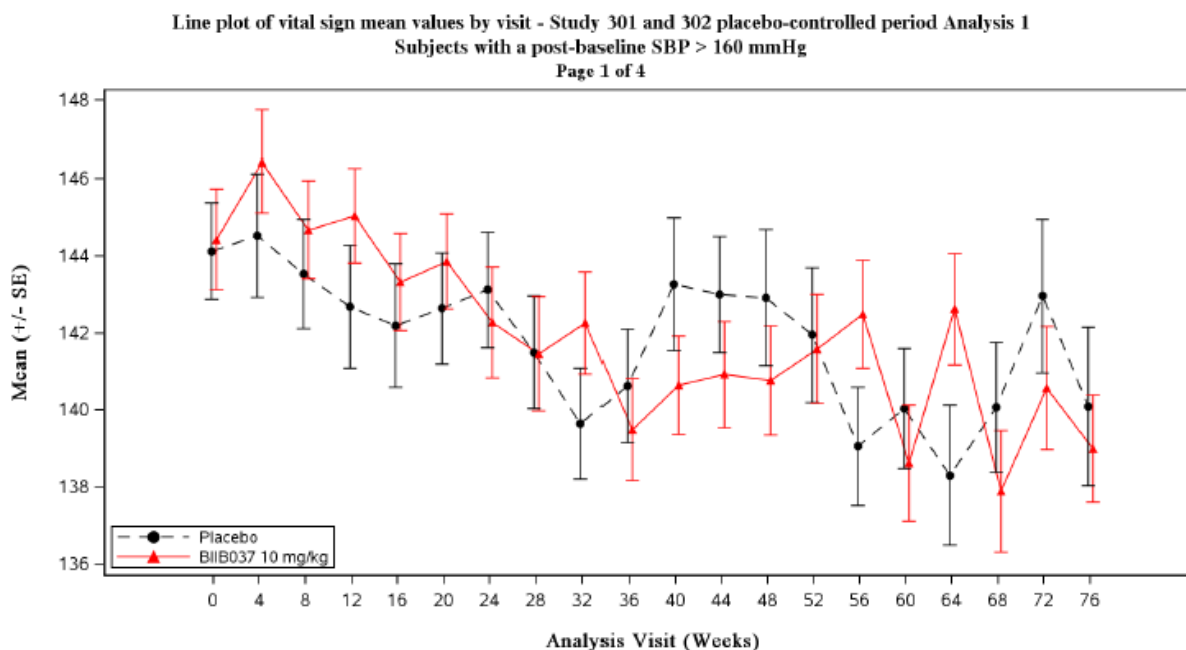
Acute vestibular syndrome; balance disorder; canvas syndrome; cervicogenic vertigo; cupulolithiasis; dizziness; endolymphatic hydrops; epidemic vertigo; inner ear disorder; inner ear disorder nos; inner ear infarction; inner ear vascular insufficiency; labyrinthine disorder nos; labyrinthitis; meniere's disease; meniere's disease aggravated; otolithiasis; persistent postural-perceptual dizziness; phobic postural vertigo; superior semicircular canal dehiscence; vertigo; vertigo aggravated; vertigo cns origin; vertigo labyrinthine; vertigo nec; vertigo positional; vestibular ataxia; vestibular disorder; vestibular disorder nos; vestibular ischaemia; vestibular migraine; vestibular neuronitis; vogt-koyanagi-harada disease.

Visual Disturbance

Acute myopia; amaurosis; amaurosis fugax; amblyopia; blindness; blindness transient; blindness unilateral; cyanopsia; erythropsia; hemianopia; hemianopia heteronymous; hemianopia homonymous; night blindness; sudden visual loss; tunnel vision; typical aura without headache; vision blurred; visual acuity reduced; visual acuity reduced transiently; visual acuity tests abnormal; visual disturbance; visual field defect; visual impairment; xanthopsia.

13.9. Line Plot of Mean Blood Pressure Values Across Study Visits in Subjects with Potentially Clinically Significant Post-Baseline Blood Pressure Values in Pooled Studies 301 and 302

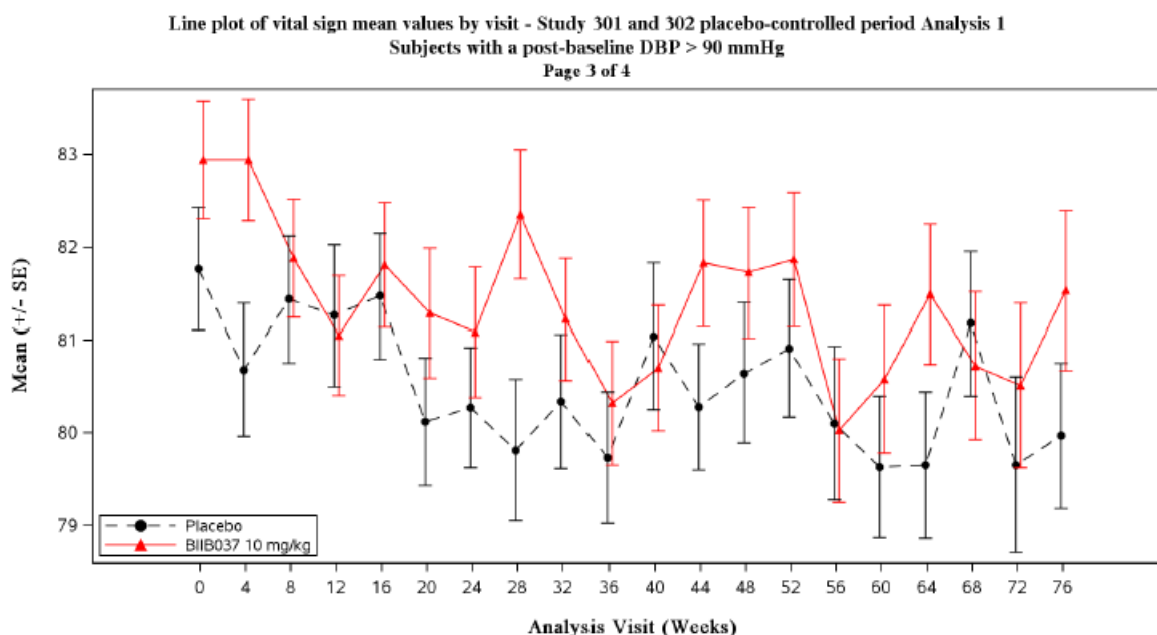
Figure 4. Line Plot of Mean Systolic Blood Pressure in Subjects with a Post-Baseline Systolic Blood Pressure of > 160 mmHg Across Study Visits in Pooled Studies 301 and 302.



Abbreviation: SE = standard error, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

The above figure was submitted by the applicant in an information response dated November 30, 2020, to an information request dated November 23, 2020 (page 5).

Figure 5. Line Plot of Mean Diastolic Blood Pressure in Subjects with a Post-Baseline Diastolic Blood Pressure of > 90 mmHg Across Study Visits in Pooled Studies 301 and 302.



Abbreviation: SE = standard error, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

The above figure was submitted by the applicant in an information response dated November 30, 2020, to an information request dated November 23, 2020 (page 7).

13.10. Subjects Who Withdrew Consent from Study 302

Table 81. List of Statements Where AEs Potentially Played a Role in Subjects Withdrawing Consent in Study 302.

Statements
PAT. WITHDRAWN CONSENT AFTER SAE SUBDURAL HAEMATOM, TO MUCH EFFORT IN HER OPINION
SUBJECT DID NOT WANT TO CONTINUE WITHN CLINICAL TRIAL AFTER SAE
SUBJECT WITHDREW DUE TO RECURRENT SYMPTOM OF PREVIOUS SAE
SUBJECT WASNT RE STARTED AFTER SAE
SUJECT SUFFERED FROM ARIA, THAT'S THE REASON OF WITHDRAWN CONSENT
HE RETIRED HIS CONSENT AFTER THE RESOLUTION OF ARIA E
SUBJECT DECIDED TO WITHDRAW FROM STUDY FOLLOWING SAE 'BACK PAIN'. SAE DID NOT DIRECTLY CAUSE TERMINATION.

SUBJECT DOES NOT WISH TO CONTINUE IN THE STUDY. SUBJECT DOES NOT TOLERATE PROCEDURES WELL, (INCLUDING INFUSIONS, BLOOD DRAWS, MRIS AND COGNITIVE TESTING). SUBJECT WILLNOT RETURN FOR
UNEASINESS FOR THE SIDE EFFECT OF THE CLINICAL EXPERIM ENTAL MEDICINE.
WITHDREW CONSENT SINCE CAN NO LONGER RECEIVE IP DU TO ARIA
SUBJECT BECAME SCARED WHEN SHE THOUGHT SHE HAD A CVA BUT THERE WAS NO EVIDENCE THAT SHE HAD THIS AND IT WAS RULED OUT
SUBJECT CONCERNED ABOUT ADVERSE EVENTS SHE EXPERIENCED WHILE SHE WAS ON IP. NO AE WAS DEEMED TO BE RELATED TO IP BY PI
THE PATIENT REPORTED MALAISE AND OTHER UNCHARACTERISTIC SINGS WHICH IN PATIENT'S OPINION WERE CONNECTED WITH IP.
ADVERSE REACTION AFTER FIRST PERFUSION AN D VISIT BURDEN CONDUCT THE PATIENT TO WITHDRAW HIS CONSENT
SUBJECT IS GOING TO DISCONTINUE AFTER WEEK 78 IS COMPLETED. SUBJECT COMPLETED TO WEEK 78 AND IS CONTINUING TO DO MRIS UNTIL ARIA IS RESOLVED.
THE SUBJECT WITHDREW CONSENT STATING SHE FELT SHE WAS HAVING SIDE EFFECTS FROM THE INFUSIONS, AS WELL AS HER HUSBAND HAVING SERIOUS HEALTH CONCERNS.
WITHDREW CONSENT DUE TO AES
SUBJECT (b) (6) WITHDREW CONSENT ON (b) (6) DUE TO AES
SUBJECT WITHREW CONSENT DUE TO STUDY VISIT BURDEN. AGREED TO MRI FOLLOW-UPS UNTIL ARIA RESOLUTION.

The reviewer created this from Study 302 ADSL dataset, Reason Spec for Discont from Period 01 = Consent Withdrawn or Reason Spec for Disc of Trt in Period 01, Tabulate by Reason Spec for Discont from Period 01 or Reason Spec for Disc of Trt in Period 01 and Actual Pooled Treatment for Period 01

Table 82. Frequency of Subjects with Statements Where AEs Potentially Played a Role In Subjects Withdrawing Consent in Study 302.

Disposition	ADU 3 or 6 mg/kg	ADU 10 mg/kg	Placebo
Study Withdrawal	0.22 (7/32)	0.27 (7/26)	0.20 (3/15)
Treatment Discontinuation	0.20 (5/25)	0.14 (3/21)	0.25 (3/12)

13.11. References

13.12. Financial Disclosure

The reader is referred to the review of clinical efficacy by Dr. Kevin Krudys for financial disclosures.

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/s/

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