CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761269
Priority or Standard	Priority
Submit Date(s)	12/14/2021
Received Date(s)	12/14/2021
PDUFA Goal Date	01/07/2023
Division/Office	Division of Neurology 1, Office of Neuroscience
Reviewer Name(s)	Deniz Erten-Lyons, MD
Review Completion Date	1/5/2023
Established/Proper Name	Lecanemab
(Proposed) Trade Name	LEQEMBI
Applicant	EISAI
Dosage Form(s)	Intravenous infusion
Applicant Proposed Dosing Regimen(s)	10 mg/kg every two weeks (biweekly)
Applicant Proposed Indication(s)/Population(s)	Early Alzheimer's disease
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of lecanemab outweigh the risks, then I recommend approval include appropriate labeling language to address adverse reactions of concern.
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of early Alzheimer's disease, including patients with Mild Cognitive Impairment and mild Alzheimer's dementia

Table of Contents

Table of Tables

Table of Figure

Glossary

AC	advisory committee
AD	Alzheimer's disease
ADAE	adverse event dataset
AE	adverse event
AR	adverse reaction
ApoE ε4	apolipoprotein ε4 variant
ARIA	amyloid related imaging abnormality
ARIA-E	amyloid related imaging abnormality edema/effusion
ARIA-H	amyloid related imaging abnormality hemorrhage
BIL	bilirubin
BLA	biologics license application
CAA	Cerebral Amyloid Angiopathy
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
CORE	double blind placebo controlled period
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia -Suicide Severity Rating Scale
CSS	Controlled Substance Staff
DSMB	data safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FMQ	FDA Medical Query
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISS	integrated summary of safety
IR	information request
ITT	intent to treat
IV	intravenous
LEC	lecanemab
LEC2.5-BW	lecanemab 2.5 mg/kg bi-weekly (once every two weeks)
LEC5-M	lecanemab 5 mg/kg monthly (once a month)
LEC5-BW	lecanemab 5 mg/kg bi-weekly (once every two weeks)
LE10-M	lecanemab 10 mg/kg monthly (once a month)

LEC10-BW	lecanemab 10mg bi-weekly (once every two weeks)
LLN	lower limit of normal
mAB	monoclonal antibody
MAD	multiple ascending dose
MAED	MedDRA-Based Adverse Event Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MQG	medical query group
MRI	magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OBP	Office of Biotechnology Products
OCS	Office of Computational Science
OCP	Office of Clinical Pharmacology _
OLE	open label extension phase
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PET	positron emission tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per oral
PP	per protocol
PPI	patient package insert
PT	preferred term
REMS	risk evaluation and mitigation strategy
QD	once daily
sBLA	supplemental BLA
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA Queries
SOC	system organ class
SUVR	standardized uptake value ratio
TEAE	treatment emergent adverse event
TFNE	transient focal neurological episodes
TIA	transient ischemic attack
tPA	tissue plasminogen activator

ULN	upper limit of normal
UTI	urinary tract infection
VHP	Voluntary Harmonization Procedure

1. Executive Summary

1.1. Product Introduction

The reader is referred to the review of clinical efficacy By 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. Benefit-Risk Assessment

See Summary Memo for Risk Benefit Assessment and Benefit Risk Dimensions

Benefit-Risk Dimensions

APPEARS THIS WAY ON ORIGINAL

1.4. Participant 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

During the review process, the Office of Clinical Pharmacology (OCP) and Office of Biotechnology Products (OBP) have determined that the applicant's ADA assay was not reliable for accurate classification of ADA status, due to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, a safety review for immunogenicity could not be conducted. Please refer to OCP and OBP reviews for further details.

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 Biologics License Application (BLA) 761269 is divided into a review of clinical efficacy (by Dr. Kevin Krudys), and this review of clinical safety. Information submitted as part of BLA 761269, and published literature are discussed in this review. I will primarily present analysis conducted mostly by myself. The primary safety review presented here will focus on Study 201 Core (double blinded placebo controlled period) and Study 201 Open Label Extension (OLE) to reflect the safety in the study that is the primary source of evidence of effectiveness. Two phase 1 studies, Study 104 and Study 101, provide supportive unblinded safety data, and ongoing Studies 301 Core and 301 Open Label Extension, and Study 303 provide additional blinded safety data.

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. Review of Safety

7.1. Safety Review Approach

The clinical data submitted to BLA 761269 on December 14, 2021, and updated with the 120-Day update April 12, 2022, as described below, presents all lecanemab data as of December 31, 2021.

The phase 2 Study 201 Core and its Open Label Extension (OLE) phase provide the main primary data set for the safety review for lecanemab. Study 101 and Study 104 are two phase 1 studies that provide supportive safety data. The two ongoing phase three studies, Study 301 and 303, provide blinded safety information. As agreed at the Pre-BLA meeting on September 10, 2021, the applicant submitted blinded listings for deaths, discontinuations due to adverse events (AEs), and serious adverse events (SAEs), including all SAEs related to Amyloid Related Imaging Abnormality-edema (ARIA)-E, ARIA-Related Imaging Abnormality Hemorrhage (ARIA-H), skin rash, and other hypersensitivity reactions, together with participant narratives and case report forms for those events in blinded ongoing studies 301 and 303. Lecanemab is administered as an intravenous (IV) infusion in these studies. These studies are described further in Table 1.

Consistent with the applicant's approach I will refer to the dose groups during this review where applicable as follows: PBO (for placebo), the lecanemab dose groups as LEC2.5-BW (for 2.5 mg/kg biweekly), LEC5-M (for 5 mg/kg monthly), LEC5-BW (for 5 mg/kg biweekly), LEC10-M (for 10 mg/kg monthly), and LEC10-BW (for 10 mg/kg biweekly). Biweekly refers to administration once every 2 weeks. The LEC10-BW dosage is proposed by the applicant as the recommended dosing regimen for labeling.

The applicant defines the Safety Analysis Set (the analysis population for safety parameters) as all participants who received at least 1 dose of study medication and had at least 1 postbaseline safety assessment (Study 201 Core) and all participants who received at least 1 dose of study medication (Study 201 OLE Phase, Study 301 Core, and Study 303).

Table 1 Studies Supporting Safety by Assigned Treatment

Study	Primary Objective	Study Design, Treatment duration and current status	Dose Assigned by Treatment (Safety Population)
BAN 2401-A001-101	Safety, Tolerability, Immunogenicity, Pharmacodynamic Response, and Pharmacokinetic	Placebo controlled combined single ascending dose and multiple ascending dose in participants with mild to moderate AD. Duration <6 months Completed: unblinded	SAD: 0.1 mg/kg (n=6) 0.3 mg/kg (n=6) 1mg/kg (n=6) 3 mg/kg (n=6) 10mg/kg(n=6) 15 mg/kg(n=6) Placebo (n=12) MAD: 0.3mg/kg monthly q4 weeks x4 (n=6) 1 mg/kg monthly q4weeks x4 (n=5) 3 mg/kg monthly q4weeks x4 (n=6) 10mg/kg q2weeks x7 (n=6) Placebo (n=8)
BAN2401-J081-104	Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Pharmacodynamic Response	Placebo-controlled study in participants with Early AD of repeated doses of study drug of a total of 5 doses Duration< 6 months Completed: unblinded	LEC2.5-BW x 5 (n=6)) LEC5-BW x 5 (n=6) LEC10-BW x5 (n=7) PBO (n=5)
BAN2401-G000-201 Core	Safety, Tolerability and Efficacy	Placebo-controlled, parallel group study, with an 18-month treatment duration, followed by a 3-month Follow-up Period. Duration =18-months Completed: unblinded	LEC2.5-BW (n=52) LEC5-M (n=51) LEC5-BW (n=92) LEC10-M (253) LEC10-BW (161) PBO (245)
BAN2401-G000-201 Open Label Extension	Safety, Tolerability and Efficacy	Open Label Extension of the 201 study. Up to 60 months Ongoing/unblinded	LEC10-BW (n=180)
BAN2401-Study 004	Safety and Pharmacokinetics of subcutaneous administration of LEC10.	Randomized, open-label, single BA < 6 months Completed: unblinded	29 participants LEC10 sq x1 30 participants LEC10 iv x1

Reviewer Comments: Study 101 was conducted in participants with mild to moderate AD, whereas the other studies in this table and the proposed indication is in participants with early AD defined as those having mild cognitive impairment and mild dementia due to AD.

Table 2 Ongoing Studies Providing Supportive Safety Data

Study	**Primary Objective**	**Study Design, Treatment duration and current status**	Dose Assigned by Treatment (Safety Population) *
BAN2401-G000-301 Core	Efficacy and Safety	A Placebo-Controlled, Parallel-Group, Study in Participants with Early Alzheimer's Disease Duration: 18-months Ongoing: blinded	10 mg/kg Q2W Placebo N=1795 randomized 1:1 to lecanemab versus placebo
BAN2401-G000-301 Open Label Extension	Efficacy and Safety	Open-Label Extension Duration: Up to 24 months Ongoing: blinded	10 mg/kg Q2W (N=159)
Study BAN2401-G000-303 Synoptic	Efficacy and Safety	Placebo-Controlled, Parallel Arm, in preclinical AD and elevated amyloid (A45) and Early Preclinical AD and intermediate amyloid (A3 Trial) Duration: ~ 4 years Ongoing: blinded	A45 55 randomized 5 mg/kg Q2W x8 weeks, 10 mg/kg Q2W through 96 weeks 10 mg/kg IV Q4W through 216 weeks. A3 23 randomized 5mg/kg Q4W, then 10 mg/kg Q4W

The numbers under this column are as of the data cutoff date of 30 Jun 2021.

Reviewer Comment: The study population for study 303 is individuals with preclinical AD (with no clinical symptoms), as opposed to early AD. The dosing regimen, given the study population of presymptomatic individuals and the resulting risk /benefit calculation, includes a slower titration schedule and a lower maintenance dose than the proposed indication and dose for early AD.

I will refer to studies by their number for the remainder of this document, modified with study type (Core, or OLE).

Study 201 is a phase 2 study that is the proposed primary source of evidence for safety. In Study 201 core participants with early Alzheimer's Disease (AD), which includes those with Mild Cognitive Impairment (MCI) due to AD and mild dementia due to AD, were randomized to one of the 5 dosing cohorts with lecanemab versus placebo for up to 18 months with a 3-month follow up period. Any participant who completed Visit 42 (Week 79) of the Core Study and completed it through the Follow-Up Visit, Visit 43 [Week 90], and/or fulfilled the OLE Phase inclusion and exclusion criteria were eligible to participate in the OLE Phase. The period between the final visit in the Core Study (Visit 42 [Week 79]) and OLE Baseline Visit is referred to as the Gap Period by the applicant and throughout this review. The OLE was initiated after analysis of the Core Study was complete and CSR finalized, resulting in an average 24-month (range 9- 56 months) Gap Period off study drug between the final visit in the Core Study (Visit 42 [Week 79] and OLE Baseline Visit.

Similar to 201 Core, where participants received study drug treatment doses without titration, in Study 201 OLE all participants received LEC10-BW without titration. Study 201 OLE is currently ongoing.

Treatment-emergent adverse events (TEAEs) for Study 201 Core and 201 OLE (Table 3) are presented separately throughout the review because there are differences in study design, eligibility criteria, discontinuation criteria, and concomitant medications that may impact the occurrence and severity of AEs, and the safety data including deaths, SAEs, discontinuations.

Table 3 Comparison of 201 Core and Study 201 OLE

Study 201 Core	**Study 201 OLE**
Eligibility and discontinuation based on APOE4 Genotype	
After DSMB review, and European Health Authority recommendations: - ApoE4 carriers* no longer randomized to LEC10-BW - ApoE4 carriers on LEC10-BW for ≤ 6 months discontinued - ApoE4 carriers only randomized to doses other than LEC10-BW – Additional safety MRIs added (see Appendix Section 12.1.1 Schedule of Assessments)	ApoE ε4 carrier were eligible to participate in 201 OLE and receive LEC10-BW
ARIA related eligibility and discontinuation	
Eligibility Exclusion if at baseline: > 4 microhemorrhages a single intracerebral hemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema. Approach to management of ARIA:-Study drug discontinued if a participant develops vasogenic edema (ARIA-E), regardless of radiographic severity, any macrohemorrhages superficial siderosis or symptomatic treatment-emergent	Eligibility Participants eligible to enroll if they had ARIA-E or, ARIA-H; during the Core study.** Approach to management of ARIA *Asymptomatic ARIA-H:* continue study as scheduled - If >10 asymptomatic cerebral microhemorrhages, superficial siderosis, or a single cerebral hemorrhage continue study drug with an unscheduled safety visit

microhemorrhages. Asymptomatic microhemorrhages continue with study dosing with one additional safety MRI scheduled approximately 30 days after the findings, and otherwise continue with scheduled MRI scans.	*Symptomatic ARIA-H* (including symptomatic microhemorrhages, symptomatic superficial siderosis, symptomatic macrohemorrhage): Drug administration temporarily stopped. Asymptomatic ARIA-E Radiographically mild or moderate ARIA-E continue study drug per schedule unless it becomes radiographically severe, or participant becomes symptomatic. Symptomatic or radiographically severe ARIA-E Study drug administration temporarily stopped until ARIA-E resolves radiographically. Resumption of treatment following symptomatic ARIA-E can only occur twice, after which the participant must be discontinued from the study. (revised per Amendment 12).
Concomitant Medications	
Anticoagulation is not allowed Antiplatelets allowed except for the CSF sub-study	Anticoagulation is allowed if stable for at least 4 weeks Antiplatelets are allowed except for the CSF sub-study

** ApoE ε4 carriers refers to both homozygotes and heterozygotes*
*** Exceptions are if participants had any intracerebral hemorrhage (greater than 10 mm at greatest diameter), which is currently symptomatic or worsened since the Core Study; any area of superficial siderosis which is currently symptomatic or worsened since the Core Study; evidence of vasogenic edema, which is severe or symptomatic;*

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The present analysis relies primarily on unblinded safety data. The current total number of participants, including the 120-Day Update with a data cutoff date of December 31, 2021, that have been exposed to at least one dose of lecanemab at any dose and have unblinded safety data is 763. Of these, as calculated by the reviewer, the exposure at the intended dose LEC10-BW was 237 for 6 months or more, 217 for 1-year or more. While the 1-year exposure to lecanemab meets the ICH guideline for exposure requirement of 100 patients at the clinically relevant dose, the ICH guidelines of at least 300 patients for 6 months are not met for the 6-month exposure.[1] These numbers were discussed and agreed upon during the during the Type B meeting held 10 Sep 2021. Of note, the ICH E1 guidance applies to "Drugs intended for long - term treatment of non-life-threatening conditions". Although the guidelines are generally

[1] https://database.ich.org/sites/default/files/E1_Guideline.pdf

followed for higher prevalence diseases, the Division considers AD a serious and life-threatening diseases for which flexibility on the size of safety databases is considered. The Division also considered that the larger number of 1-year exposures at one year offset the limitations of the smaller number of exposures at 6 months and one year.

In the ongoing studies with blinded data, in 301 Core and OLE, a total of 1899 participants have been enrolled, and in the ongoing 303 study 65 participants have enrolled in the sub-study A3 and 142 have enrolled in the sub-study A45 arm.

There are 763 participants who have been exposed to the study drug and contribute to the safety data set with unblinded safety data (Table 4).

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to lecanemab at any dose and duration in completed trials as part of the development program for the indication under review N=763[2] (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	New Drug (n=763)	Placebo (n=220)
Controlled trials conducted for this indication[2]	718	265[3]
Uncontrolled trials (new exposures in the long-term extension phase of Study 201)	45	N/A

[1] Study drug in this table refers to iv formulation of lecanemab
[2] This number is obtained by adding the following drug exposures n (study number): 19 (101) + 60 (104) + 609 (201 Core) + 45 (201 OLE new exposures from previous placebo), + 30 (004 LEC10-BW iv arm)
[3] Placebo here is the sum of placebo groups from studies 201 core, 101 and 104. For 201 core the placebo number was 245, of which 45 went on to receive study drug in the OLE period. These 45 are included under the row "all other trials conducted for this indication, under new drug.

Table 5 Duration of Exposure at the Dose Proposed Based on the Division's Approach.

		Number of patients exposed to the study drug at the proposed dose in the label:			
Dosage		≥ 1 dose	≥ 6 months[1]	≥ 12 months	≥ 18 months
10 mg/kg biweekly		N= 255*	N=237	N= 217	N= 186

Exposure as of the 120-Day Update (cutoff date of 21 December 2021)
** This number is obtained by adding the following drug exposures n (Study ID number): 161 (201 Core)+ 45 (201 OLE new exposures)+ 7 (104) +12 (101), and 30 (004).*

In the placebo-controlled 201 Core Study alone, 106 patients were exposed to 10mg/kg biweekly for at least 6 months, 97 patients to at least 12 months, and 76 patients for at least 18 months.[2]

[2] Table 2.7.4–3, Summary of Clinical Safety.

There are differences in the calculation of exposures between the applicant's and my approaches.

I calculated exposure based on uninterrupted exposure during the Core or the OLE periods for Study 201 without adding up Core and OLE exposures because of the gap period of 9-56 months, starting when a study participant finished the Core Study and ended when a participant started the 201 OLE study. In addition to the gap period, not all participants received the same dose during the OLE that they received in the 201 Core which was another reason for my approach. Participants who participated in the OLE and CORE were only counted once under my exposure calculations. Using this approach, the total exposure number in 201 Core and OLE was 654 (including 609 participants that were exposed to lecanemab during the Core, and 45 PBO participants who were exposed to the drug for the first time in the OLE).

The applicant calculated the duration of exposure by adding exposure during the Core plus OLE and ignoring the Gap Period. Additionally, according to the applicant's methodology, each participant was counted under the highest lecanemab dose regimen received. For example, a participant who received LEC5-M in the Core and who also participated in the OLE (LEC10-BW) had their total duration of exposure (Core + OLE) captured under LEC10-BW. With this methodology, the applicant considered 243 participants to have been exposed for at least 6 months, and considered 231 participants to have been exposed for 12 months (including 6 participants that achieved 6-month exposure and 14 participants that achieved 12-month exposure, respectively, inclusive of duration of exposure to a lower dose or less frequent dosing regimen during the Core period combined with exposure during OLE to LEC10-BW). Based on my calculation 237 participants were exposed for > 6 months, and 217 exposed for > 18 months. Similar to differences observed for 6 and 12 months exposure numbers due to different methodologies, I found that 184 participants were exposed for 18 months (including a participant with 17.8 months exposure in the OLE)., whereas the applicant considers 209 participants to have been exposed for 18 months. With the 120-day update the number of participants exposed for 18 months or more was 186.

On July 9, 2014, Study 201 Core protocol was amended (Version 5 to Version 6) based on Data Safety Monitoring Board recommendations. The amendments included addition of a safety MRI at week 8, visit 7 (to be completed prior to the 5^{th} dose) to prevent dosing of participants with early ARIA-E to minimize the risk of further progression, and the randomization algorithm was modified so as not to randomize ApoE homozygous participants to the LEC10-BW dose. On August 11, 2014, following interaction with the European Health Authorities through the Voluntary Harmonization Procedure (VHP) another amendment (version 6 to version 7) was implemented that would not allow ApoE ε4 positive participants (homozygous and heterozygous) to be administered the 10 mg/kg biweekly dose of BAN2401. Additionally, all such participants who were on this dose for 6 months or less were to be discontinued. On July 30, 2016, the European Regulatory Authorities requested another amendment to add a safety

MRI at European sites only at Visit 6 (week 7) prior to the 4th dose of study drug. As a result, 25 ApoE carriers that were in the LEC10-BW arm less than 7 months were discontinued from study participation and for the last 2.5 years of the study recruitment period no participants were randomized to this dose. This not only impacted the number of overall participants in the LEC10-BW arm and duration of exposure, but specifically led to smaller number of participants who are ApoEε4 carriers being exposed to study drug (Table 6). In the 201 Core study, duration of exposure in the LEC10-BW arm was on average 173 days (range 32-550, median 85) days for ApoE ε4 homozygotes (n=10), 211 days (range: 15-561, median 115) for ApoE ε4 heterozygotes (n=39), and 438 days (15-559, median 547) for noncarriers (n=112). Since the risk of ARIA is higher in those who are carriers of the ε4 allele, limited exposure in this specific participant population limits the safety assessments in this population.

Table 6 Duration of Exposure at the Dose Proposed in ApoE ε4 allele carriers

	Number of patients who are ApoE ε4 carriers exposed to the study drug at the proposed dose in the label:			
Dosage	≥ 1 dose	≥ 6 months	≥ 12 months	≥ 18 months
10 mg/kg biweekly	49	18	12	10

7.2.2. Relevant Characteristics of the Safety Population

The proposed target population is patients with early AD, which is defined as patients with MCI or mild dementia due to AD. Study 104, 201 Core and OLE, and Study 301 enrolled patients with early AD, and Study 101 included individuals with mild and moderate dementia due AD. Study 303 is only enrolling participant with preclinical AD. Study 004 enrolled healthy controls.

Since the placebo-controlled arm of Study 201 will constitute the main safety database, the demographics of this study are summarized below (Table 7). Overall, the demographic distribution between the LEC10-BW and the placebo arms is notable for the following differences:

There is a higher percentage of women in the placebo arm compared to the LEC10-BW. The LEC10-BW group has a smaller percentage of participants who are <64 years old, and higher percentage of participants who are over 80 years old. The percentage of ε4 allele carriers is also smaller in the LEC10-BW arm compared to the placebo arm. Both the lower frequency of those < 64 years old (since ApoE carrier status affects age at onset), and lower frequency of participants that are ε4 carriers are due to changes in the study after DSMB and European Health Authority requests after identifying higher risk of ARIA-E in ε4 allele carriers (see Section 7.2.1) .

Table 7 Baseline Demographics by Treatment Group in Study 201 Core

	LEC2.5-BW N=52 n(%)	LEC5-M N=51 n(%)	LEC5-BW N=92 n(%)	LE10-M N=253 n(%)	LEC10-BW N=161 n(%)	Placebo N=245 n(%)
Sex						
F	26 (50%)	26 (51%)	50 (54%)	112 (44 %)	70 (44%)	138 (56%)
M	26 (50%)	25 (49%)	42 (46%)	141 (56%)	91 (56%)	107 (44%)
Age (years)						
Mean (SD)	70.5 (8.3)	70.5 (7.4)	70.6 (7.4)	71.2 (7.5)	72.7 (8.7)	71.1 (8.9)
Median (min, max)	70.5 (50, 86)	71 (55,84)	72 (52,87)	71 (53, 90)	73 (51,88)	72 (50,89)
Age Groups						
<65 years old	11 (21%)	9 (18%)	20 (22%)	46 (18%)	28 (17%)	56 (23%)
65 to <80 years old	35 (67%)	38 (74%)	63 (68%)	173 (68%)	99 (62%)	150 (61%)
≥ 80 years old	6 (12%)	4 (8%)	9 (10%)	34 (13%)	34 (21%)	39 (16%)
Race						
Asian	2 (4%)	1 (2%)	9 (10%)	17 (7%)	7 (4%)	17 (7%)
Black or African American	2 (4%)	1 (2%)	4 (4%)	5 (2%)	4 (2%)	5 (2%)
Other	0 (0%)	0 (0%)	3 (3%)	3 (1%)	0 (0%)	1 (0.4%)
White	48 (92%)	49 (96%)	76 (83%)	228 (90%)	150 (93%)	222 (91%)
Ethnicity						
Hispanic or Latino	4 (8%)	1 (2%)	3 (3%)	10 (4%)	10 (6%)	10 (4%)
Not Hispanic or Latino	48 (92%)	50 (98 %)	89 (97%)	243 (96%)	151 (94%)	235 (96%)
Region						
Asia	1 (2%)	1 (2%)	12 (13%)	16 (6%)	7 (4%)	16 (6%)
North America	47 (90%)	43 (84%)	73 (79%)	222 (88%)	142 (88%)	201 (82%)
Western Europe	4 (8%)	7 (14%)	7 (8%)	15 (6%)	12 (8%)	28 (11%)
Body Mass Index (kg/m^2)						
Mean (SD)	26.2 (3.9)	26.3 (3.9)	24.8 (4.1)	26.3 (3.9)	26.2 (3.9)	25.6 (3.8)
Median (min, max)	26.1(19.1-34.4)	25.7 (18.7-35.4)	24.6(17.3-37.1)	26.0(18.4-34.9)	25.9 (17.7-34.9)	25.3 (17.7-34.9)
ApoE ε4 Carrier Status						
Carrier	38 (73%)	40 (78.4)	84 (91.3 %)	225 (89%)	49 (30.4)	173 (70%)
Non-Carrier	14 (27%)	11 (21.6%)	8 (8.7%)	28 (11%)	112 (69.6)	72 (29%)
ApoE Gene Allele						
Homozygote	5 (10 %)	12 (23 %)	14 (15%)	60 (24 %)	10 (6 %)	40 (16%)
Heterozygote	33 (63 %)	28 (55%)	70 (76 %)	165 (65 %)	39 (24 %)	134 (55 %)
Noncarriers	14 (26.9)	11 (21.6)	8 (8.7)	28 (11.1)	112 (69.6)	71 (29)
Baseline Alzheimer's Disease Stage						
Mild Cognitive Impairment	33(63%)	36(71%)	54(59%)	168(60 %)	96(60 %)	158 (65%)
Mild AD	19(36%)	15(29%)	38(41%)	85(40%)	65(40%)	87(35%)

Baseline MMSE Score						
20 to 25	25 (48 %)	29 (57 %)	45 (49%)	121 (48 %)	80 (50 %)	103 (42 %)
26 to 30	27 (52 %)	22 (43 %)	47 (51%)	132 (52 %)	81 (50 %)	142 (58 %)
Baseline Alzheimer' Disease Medications						
Yes	27(52%)	25(49%)	59(64)	132 (52%)	83 (52%)	132 (54%)

Reviewer comment: Patients with moderate or severe dementia due to AD were not eligible for enrollment in Study 201. Therefore, the safety outcomes from this study, which enrolled individuals with early AD (MCI and mild dementia due to AD), may not represent the risks in patients with moderate or severe dementia due to AD.

The following comments compare demographics of the 201 Core with the general population with AD. The data for the general population is obtained from the Alzheimer's Association 2021 Alzheimer's Disease Facts and Figures Report.[3]

Of the 6.2 million Americans aged 65 and older with AD, approximately 27 % are between ages 65-74 years old, 37 % between 75-84 years old, and 36% over 85 years old. These numbers are inclusive of patients with AD of any stage (mild, moderate or severe). In contrast, in the 201 Core Study the study population consisted only of those with MCI and mild dementia due to AD.

In 201 Core the percentage of participants with AD in the age range of 65 to 80 years ranged from approximately 61% to 74 % across study arms, comparable to the prevalence of patients aged 65-84 years old in the AD population, which is approximately 64 %.

While most study arms had fewer than 16% of individuals over 80 years old, the LEC10-BW arm, which is the proposed dose, had approximately 21 % of participants who were at least 80 years old, which is closer to the 36 % seen in the general population of AD patients over 84 years old. The higher prevalence of those over 80 years old in the LEC10-BW group is driven by study design changes after an interim safety analysis resulted in the discontinuation of 25 ε4 carriers from the LEC10-BW group and enrollment was halted for ε4 carriers to the proposed dose of LEC10-BW for the last 2.5 years of the study. This eliminated enrollment of participants with an earlier age at onset as the ε4 allele is known to reduce the age at onset of AD.

In the general population, the reported prevalence of ApoE ε4 allele carriership in patients with AD ranges between approximately 30-70 % depending on the study population, with patients with Northern European ancestry having a prevalence of ~ 60 %. [4] *Due to the study design changes noted above, in the proposed dose of LEC10-BW only 30 % are ε4 carriers. The exposure of smaller number of participants who are ε4 carriers (49/161) in the proposed dose of LEC10-BW compared to the general population limits the study's ability to determine the risk of ARIA,*

[3] https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf (Accessed 11/17/2022)
[4] *Ward A, et al: Prevalence of Apolipoprotein E4 Genotype and Homozygotes (APOE ε4/4) among Patients Diagnosed with Alzheimer's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2012;38:1-17.*

or otherwise characterize safety of lecanemab, at the proposed dose in patients with AD who are carriers of the ε4 allele.

Approximately 2/3 of Americans with AD are women. In Study 201 Core, the overall distribution was closer to 50/50. In the LEC10-BW arm approximately 43% were women, thus compared to the general population, women were underrepresented in the 201 Core study.[2] The underrepresentation of women in Study 201, are not expected to have a significant impact on the interpretation of the safety of the study results in women versus men.

Compared with non-Hispanic Whites, Blacks and Hispanics are at increased risk for AD.[3] In Study 201 Core Black or African American and Hispanics were underrepresented compared to the U.S. population limiting the generalizability of the safety observations from Study 201 Core for black or Hispanic patients with AD.

The demographics of OLE study participants are summarized in **Table 8**. Overall, 125/ 180 (69 %) of patients who were ε4 carriers were exposed to the proposed dose of LEC10-BW in the OLE group.

Table 8 Baseline Demographics in Study 201 OLE

N=180	
Sex (n, %)	
F	87 (48)
M	93 (52)
Age (yrs.)	
Mean (yrs.)	74
Standard Deviation	7.7
Minimum	52
Maximum	87
Race (N, %)	
Asian	30 (17)
Black or African American	2 (1)
Other	0
White	148 (82)
Ethnicity (n, %)	
Hispanic or Latino	1 (1)
Not Hispanic or Latino	179 (99)
Region	
Asia	29 (16)
North America	139 (77)
Western Europe	12 (7)
ApoE ε4 Gene Allele Status	
Homozygote	28 (15.6%)
Heterozygote	97 (53.9 %)
Non-Carriers	55 (30.6%)
OLE Baseline MMSE Score	
1-14	30
15-20	50
21-25	47
26-30	53
OLE Baseline Alzheimer' Disease Medications	
Yes	122

7.2.3. Adequacy of the safety database:

The current total number of participants in Phase 1 and 2, that have been exposed to at least one dose of lecanemab and have unblinded safety data is 763. Of these, the exposure at the intended dose of LEC10-BW was 237 for 6 months or more, 217 for 1-year or more. While the 1-year exposure to lecanemab meets the 100 patients for one year ICH guideline for exposure at the clinically relevant dose, they do not meet the ICH guidelines for non-life-threatening conditions of at least 300 patients for 6 months. These numbers were discussed and agreed upon during the Type B meeting held 10 Sep 2021, because of the large number of 1-year exposures and the Division's determination that AD is a serious and life-threatening disease.

ApoE ε4 carriers, Black, Asian and other non-Caucasian races were underrepresented at the proposed dose arm in 201 Core.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

Some of the aspects of the quality of the integrated summary of safety dataset were evaluated by the Office of Computational Science Jumpstart team. Overall, the application was well-organized, and information was easy to find. Some of the issues identified regarding traceability of the data across datasets were addressed via IR by the applicant and did not impact the data analysis.

During the course of the safety review process, I identified other issues related to submission quality.

First it was noted that in the ISS safety dataset, some ARIA-related columns in the ADAE (Adverse Event) dataset where left blank for the 201 Core period, and only provided for the OLE period. Additionally, a column titled "symptomatic flag" in the ADAE dataset was checked "yes" for participants that did not have symptomatic ARIA-E events. The applicant provided an updated ADAE dataset on April 13, 2022 addressing this in response to an IR from the Agency dated May 24, 2022. The applicant clarified that the clinical symptoms associated with an MRI abnormality (including ARIA) were captured in a separate a clinical database (not in the ADAE dataset). This information was obtained from the Case Report Forms for MRI abnormalities, based on the following question: ""Were there any associated clinical features of the AE abnormality identified via MRI?" which, according to the applicant was not always correctly completed by some of the clinical sites. For example, in some cases this was answered as "yes" for the existence of an MRI abnormality even if there were no associated clinical symptoms. Other times, clinical symptoms associated with ARIA were not adequately documented on this form by the clinical sites. The sponsor acknowledged, after reviewing the CIOMS of all participants with ARIA-E and ARIA-H, and compared with clinical database, that there were two additional participants with symptomatic ARIA-E which were not correctly captured in these forms, as well as additional clinical symptoms in 5 participants with symptomatic ARIA which were not captured on this form. The applicant stated that in light of these findings, for ongoing and future studies, they instituted a review process with the clinical investigators to ensure that all clinical symptoms associated with ARIA-E and ARIA-H are included in the clinical database.

Second, it was noted that the applicant categorized the severity of ARIA- H events solely based on mild, moderate, severe determination using a clinical rating scale based on a participant's function. Since ARIA-E and ARIA-H are radiographic events, severity is described based on radiographic criteria, and severity of symptoms associated with ARIA are described based on a

scale which relies on participant functioning. An IR was sent to the applicant to clarify how the severity of ARIA-H was classified as there was no description in the protocol. The applicant explained that the investigators defined the severity of symptoms as follows:

> Mild: Discomfort noticed, but no disruption of normal daily activity
> Moderate: Discomfort sufficient to reduce or affect normal daily activity
> Severe: Incapacitating, with inability to work or to perform normal daily activity

The applicant acknowledged that there were 68 ARIA-H events in 201 Core, all of which were asymptomatic, and presumed that the "investigators determined ratings of severity likely based on radiographic evidence". Based on a request from the Division the applicant reassigned severity ratings based on a radiographic rating system that is described in further detail in Section 7.5.1, and that is currently the standard approach to the Division's evaluation of ARIA-H radiographic severity. The applicant submitted an updated ADAE dataset with ARIA-H radiographic severity ratings on April 25, 2022.

During the review of the narratives, it was noted that some of the narratives were written in a chronologically confusing order and had conflicting or missing information. Some narratives included descriptions of AEs that were not included in the ADAE dataset (such as a subdural hematoma described in the narrative but not included in the ADAE dataset). It was also noted that not all clinical symptoms associated with symptomatic ARIA, were included in the dataset. As an example, a participant in 201 Core had a seizure due to ARIA-E. This seizure was not coded as an AE in the CRF, and was not captured in the ADAE dataset under the data column for symptoms of ARIA-E. It was described in the CIOMS form, and in the narrative for this participant, and mentioned in other text in the ISS. Additionally, one participant had contradicting ApoE genotypes in the ADAE dataset and the narrative. In response to an IR from the Agency on May 24, 2022, the applicant reviewed and revised ARIA related narratives for studies 201 Core and OLE, and Study 301 Core and OLE. During this process the applicant identified 2 additional participants who had ARIA-E that were symptomatic which were not identified earlier (b) (6) bringing the number of participants with symptomatic ARIA in 201 Core from 5 to 7 participants. The applicant additionally identified two other ARIA-H events that were previously not included in the ADAE dataset (a new ARIA-H event for participant (b) (6), and a second ARIA-H event identified for participant (b) (6). The applicant provided updated the ADAE datasets based on these updates and on June 1 and June 8, 2022.

In August 2022, as part of the data reconciliation activities for Study 201 OLE in preparation for the future sBLA submission at the end of the year (pending the outcome of the current BLA under review) the applicant became aware of some ARIA-H events that, although captured in the safety MRI dataset, were not captured in the ADAE dataset. This resulted in identification of ARIA-H events in 2 participants from the Core and 8 participants from the ongoing OLE that were not captured in the ADAE dataset. The applicant provided an updated ADAE dataset to

include these ARIA-H events (with the exception of one of the ARIA-H events in 201 Core due to inability to obtain additional information from the study site) on August 12, 2022.

The above limitations, and problems identified with the dataset have been addressed with updated ADAE datasets by the applicant. Presuming that the updated information from the applicant is accurate and dependable, the actions taken to address these limitations enabled this reviewer to still be able to assess the safety of the drug.

7.3.2. Categorization of Adverse Events

In Study 201 (Core and OLE) an AE was defined as: any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product any new disease or exacerbation of an existing disease; any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug; recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline); and, an abnormal laboratory test result that leads to any type of intervention, whether prescribed in the protocol or not. This included laboratory values that worsened (increased) to Grade 2 or higher based on the Applicant's Grading for Laboratory Value (the CTCAE toxicity grading).

An SAE was defined as any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug). Also included were AEs that may jeopardize the participant or may require intervention to prevent 1 of the outcomes above.

A TEAE in Study 201 Core was defined as an AE that: emerged during treatment or within 90 days following the last dose of study drug; reemerged during treatment, having been present at pretreatment (Baseline); or worsened in severity during treatment. In the ISS the applicant defined TEAEs as those emerging within 30 days of last administration (except in Study 104 that was within 56 days of last administration).

Reviewer Comment: Of note is that while in the 201 Core study the TEAE definition was based on a 90- day observation period after the last dose, this definition was revised in the ISS dataset to include changes that occurred within 30 days in the OLE, and the ISS ADAE dataset. Given the study drug's pharmacokinetic (PK) half-life of ~ 5 days this may be acceptable. While the pharmacodynamic (PD) half-life is not exactly known, to better characterize ARIA during treatment with lecanemab, I examined ARIA in the ADAE dataset both limiting to 30 days after the last dose of study drug and evaluating through the end of the study (See section 7.5.1).

Other events of interest included: pregnancy, any treatment-emergent significant laboratory abnormality, vasogenic edema, cerebral hemorrhages > 1 cm, superficial siderosis, or new microhemorrhages in the brain MRI, infusion reactions, skin rash considered to be due to study drug, other hypersensitivity reactions, or a "yes" response to Columbia -Suicide Severity Rating Scale (C-SSRS) suicidal ideation type 4 or 5, an increase in body temperature to greater than 38ºC within 24 hours post dose, or AEs associated with study drug overdose, or medication error.

The applicant states that AEs were graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions were as follows: Mild: Discomfort noticed, but no disruption of normal daily activity; Moderate: Discomfort sufficient to reduce or affect normal daily activity; Severe: Incapacitating, with inability to work or to perform normal daily activity.

Adverse events were coded using MedDRA Version 20.1 for Study 201 Core, MedDRA24.0 for the OLE, and the ISS datasets. There were 109 records (21%) that were mismatched for the Preferred Term and 5 records (0.99%) mismatched for the Body System and Organ Class Term between 201 Core and ISS. Mismatches caused by differences in the MedDRA versions were reviewed individually, to identify any mismatch that may impact AE identification. None were found to impact the safety assessment.

Reviewer Comment: "Visual field deficits" which were initially listed under nervous system MedDRA 20.1, were recoded as "eye disorders" using MedDRA24. This may have reduced the number of Nervous System Adverse events using the ADAE dataset. However, this had no impact on the overall safety assessment. The 5 cases of visual field deficits documented in the ADAE dataset were not related to study drug and were not associated with ARIA. There were two cases of visual field deficits not documented in the ADAE dataset which were associated with ARIA events. Overall, the use of different MedDRA versions did not impact this safety review.

The FDA Office of Computational Science (OCS) Adverse Events Coding Quality table summarizes reported terms and their mapped MedDRA Lower Level and MedDRA Preferred Terms. Of these, 336 were identified as "Could not match", 403 were identified as "Alternate Spelling of Lower Level Term", 1573 were defined as "Partial Match to Preferred Term", 821 were "Direct Match to Lower Level Term". I reviewed all terms that were not a Direct Match and found that the applicant's coding appeared to be adequate.

There were two participants who had a reported term of cerebellar microhemorrhage. In one participant the corresponding dictionary derived term was cerebellar microhemorrhage and in the other participant it was right inferior cerebellar microhemorrhage (b) (6) One participant (b) (6) had verbatim terms of cerebellar microhemorrhage and a cerebral microhemorrhage and both of these were captured under the dictionary derived term of cerebral microhemorrhage. After an Information Request (IR) in May 2022, the applicant

updated the definition of ARIA-H microhemorrhage to include both cerebellar and cerebral microhemorrhages, therefore these mismatches from verbatim to dictionary derived terms did not impact the safety analysis.

7.3.3. Routine Clinical Tests

In both Study 201 Core and 201 OLE, safety assessments included monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations and suicidality assessments. Additional safety assessments specific to this study will included brain MRI, and anti-BAN2401 antibody assays.

Vital Signs:
In the placebo-controlled period for Study 201, vital sign measurements were obtained at screening, baseline, every two weeks until week 79, and the follow up visit at week 90.

Laboratory Tests
In the placebo-controlled period for Study 201, laboratory tests were completed at screening, baseline and weeks 1,3,7,13,19,27,39, 53, 65,79, early termination visit, or follow up visit at week 90. Blood was drawn post infusion at week 1, and pre-infusion at all other time points. In the long -term extension phase of Study 201 OLE blood collection occurred at screening, and then starting at week 3, occurring pre-dose at all collection points (See Appendix section 12.1.1 for Schedule of Assessments).

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 (Table 10).

I reviewed the applicant's criteria for potentially clinically significant laboratory values which partially relies on the CTCAE criteria The CTCAE grading for laboratory values (Table 9 Applicant's Grading for Laboratory Values) is originally created for clinical trials in cancer. Therefore, reliance on the CTCAE grading alone for some of the laboratory values may miss some clinically significant laboratory findings that are not included in the CTCAE grading. For example, elevation in white cell count, is not captured by the CTCAE grading system above, but may be important in non-cancer trials. Therefore, the applicant was asked in an IR to also provide laboratory shift tables identifying individuals who had one or more laboratory values that fell under a specified low or high value as identified by the Division.

Table 9 Applicant's Grading for Laboratory Values

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L hospitalization indicated	> 7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L hospitalization indicated	< 2.5 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	> 300 – 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 – 1000 mg/dL >5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

ECGs:

In the placebo-controlled period of Study 201 Core, 12-lead ECG was collected at screening, baseline and Weeks 9, 17, 27, 39, 53, 65, 79, 90.

An IR was sent to the applicant on January 24, 2022, to clarify what ECG parameters were included in the datasets submitted for Study 201 Core. The applicant clarified that quantitative ECG data was captured in studies 104 and 201 OLE, but was not captured in studies 101 and 201 Core. The applicant further explained that in studies 101, 104, 201 Core and 201 OLE qualitative ECG findings (normal, abnormal-not clinically significant, abnormal-clinically significant) as evaluated by the investigator were reported. The incidence of participants who had shifts from normal to abnormal was reported in the Clinical Study Reports in the BLA.

In response to an IR from the Division sent on August 23, 2022, the applicant clarified that the determination of whether the ECG abnormality is clinically significant or not clinically significant was per investigator judgement, and that all ECG findings that were abnormal clinically significant required the PI to capture the diagnosis or adverse event identified during the ECG in the eCRF.

7.4. Safety Results

7.4.1. Deaths

In Study 201 CORE, there was not an excess of deaths in the lecanemab-treated group compared to placebo (0.8% in each group). As of a data cutoff date of 31 December 2021 (120-Day Update), a total of 24 deaths have occurred across the lecanemab clinical development program. There were 10 deaths in lecanemab-exposed participants in the 201 Core (5) and OLE

(5), and there have been 9 deaths in blinded 301 Core and 4 deaths in the 301 OLE study (one of which was reported to the Agency on December 20, 2022 [Mfr. Control No. :EC-2022-123944(0), subject (b) (6)]). There did not appear to be clusters of unusual deaths and none of the deaths were preceded by ARIA-E or ARIA-H (microhemorrhage or superficial siderosis), although additional requested information on the recent death of participant (b) (6) which the FDA was notified on December 20, 2022, is pending. One of the deaths in Study 301 Core (Participant (b) (6)) was due to a cerebral hemorrhage (> 1cm) and is described under deaths. In response to an IR the applicant informed the Agency on December 14, 2022, (after 301 Core was unblinded), that this participant was randomized to receive placebo. While this review was ongoing the Agency became aware of two additional deaths due to cerebral hemorrhage in 301 OLE. Section 7.5.2 for details. There were no deaths reported in completed studies 101, 104, 004, and in the ongoing Study 303.

The combined incidence of death by person-years of exposure in 201 Core and OLE for LEC10-BW of 9.3/1,000 person years (10/1073.3 person years[5]) does not exceed the reported incidence from AD in the US of 133.8/1,000 person years.

Reviewer Comment: This reviewer notes the limitation of comparing death rate of participants in the early stage of AD, with the overall AD population inclusive of later stages, as those who are at later stages have a higher morbidity and those that are able to participate in clinical trials are healthier in general.

Deaths in Study 101, 104 and 004
There were no deaths reported in studies 101, 104 and 004.

Deaths in the Study 201 Core and OLE

Study 201 Core

There were 7 deaths (b) (6) out of 845 participants in the placebo controlled 201 Core study. Of the 7 deaths, two were in the placebo group (2/245), and 5 in the lecanemab group (5/609). Six of the 7 deaths occurred within 30 days of last study drug administration. One of the deaths occurred beyond 30 days after the last dose of study drug administration and was in the placebo arm.

There was not a higher incidence of deaths in the lecanemab arm compared to placebo in the placebo-controlled period of study 201 (Table 10).

Table 10 Incidence of Deaths in the Placebo Controlled Period of Study 201

[5] 120-day cut-off updated death by person-years provided by the sponsor on October 26, 2022 in response to an IR from the Agency.

Study	Lecanemab	Placebo
201	5/609 (0.8 %)	2/245 (0.8%)

In the placebo-controlled period of Study 201, the preferred terms of TEAEs with fatal outcomes were: brain neoplasm, cardiac arrest, multiple organ dysfunction syndrome (hepatic failure, acute kidney injury, coagulopathy, bacteremia, leukopenia, metabolic encephalopathy), spinal cord injury, respiratory failure. In the placebo group, the preferred terms of TEAEs with fatal outcome were acute respiratory failure and sarcoma (Table 10). None of the cases of death were preceded by ARIA.

Study 201 OLE

As of data cutoff day of December 31, 2021, there were 5 deaths (b) (6) out of 180 participants in Study 201 OLE (incidence of 2.8 %). All but two (b) (6) of these deaths occurred within 30 days of the last dose of study administration. Two deaths (b) (6) occurred after 30 days of study drug administration.

The preferred terms of TEAEs with fatal outcomes for deaths during the 201 OLE period were: metastases to central nervous system, neuroendocrine carcinoma, cervical vertebral fracture, COVID 19 pneumonia, and Alzheimer's Dementia. None of the cases of death were preceded by ARIA (**Table 11**)

Description of Deaths in Study 201 Core and OLE

Table 11 Deaths in Lecanemab-Treated Participants in Study 201 Core and OLE

Subject ID	Age, Race, Sex	Dose (mg/kg)	AE listed as cause of death	Risk Factors
Study 201 Core				
(b) (6) Treatment-emergent	81 year-old white female	LEC2.5-BW	Brain neoplasm with surrounding vasogenic edema	Unknown
(b) (6) Treatment-emergent	75 year-old white female	LEC2.5-BW	Cardiac Arrest	History of hyperlipidemia, hypertension, history of cardiac catheterization
(b) (6) Treatment-emergent	79 year-old white female	LEC5-5BW	Multiple Organ Dysfunction Syndrome	Lymphoma
(b) (6) treatment emergent	78 year-old white male	LEC10-M	Spinal Cord Injury	Fall (Possible Syncope)

(b) (6) Treatment emergent	82 year-old, white, male	LEC10-M	Respiratory Failure	History of myocardial infarction, congestive cardiac failure, atrioventricular block complete
Study 201 OLE				
(b) (6) Treatment emergent	80 year-old white female	LEC10-BW	cervical vertebral fracture	Car accident
(b) (6) Treatment emergent	76 year-old white female	LEC10-BW	COVID-19 pneumonia	COVID Epidemic, age
(b) (6) Not treatment emergent	82 year-old white female	LEC10-BW	Alzheimer's type dementia	Alzheimer's disease, age
(b) (6) Treatment emergent	79 year-old white male	LEC10-BW	Metastatic malignant neoplasm of brain	Presence of malignancy (metastatic lung cancer)
(b) (6) Treatment emergent	76 year-old white male	LEC10-BW	Metastatic Neuroendocrine carcinoma	Diabetes Mellitus

The deaths that occurred on lecanemab in Study 201 Core and OLE are further described in the Appendix 12.1.2 Narratives for 201 Core. Overall based on the review of these death narratives, none of the deaths seem to be directly related to study drug. None of the deaths was due to complications of ARIA. On review of these narratives, I could not identify a clear role of the study drug in most of these deaths in Study 201 Core and OLE and most had other risk factors. One participant (b) (6) was diagnosed with high-grade infiltrating astrocytic neoplasm which was diagnosed after exposure to study drug for 1 year and 2 months and led to death. I could not identify a clear role of study drug given the relatively short duration of treatment compared to the latency for the development of malignancies.

Deaths in the Blinded Study 301 Core and OLE:

As of the data cut off of December 31, 2021, for the 120-day safety update, 12/1899 (0.6%) deaths had been reported in the ongoing blinded Study 301 Core and OLE. An additional notable death in the 301 OLE (Mfr. Control No. :EC-2022-123944(0), subject (b) (6)), was reported to FDA on December 20, 2022, and noted in the journal, Science (https://www.science.org/content/article/scientists-tie-third-clinical-trial-death-experimental-alzheimer-s-drug), on December 21, 2022 and will be described below. The review team has not been able to fully assess the potential relationship to study drug for that death due to lack of information.

Of the 9 deaths in the 301 Core study, 7 occurred within 30 days after the last dose of study treatment and 2 occurred more than 30 days after last study dose administration. All of the 3 deaths in Study 301 OLE reported as of the 120 day safety update occurred within 30 days of last study dose administration. None of the cases of death were preceded by ARIA but one of the deaths (b) (6) was due to an intracranial hemorrhage (cerebral hemorrhage > 1 cm) while on placebo. The study drug blinded narratives of these deaths have been reviewed and summarized below. During the review, the Agency became aware of two additional deaths due to cerebral hemorrhage in 301 OLE which are further described in Section 7.5.2.

Description of Deaths from ongoing Study 301 Core and OLE

The 120-Day Updated narratives of deaths in 301 Core and OLE were reviewed. Of the 12 deaths occurring in 301 Core and OLE (Table 12), one (b) (6) was due to an intracranial hemorrhage (cerebral hemorrhage > 1cm) while on placebo . This participant's narrative will be described in more detail in this Section 7.5.2 Cerebral Hemorrhage . One of the deaths was due to cerebrovascular infarction in a participant with multiple stroke risk factors (b) (6), three of the deaths were due to myocardial infarction in participants with cardiovascular disease risk factors (b) (6) and four appeared to be related to COVID-19 infection (b) (6) One participant died of pancreatic cancer (b) (6) In addition to the cerebral hemorrhage, two deaths stand out: one belonging to a participant who died 3 days after the first dose of study drug (b) (6) and one due to a death from an acute cardiac failure in a participant (b) (6) with no known cardiovascular risk factors mentioned in the narrative.

Participant (b) (6), who was found unresponsive by her husband, three days after the first dose of blinded study drug, was diagnosed with acute respiratory failure and acute kidney failure in the hospital and placed on comfort measures and died. She had underlying cardiovascular disease as a potential risk factor. Participant (b) (6) died of a myocardial infarction after the 11th dose of study drug with no clear risk factors identified in the narrative. All the death narratives in Study 301 Core and OLE can be found in Appendix Section 12.1.3. The interpretation of these deaths in the context of blinded study drug is limited.

Two additional deaths (b) (6) in 301 OLE due to one or more cerebral hemorrhage > 1cm while participating in 301 OLE which occurred during the review, are not included in the table below, and will be discussed in Section 7.5.2 Cerebral Hemorrhage.

Table 12 Treatment Emergent Deaths in Blinded Study Drug Treated Participants in 301 Core

Subject ID	Age, Race, Sex	Number of infusions prior to death	Day of death in relation to last dose	AE listed as cause of death	Risk Factors
301 Core					

(b) (6)	79 year-old white male	18	46	Cerebrovascular accident	Hypertension, hyperlipidemia cardiovascular disease, atrial fibrillation, COPD, impaired fasting glucose
(b) (6)	82 year-old white female	1	4	Acute Respiratory Failure	Bronchospasm hyperlipidemia hypertension implantable cardiac monitor insertion (since Dec 2019) first degree AV block
(b) (6)	70 year-old white male	17	10	Myocardial infarction	Hyperlipidemia Diabetes, Coronary Artery Disease, previous Myocardial infarction hypertension
(b) (6)	79 year-old white male	3	5	Myocardial infarction	Coronary Artery Stenosis, stent placement, hyperlipidemia, hypertension, diabetes mellitus
(b) (6)	79 year-old white male	19	49	Cardio-respiratory arrest	Developed COVID symptoms (wife was positive participant never tested), then a week later developed cough/dizziness and died; Hyperlipidemia
(b) (6)	86 year-old white female	26	24	COVID 19	Age, COVID 19
(b) (6)	85 year-old white male	6	249	Pancreatic Cancer	Age

(b) (6)	76 year-old white male	20	23	COVID-19	Age, COVID 19
(b) (6)	72 year-old white male	26	41	Intracranial hemorrhage	Unknown risk factors
301 OLE					
(b) (6)	78 year-old white female	1	11	Myocardial infarction	Carotid artery stenosis, sleep apnea, hypertension, hyperlipidemia, cardiac murmur, history of 1st degree AV block
(b) (6)	68 year-old white male	46	5	COVID-19 pneumonia	COVID19 Age
(b) (6)	81 year-old Asian male	11	19	Acute cardiac failure	None found in the narrative

* One death not identified as treatment emergent because the death occurred prior to the participant receiving the first study dose in 301 Core was not included (participant (b) (6)).

An additional report of death in the 301 OLE (Mfr. Control No. :EC-2022-123944(0), subject (b) (6)), was submitted to FDA on December 20, 2022, and reported in the journal, Science, on December 21, 2022. This was a 79 year old female with early Alzheimer's disease who completed 301 Core on placebo and was enrolled in the OLE in (b) (6). The patient was homozygous for ApoE ε4. The patient received 3 doses of lecanemab 10 mg/kg every two weeks in the OLE. The last dose of study drug was administered on (b) (6) According to the CIOMS report, 1 week after the last dose the subject experienced a sudden onset of difficulty speaking, staring into space, and left side weakness, reported as a "possible CVA (cerebrovascular accident)" and "possible seizure". The subject was taken to an emergency department, was intubated, and hospitalized. An MRI with and without contrast was reported as showing "no mass, no definite bleeding or edema or stroke". A prior MRI from (b) (6), was notable only for a "a previously noted left parietal < 1 cm meningioma". A seizure was suspected but no definite seizure activity was noted. It was reported that the subject had never been on anticoagulation during the study or in the hospital. The subject was extubated and 5 days after the original event, developed respiratory distress and passed away. According to the CIOMS report, the subject had risk factors for seizures, including underlying Alzheimer's disease, and for cerebrovascular disease, including advanced age, hyperlipidemia, aortic atherosclerosis, chronic kidney disease, and prediabetes. According to the CIOMS form, an autopsy was performed but results had not been reported to the investigator site. Descriptions

of brain bleeding and swelling, treatment of the event with steroids, and multiorgan failure noted in the Science description, are not noted in the CIOMS form and have not been submitted to the Agency for review. The Agency has requested that the applicant provide additional information on the case, including MRI images and the autopsy report. The applicant has not been able to obtain additional information as of January 3, 2023. The confirmation of the events reported in the Science article and their relationship to study drug cannot be determined at this time.

7.4.2. Serious Adverse Events

In the placebo-controlled Study 201 Core, serious adverse events (SAEs) occurred in 13% (21/161) of LEC10-BW-treated participants and in 17.1% (42/245) of placebo-treated participants. The most frequently reported SAEs included 3 participants with ARIA-E events (2% for LEC10 BW vs 0 in placebo), arthralgia (1.2% for LEC10-BW vs 0 in placebo), and cerebral microhemorrhage (ARIA-H) that occurred in 2 participants (1.2%) for LEC10-BW vs none in placebo.

The data sources I used for this summary of treatment emergent SAEs included primarily the Integrated Summary of Safety (ISS), ISS ADAE dataset for Study 201, Study 201 Clinical Study Report, narrative summaries for studies 201, 301, and 303, and case report forms (CRF) submitted by the applicant. The CRFs were reviewed as needed when additional information was needed.

The SAE data were evaluated separately in 201 Core and 201 OLE due to differences in study design, inclusion, exclusion criteria, discontinuation criteria, and allowed medications that may impact type and frequency of adverse events. These differences in study design are outlined in Table 3.

201 Core Period

Table 13 Incidence of a participant experiencing at least one SAE in the Study 201 Core (inclusive of those with fatal outcomes)

# of SAEs	LEC2.5-BW N=52	LEC5-M N=51	LEC5-BW N=92	LEC10-M N=253	LEC10-BW N=161	Placebo N=245
≥ 1	8 (15%)	4 (8%)	16 (17)	29 (11%)	21 (13%)	42 (17%)

Reviewer Created using the ADAE dataset submitted with sequence 45 (120-day updated) selected for Study ID= BAN2401-G000-201, SAFFL=Y, AESER: Y, TRTEMFL Serious=Yes, grouped USUBJID, and Actual treatment for Period 01, and tabulated by Actual Treatment for Period 1.

Table 13a Incidence of Treatment Emergent SAEs by primary system organ class in 201 Core occurring in > 1 participant receiving lecanemab and at a higher frequency than placebo

System Organ Class	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N=245 N(%)
Nervous system disorders	1 (1.9)	2 (3.9)	6 (6.5)	6 (2.4)	4 (2.5)	9 (3.7)
Cardiac disorders	4 (7.7)	0	2 (2.2)	3 (1.2)	2 (1.2)	4 (1.6)
Gastrointestinal disorders	1 (1.9)	1 (2)	1 (1.1)	3 (1.2)	3 (1.9)	3 (1.2)
Infections and infestations	0	0	2 (2.2)	3 (1.2)	3 (1.9)	5 (2)
General disorders and administration site conditions	0	0	3 (3.3)	2 (0.8)	2 (1.2)	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9)	0	1 (1.1)	3 (1.2)	1 (0.6)	4 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	0	0	3 (1.2)	2 (1.2)	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	1 (1.1)	1 (0.4)	3 (1.9)	4 (1.6)
Psychiatric disorders	0	0	4 (4.3)	1 (0.4)	0	2 (0.8)
Hepatobiliary disorders	0	0	1 (1.1)	0	1 (0.6)	0
Renal and urinary disorders	0	1 (2)	1 (1.1)	0	0	1 (0.4)

Reviewer Created using the ISS ADAE by Study ID= BAN2401-G000-201, SAFFL=Y, AESER: Y, TRTEMFL = Y; Serious= Yes, Group by USUBJID, primary organ system class; Actual Treatment for Period 01, tabulated by Primary Organ System Class and Actual Treatment for Period 01.

The incidence of treatment emergent SAEs by primary organ system was similar between treatment arms (Table 13a)

In the placebo-controlled period of Study 201, the most frequently reported SAEs using dictionary derived terms that were observed in at least 2 or more participants by treatment arm were: fall in 4 (2 %), osteoarthritis in 3 (1%), and syncope in 3 (1%) participant in the placebo arm; transient ischemic attack in 2 (4 %) participants in the LEC5-M arm, non-cardiac chest pain in 2 (0.8%) participants in the LEC10-M arm and ARIA–E in 3 (2 %), arthralgia in 2 (1 %) and cerebral microhemorrhage (ARIA-H) in 2 (1%) participants in the LEC10-BW arm (**Table 14)**.

Table 14 Incidence of Treatment Emergent SAEs in 201 Core by Preferred Term Occurring in > 1 participants receiving Lecanemab and at higher frequency than placebo

Dictionary Derived Term	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
ARIA-E	0	0	0	1 (0.4)	3 (1.9)	0
Cerebral microhemorrhage (ARIA-H)	0	0	0	0	2 (1.2)	0
Arthralgia Arthritis	0 0	0 0	1 (1.1) 0	0 0	2 (1.2) 1 (0.6)	0
Transient ischemic attack	0	2 (3.9)	0	1 (0.4)	1 (0.6)	1 (0.4)
Seizure/focal dyscognitive seizures	0	0	1 (1.1)	1 (0.4)	0 *	0
Syncope	0	0	1 (1.1)	1 (0.4)	1 (0.6)	2 (0.3)
Atrial fibrillation	1 (1.9)	0	0	0	1 (0.6)	0
Cardiac failure congestive	0	0	1 (1.1)	1 (0.4)	0	0
Myocardial infarction	1 (1.9)	0	0	1 (0.4)	0	0
Non-cardiac chest pain	0	0	0	2 (0.8)	1 (0.6)	0
Chronic Obstructive Pulmonary Disease	0	0	0	1 (0.4)	1 (0.6)	0
Hallucination	0	0	1 (1.1)	1 (0.4)	0	0

Reviewer created using the ISS ADAE by Study ID= BAN2401-G000-201. SAFFL=Y, , TRTEMFL = Y; Serious= Yes, Group by USUBJID, Dictionary Derived Term; Actual Treatment for Period 01, tabulated by Dictionary Derived Term and Actual Treatment for Period 01.

**one participant (b) (6) in the LEC10-BW arm had a possible seizures related to ARIA-E. As the applicant did not separately include the clinical symptoms of ARIA-E in the ADAE datasets, this participant was not included in this table which was created using the ADAE dataset.*

*** Both of the participants with a serious ARIA-H microhemorrhage in the LEC10-BW arm had serious cerebral microhemorrhage events.*

Adverse events in this review were evaluated by individual preferred term (or dictionary derived terms) and by groupings of closely related preferred terms called medical query groups (MQG) SAEs by MQG are presented in Table 15. The reader is referred to the Section 12.1.4 for a list of MQG in this review and the preferred terms that make up the Groupings for this study.

Table 15 Serious Adverse Events by MQGs occurring in > 1 participants in the LE10BW arm and at higher frequency compared to placebo in Study 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Infection, all ODE-1[6] MQG	0 (0)	0 (0)	2 (2.2)	3 (1.2)	3 (1.9)	4 (1.6)
Arthralgia, FDA N, MQG	0 (0)	0 (0)	1 (1)	0 (0)	3 (2)	3 (1)
Hemorrhage, FDA N MQG	1 (1.9)	0 (0)	0 (0)	1 (0.4)	2 (1.2)	2 (0.8)
Chest pain (non-cardiac or unknown), ODE-1 MQG	0	0	0	2 (0.8)	2 (1.2)	0

Reviewer created using the ISS ADAE by Study ID= BAN2401-G000-201. SAFFL=Y, SER= Y, TRTEMFL = Y; Group by USUBJID, FDA-created queries; Actual Treatment for Period 01, sort by frequency and select those with 2 or more participants in the LEC10-BW. Medical Query Groups that only included one Dictionary Derived Term were excluded from this table.

The hemorrhage MQG of FDA N, includes hemorrhages that are SAEs that occur both in the CNS and outside of the CNS and includes the following SAEs: one participant (b) (6) with hemorrhagic conversion of stroke in the LEC2.5-BW group, one participant (b) (6) with gastrointestinal hemorrhage in the LE10-M group, two participants (b) (6) with cerebral microhemorrhage (ARIA-H) in the LEC10-BW, group, and one participant (b) (6) with subdural hemorrhage and one (b) (6) with post procedural hemorrhage in the placebo groups. When just examining intracranial hemorrhage using the OD1-MQG of intracranial hemorrhage, the frequency of SAEs was 2 (1.2 %) in the LEC10-BW group compared to 1 (0.4) in the placebo group.

Of the total 104 SAEs observed in 78 lecanemab treated participants 7 resulted in deaths during the 201 CORE study, and 53 resulted in discontinuations.

Analyses of SAEs by Maximum Dose Received

In the placebo-controlled period of Study 201, the most frequently reported SAEs by dictionary derived term in the LEC10-BW arm compared to placebo were ARIA-E (1.9 % vs 0), arthralgia (1.2 % vs 0), and ARIA-H (cerebral microhemorrhage) (1.2 % vs 0).

201 Open Label Period

The incidence of SAEs in the 201 OLE was 24.4 % (44/180) which is higher compared to 13% in the LEC10-BW arm of the 201 Core study. This may partially be related to longer duration of exposure of 24.2 (10.3, S.D.) months in the OLE versus ~ 12 (7, S.D.) months in the LEC10-BW arm in the 201 Core study. Three participants had SAEs that were not considered treatment emergent by the applicant because they occurred 30 days after study dose administration

[6] ODE-1 refers to Medical Query Groups developed by Dr. Ellis Unger

(b) (6). Participant (b) (6) had 2 SAEs within 30 days of study drug administration (hip fracture /sepsis) and one SAE after 30 days of study drug administration (recurrent sepsis one month later).

The SAEs that that occurred beyond 30 days after study drug administration were COVID19 pneumonia, sepsis, Dementia Alzheimer's. These will not be included in the narratives below which were identified using the treatment emergent definition for AEs occurring within 30 days of study drug administration.

Table 16 SAEs by Primary Organ System Class and Dictionary Derived Term in Study 201 OLE

Primary Organ System Dictionary Derived Term	N =180
Injury, poisoning and procedural complications	**16**
Cervical vertebral fracture	2
Fall	2
Hip fracture	2
Rib fracture	2
Craniofacial fracture	1
Infusion related reaction	1
Joint injury	1
Post procedural hypotension	1
Spinal cord injury	1
Subdural hematoma	1
Subdural hemorrhage	1
Traumatic renal injury	1
Nervous system disorders	**13**
Transient ischemic attack	3
Acquired epileptic aphasia/seizure/generalized tonic-clonic seizures	3
Amyloid related imaging abnormality-oedema/effusion	1
Cerebral hemorrhage	1
Cerebral infarction	1
Subdural hygroma	1
Superficial siderosis of central nervous system (ARIA-H)	1
Syncope	1
Thalamic infarction	1
Cardiac disorders	**6**
Atrial fibrillation	2
Angina pectoris	1
Aortic valve stenosis	1
Coronary artery disease	1

Myocardial infarction	
Infections and infestations	**6**
Pneumonia	2
Gastroenteritis	1
Sepsis	1
Urinary tract infection	1
Urosepsis	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6**
Adenocarcinoma of colon	1
Breast cancer metastatic	1
Lung adenocarcinoma	1
Metastases to central nervous system	1
Neuroendocrine carcinoma	1
Transitional cell carcinoma	1
Gastrointestinal disorders	**5**
Ascites	1
Constipation	1
Nausea	1
Small intestinal obstruction	1
Vomiting	1
General disorders and administration site conditions	**4**
Chest discomfort	2
Asthenia	1
Chest pain	1
Renal and urinary disorders	**4**
Acute kidney injury	3
Hematuria	1
Musculoskeletal and connective tissue disorders	**2**
Rotator cuff syndrome	1
Spinal stenosis	1
Psychiatric disorders	**2**
Mental Status Changes	2
Respiratory, thoracic and mediastinal disorders	**2**
Pneumonia aspiration	1
Pneumothorax	1
Blood and lymphatic system disorders	1
Pancytopenia	1
Ear and labyrinth disorders	**1**
Vertigo	1
Metabolism and nutrition disorders	**1**
Dehydration	1

Reproductive system and breast disorders	**1**
Benign prostatic hyperplasia	1

Reviewer created using the 120-day updated ISS ADAE dataset, Study ID= BAN2401-G000-201-OLE SAFFL=Y, SER=Y, TRTEMFL = Y, grouped by USUBJID, dictionary derived term and system organ class.

Approach to Review of Narratives for Study 201 Core and OLE

I reviewed the narratives of SAEs related to events of special interest across the clinical program, SAEs occurring in at least 2 or more participants receiving lecanemab compared to placebo across the clinical program, most common SAEs reported in the placebo-controlled period of Study 201, and narratives of potentially medically significant events and designated medical events in both the 201 Core and OLE studies.

The following FDA designated medical events using MedDRA Preferred Terms were identified in this review of SAEs in the 201 Study: acute respiratory failure, leukopenia, pancytopenia, aplastic anemia, hepatic failure/liver failure, renal failure (acute kidney failure), seizure.

The following FDA designated medical events using MedDRA Preferred Terms were not identified: acute pancreatitis, amyotrophic lateral sclerosis (ALS), anaphylaxis and anaphylactoid reactions, blind, ischemic colitis, congenital anomalies, deaf, disseminated intravascular coagulation endotoxic shock, confirmed or suspected, hemolysis, hemolytic anemia, liver necrosis, liver transplant, neuroleptic malignant syndrome, progressive multifocal leukoencephalopathy, product infectious disease transmission, pulmonary fibrosis, pulmonary hypertension, rhabdomyolysis, serotonin syndrome, Stevens-Johnson syndrome, sudden death, suicide, Torsade de Pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

I defined the following to be included as SAE narratives of events of special interest: ARIA-E; ARIA-H microhemorrhages and hemosiderin deposits; superficial siderosis of the central nervous system; intracranial hemorrhage (cerebral hemorrhage > 1 cm) immunogenicity; hypersensitivity; injuries and accidents; syncope; encephalopathy; seizures, psychosis, delusions, hallucinations; and pulmonary embolism.

For narratives related to most common SAEs occurring in the placebo-controlled period of Study 201, I identified the following preferred terms or MQGs that occurred in two or more participants in the LEC10-BW arm and were 1 % or higher compared to placebo: ARIA-E, cerebral microhemorrhage, non-cardiac chest pain MQG, , and Arthralgia FDA N.

Narrative of Events of Special Interest.
These narratives will be described individually in more detail under the Appendix 201 Core and 201 OLE Selected ARIA narratives and Tables. A brief summary description is provided below.

ARIA

There were 4 SAEs of ARIA-E, three at the proposed dose arm (b) (6) and one in the LE10-M arm (b) (6) See Sections 7.5.1 and 12.1.5 for description and narratives of these cases.

Infusion and Hypersensitivity Reactions

There was one SAE of infusion related reaction in Study 201 Core (b) (6) and one SAE of infusion related reaction reported in the OLE (b) (6). These will be further described under section 7.5.2 under Infusion Related Reactions.

Seizures

In Study 201 Core there were a total of 3 treatment emergent seizures in participants treated with lecanemab and no SAEs of seizure in the placebo arm. I reviewed these narratives and could not identify a role of study drug in the occurrence of SAE of seizure in two of the participants (b) (6) Both had other potential causes, including electrolyte abnormalities (b) (6) and electrolyte abnormalities and brain surgery (b) (6) Neither of these participants had ARIA. Participant (b) (6), who was started on levetiracetam completed study without any further seizures. Participant (b) (6) discontinued study due to SAE of seizure with acute respiratory failure.

In one participant (b) (6) seizure occurred in the setting of an SAE of ARIA-E and is further described under Section 7.5.2 ARIA.

One additional seizure occurred beyond 90 days after the last dose of lecanemab (b) (6) The seizure was due to hypoglycemia and not related to study drug. This participant also did not have ARIA.

In the OLE there were 4 SAEs of seizure (b) (6) I identified a potential role of study drug in one of these SAEs (b) (6) While there was no clear etiology for a seizure in two participants (b) (6) both completed study participation without recurrence of seizures (with treatment with levetiracetam (b) (6) and with no treatment (b) (6) Because older age and AD can both increase risk of seizure, and given lack of ARIA in these participants, it is less likely that the study drug played a role. Participant (b) (6) had a seizure in the setting of aspiration pneumonia.

Participant (b) (6) had a focal seizure (language disturbance) after the 6th dose of study drug. Initially this was thought to be a symptom of an ischemic stroke and she was given fibrinolytic. Work up revealed a left basal ganglia lacunar infarct and a left occipital microhemorrhage. She had recurrent symptoms and was started on brivaracetam and did not have any further seizures until she completed the study. In this participant the seizure was either related to left basal ganglia infarct, or the left occipital microhemorrhage. Unlike cerebral hemorrhages, cerebral microhemorrhages are not commonly known to be associated with

seizures, and the association is only described in case reports.[7] Transient focal neurological episodes (TFNEs), however, which are a unique clinical symptom described in cerebral amyloid angiopathy (CAA) [which shares features with ARIA associated with treatment with anti-amyloid monoclonal antibodies], may resemble a seizure or transient ischemic event, and are thought to be related to cerebral microhemorrhages and superficial siderosis seen in CAA.[8] Thus it is possible that the presumed seizure which presented as transient aphasia in participant (b) (6) is related to the occipital cerebral microhemorrhage.

Subdural Hemorrhage/Subdural Hematoma

In study 201 Core, there were two participants (b) (6) on placebo and 3 participants (b) (6) on lecanemab with an SAE of subdural hemorrhage or subdural hematoma. One participant (b) (6) had a subdural hemorrhage in the setting of serious ARIA-E and ARIA-H and is further described under Section 7.5.1. In two of the participants on lecanemab (b) (6) subdural hemorrhage occurred beyond 30 days after the last dose of study drug, and both resulted from falls due to orthostatic hypotension (only potential risk identified was taking rivastigmine) (b) (6) and Parkinson's disease (b) (6) Given these occurred after 30 days after the last dose of study drug, I could not identify a clear role of study drug in these two falls and resulting subdural hemorrhage/ hematoma.

In study 201 OLE two participants (b) (6) had an SAE of subdural hemorrhage or subdural hematoma, one due to a fall and the other due to a biking accident (b) (6)

Cerebrovascular Event

In Study 201 Core 7 participants were identified as having had an SAE of TIA or stroke. In the following three cases, I believe study drug may have played a role: participant (b) (6), who was randomized to LE10-M, had transient right-hand numbness and aphasia which occurred in the setting of ARIA-E. These transient symptoms were likely not related to a cerebrovascular ischemic event and were related to ARIA-E. This event will be further described under Section 7.5.1 ARIA. Participant (b) (6), who was randomized to LEC5-M, and had multiple stroke risk factors, had a TIA and no MRI changes. On a study follow up MRI obtained several months later a new left frontal cortical infarct was seen. The participant experienced a second occurrence of TIA with dizziness, and repeat MRI showed an area of superficial siderosis, in the left frontal cortical area, which was interpreted as related to stroke evolution rather than being identified as ARIA-H superficial siderosis. While this is possible, I cannot rule out that this finding of superficial siderosis and the related transient dizziness is due to study drug related symptomatic ARIA-H superficial siderosis. Participant (b) (6) had an ARIA-E event, and within a month of the ARIA-E, had an infarct. Since his narrative is silent to stroke risk factors

[7] Jeon et al. Epilepsia. Acute cerebral microbleeds in refractory status epilepticus. 2013 May;54(5):e66-8. https://doi.org/10.1111/epi.12113
[8] Ramirez et al. . Cerebral microbleeds: overview and implications in cognitive impairment. Alz Res Therapy 6, 33 (2014). https://doi.org/10.1186/alzrt263

and given the proximity in timing to ARIA-E, I cannot rule out a role of study drug in this infarct. Participants [redacted], all had underlying risk factors for cerebrovascular disease, and I cannot identify a role of the study drug in the occurrence of TIA or stroke.
In the OLE 4 participants experienced a stroke or TIA. All of these participants [redacted] had one or more underlying risk factor, and I could not identify a clear role of study drug in these events.

Cerebral Hemorrhage (> 1 cm)

Cerebral hemorrhage > 1 cm occurred in one participant [redacted] in 201 Core, one participant [redacted] in 201 OLE, one participant [redacted] in Study 101, 5 participants [redacted] on blinded study drug and in one participant [redacted] on placebo (cerebral hemorrhage resulting in death) in 301 Core study, and one participant in 301 OLE. See Section 7.5.2 and Section 12.1.3 for discussion and narratives for these participants as well as discussion of 2 additional cerebral hemorrhages and deaths in 301 OLE which occurred during this review after the 120-Day Cut Off date.

Cardiac Disease

In 201 Core, there were 3 cardiac-related treatment emergent SAEs: atrial fibrillation [redacted] and AV block [redacted]. In Study 201 OLE there were 6 cardiac related SAEs: atrial fibrillation and chest discomfort [redacted], angina pectoris [redacted] coronary artery disease [redacted], aortic valve stenosis [redacted] myocardial infarction [redacted] and atrial fibrillation and transient ischemic attack [redacted] I reviewed these narratives and all of the participants, had pre-existing cardiovascular disease risk factors, and I could not identify a clear role of study drug in these events.

Arthralgia/Arthritis/Joint injury

In Study 201 Core, arthralgia or arthritis was reported in four participants [redacted] receiving lecanemab, and in none of the participants on placebo. One participant in201 OLE [redacted] also had an SAE of joint injury. I reviewed these narratives and could not identify a clear role of study drug. These events were either related to worsening of underlying joint disease requiring intervention or related to fall or trauma. None were consistent with arthralgia due to a hypersensitivity reaction.

Chronic Obstructive Pulmonary Disease

Two participants [redacted] experienced treatment emergent SAEs of chronic obstructive pulmonary disease in 201 Core. I reviewed these cases and could not identify a role of the study drug. Both of these appeared to be related to underlying lung disease.

Chest Discomfort/Chest Pain

I reviewed the narratives of four participants, two on LEC10-BW [redacted] and two on LE10-M [redacted] who had a TEAE of chest pain or chest discomfort occurring within 1-13 days after an infusion. I could not identify a clear role of study drug in any of these

events. Participants (b) (6) had accompanying shortness of breath, participants (b) (6) had accompanying diaphoresis and (b) (6) also had elevation in transaminases. All of these participants were admitted to the hospital and a workup was negative for cardiac or pulmonary cause of these symptoms and were diagnosed with noncardiac chest pain. In all of these participants symptoms resolved within a few days. All participants continued with study drug until completion of study with the exception of participant (b) (6) who was discontinued after the 12th dose due to being an ApoE ε4 carrier. Participant (b) (6) experienced a rash after the 19th and 25th infusions. Participant (b) (6) experienced AEs of mild pruritis twice, a few days after the 6th and 30th dose of study drug. There was no action taken with study drug in any of these and both completed study, with no further events and without any treatments. Given the few occurrences, mild symptoms and resolution without intervention, it does not appear that these events support that the chest pain was related to a hypersensitivity reaction.

In study 201 OLE, 3 participants (b) (6) experienced and SAE of chest pain. All resolved within a few days after onset. I could not identify a clear role of study drug in these events. During the hospitalization participant (b) (6) also was found to have thrombocytopenia which resolved within a few weeks. Participant (b) (6) was found to have a tricuspid valve incompetence which is likely unrelated to the chest pain. Participation in the extension phase was ongoing for all three participants at the time of the data cutoff date of December 31, 2021, with no further episodes of chest pain.

Acute Kidney injury:

There was one participant (b) (6) in the Core study and 3 participants (b) (6) in the OLE on lecanemab with treatment emergent SAE of acute kidney injury, and two participants (b) (6) in 201 Core with non-treatment emergent SAE of acute kidney injury. In all of these cases there were likely explanations for these events including dehydration, obstructive uropathy, urinary tract infection (UTI), and sepsis, and I could not identify a clear role of the study drug. With the exception of participant (b) (6) who died from underlying lymphoma, most of the other cases of treatment emergent acute kidney injury resolved with hydration and treatment of underlying condition. Acute kidney injury was ongoing at the time of discontinuation for one participant with nontreatment emergent acute kidney injury (b) (6) in the setting of hypertensive emergency.

Mental Status Changes:

There were 3 participants (b) (6) in the 201 Core, and one participant in 201 OLE (b) (6) who had treatment emergent serious mental status changes. I reviewed the narratives of these participants and did not identify a clear role of the study drug in any of these cases. In all of these cases, there were likely explanations for these events including dehydration, acute bronchitis, metabolic encephalopathy with underlying lymphoma, fall and possible concussion. Mental status changes due to other medical events is not

uncommon in AD. All of these mental status changes, (except in participant (b) (6) who died of complications of lymphoma) ultimately resolved.

Aggression/Agitation
I reviewed the narrative of one participant (b) (6) who had a hospital admission for an SAE of agitation, culminating from gradually increasing paranoia in the context of alcohol use. I do not believe that the study drug played a role in this participant's agitation.

Hallucinations
I reviewed the narratives of the two participants (b) (6) in 201 Core who had an SAE of hallucinations. In both of these cases, study drug was ultimately discontinued due to worsening hallucinations. As hallucinations are not uncommon in patients with AD during the course of their disease, it is difficult to ascertain whether the study drug played a role in these two participants' hallucination.

Falls/ Injury /Fractures/Musculoskeletal Injury
There were 7 participants (b) (6) in 201 Core and 11 participants in OLE study (b) (6) (b) (6) who had a treatment emergent, serious fall, fracture, or musculoskeletal injury. I reviewed these narratives and could not identify a clear role of study drug. The falls were either mechanical in nature (tripping, slipping), due to underlying risk factor (such as spinal stenosis, osteoarthritis, poor vision, pre-existing gait problem or history of falls, pre-existing musculoskeletal injury) or accidents (bike or MVA accident). I also could not identify drug induced hypotension, dizziness or vertigo as a clear cause of the fall or injury in these participants. In one participant (b) (6), I identified AEs of dizziness (on Study Day 241) and vertigo (on Study Day 456). This study participant sustained a fall after slipping in the bathroom on Study Day 443. This participant had a pre-existing medical history of dizziness and vestibular neuronitis. Participant (b) (6) tripped and sustained a mechanical fall on Study Day 634, and was hospitalized for hip fracture. She had hypotension listed as an AE on Study Day 897, but there is no narrative related to this to provide context to the AE of hypotension.

Retinal Detachment/Monocular Blindness:
Participant (b) (6) experienced loss of right monocular vision due to retinal detachment 13 days after he received the 38th dose of study drug. He had a medical history of hypertension which may be a potential risk factor for retinal detachment. I could not identify a clear role of study drug in this participant's retinal detachment, and resulting monocular blindness, who went on to complete study after 39 doses.

Hepatic Failure/Hepatitis Acute/Cholangitis Acute/ Cholecystitis Chronic
In study 201 Core there were two participants who received lecanemab ((b) (6) and (b) (6)) who had a hepatic related SAE in the 201 Core study. I could not identify a role of

study drug in these events. Participant (b) (6) had hepatic failure due to complications of lymphoma, and is further described under Section 7.4.1. Participant (b) (6) had chronic cholecystitis and hospitalized for sepsis and acute cholangitis. Study drug, which was temporarily interrupted, was resumed after cholangitis and sepsis resolved with treatment. The participant went on to receive 36 doses of study drug and completed study as planned. There were no participants in Study 201 OLE with an SAE of hepatic disease.

Pulmonary Embolism

There was one participant (b) (6) in 201 Core who had an SAE of pulmonary embolism 6 days after the 28th dose of LE10-M. During hospitalization he also was found to have atrial fibrillation requiring lifelong anticoagulation, which led to discontinuation from study treatment due to initiation of a prohibited medication per protocol. There was no clear etiology identified for his pulmonary embolism in his narrative I cannot rule out a role of the study drug in this case. This said, the participant went on to participate in the 201 OLE study, and as of the data cutoff of December 31, 2021, he has received 55 doses of study drug and participation ongoing.

Suicidal Ideation

In Study 201 Core, there was one participant (b) (6) on lecanemab, who had an SAE of suicidal ideation occurring after the 19th dose of study drug. Her risk factors were a history of depression and suicide attempt. I could not identify a clear role of study drug in suicidal ideation. She was admitted for suicidal ideation and her psychiatric medications were optimized. The event of suicidal ideation resolved, and study drug was restarted. The participant received the 34 doses of study drug and completed study as planned.

The following designated medical events were identified among the SAEs:

Acute respiratory failure

Participant (b) (6) had acute respiratory failure during a seizure described under Seizures.

Sudden death due to a cardiac arrest

Participant (b) (6) had s cardiac arrest and is described under deaths in Section 12.1.2.

Pancytopenia or Leukopenia

In Study 201 Core no participant had an SAE of pancytopenia. One participant (b) (6) had an SAE of leukopenia in the setting of multiorgan failure and lymphoma leading to death. See Section 12.1.2 for this participant's narrative.

In Study 201 OLE there was one participant (b) (6) with an SAE of pancytopenia which was discovered after the 57th dose of study drug during the extension phase. I reviewed the narrative of this case, including additional information provided by the applicant in response to an Agency request on September 12, 2022. This participant was ultimately diagnosed with post-myeloproliferative neoplasm acute myeloid leukemia. She had a past medical history of

Jak2 + essential thrombocytopenia which is a known risk factor for AML. I could not identify a clear role of study drug in this case.

SAEs in Study 101

The following table obtained from the applicant's clinical study report for Study 101 summarizes the SAE observed in Study 101.

Table 17 Summary of Serious Adverse Events in Study 101

Table 30 Summary of Serious Adverse Events Described in Narratives

Subject Number	Cohort	BAN2401 dose	Description	Relatedness
(b) (6)	SAD3	1 mg/kg	Cerebral macrohemorrhage	Possibly related
	SAD4	3 mg/kg	Vasogenic cerebral edema, pulmonary mass, and intracranial mass	Not related
	SAD4	Placebo	Carbamazepine drug rash, bacteraemia, acute renal failure, and Red Man syndrome	Not related
	SAD6	15 mg/kg	Silent coronary event (acute coronary syndrome) and noncardiac chest pain	Not related
	MAD1	0.3 mg/kg	Jaundice, pancreatic adenocarcinoma, and pancreatitis	Not related

MAD = multiple ascending dose, SAD = single ascending dose, SAE = serious adverse event
Source: Listing 16.2.7.

The narratives for these SAEs were reviewed. One of these SAEs of interest is intracerebral hemorrhage (cerebral hemorrhage > 1 cm in diameter) in participant (b) (6). See Section 7.5.2 for the narrative of this participant.

Participant (b) (6) had vasogenic edema which preceded study drug administration (initially read as old infarct), and ultimately found to be an intracranial mass and lung mass that on biopsy was shown to be lung cancer. I don't believe that the study drug played a role in this participant's vasogenic edema related to a brain metastasis from lung cancer. I could not identify a clear role of study drug in pancreatic cancer in participant (b) (6), due short duration of exposure (4 months), and in the morbilliform rash in (b) (6) which occurred after dose increase in carbamazepine. Acute coronary syndrome in participant (b) (6), was less clear cut, as the initial ECG changes occurred on day 1 and 2 of the study drug administration, however, she had pre-existing risk factors of hypertension and hypercholesterolemia.

SAEs in Study 104

There were two treatment emergent SAEs in Study 104, post-LP headache (b) (6) and acute pancreatitis and increase in liver enzymes (b) (6) in the context of heavy alcohol use, and poor po intake. I could not identify a clear role of study drug in these SAEs.

SAEs in Study 004

There were no treatment emergent SAEs in study 004.

SAEs in Study 301 CORE

As per the pre-BLA meeting on September 10, 2021, blinded narratives for Study 301 Core and OLE were provided for deaths, discontinuations, and adverse events of interest. Blinded narratives for all SAEs were not provided. Given the blinded nature of these events, it is not possible to assign causality in these occurrences. Selected Narratives can be found in Section 12.1.3.

Of the 309 SAEs in Study 301 Core, the following (Table 18) were identified as SAE of interest. I also identified additional SAEs of interest through key word searches for narratives for 301 Core. For example, additional seizure events were identified using a keyword search in the narratives that were not included in sponsor provided Table 16.2.7.2 as these were not coded as a separate TEAE, similar to Study 201 Core.

Table 18 Listings of Study Drug Blinded SAEs in Study 301 Core

Dictionary Derived Term	**N**
Seizure*	5
Confusion/acute metabolic encephalopathy**	6
Stroke/TIA	12
Hepatic disease	2
Non-CNS bleeding	4
Accidental overdose	1
Respiratory failure/hypoxia/acute hypoxia/respiratory insufficiency ***	8
Cardiac arrest	2
ALS/motor neuron disease	1
Syncope/near syncope [#]	11
Pulmonary embolism	4
Pulmonary edema	4
Pyrexia	1
Ischemic colitis	2
Anemia	4
Suicide /suicidal ideation [$]	3
Acute renal failure	2
Other neurological symptoms (ataxia, tickling and numbness on right cheek and right side of tongue (in the setting of ARIA), trigeminal neuralgia, myasthenia gravis, CSF fluid leakage, hemiataxia)	6
Avascular necrosis	1

Pancreatitis	1

This table was created based on sponsor Table 16.2.7.2 provided by the applicant listing 120-Day Updated Serious Adverse Events for 301 Core

* Three participants (b) (6) were identified to have SAEs of seizures in Study 301 Core based on review of applicant Table 16.2.7.2. From these participants only the narrative for participant (b) (6) was provided as this participant presented with a seizure in the setting of a subarachnoid hemorrhage/ ARIA-E and ARIA-H superficial siderosis. Performing a key word search for seizure, convulsion or epilepsy on all the provided narratives for Study 301 core I identified additional seizure events which occurred in the setting of ARIA and were not separately reported as an SAE in Table 16.2.7.2 for participants (b) (6)

** Participant (b) (6) had confusion in the setting of an intracranial hemorrhage (cerebral hemorrhage > 1 cm) and is further described in Section 12.1.3.

*** Participant (b) (6) died of respiratory failure 4 days after the first dose of study drug, and is described in Section 12.1.3.

Participant (b) (6) had hypotension in the setting of seizures and subarachnoid hemorrhage. Participants (b) (6) had syncope in the setting of infusion related reaction and will be described in Section 12.1.3.

$ Participant (b) (6) had an SAE of self-inflicted gunshot (intentional self-injury)

Narratives of ARIA E, ARIA H and Hypersensitivity reactions in 301 Core can be found under Section 12.1.3

Study 301 OLE

SAEs related to ARIA, infusion related reactions or hypersensitivity reactions occurred in the following participants: (b) (6) . Blinded narratives can be found in Section 12.1.3. Similar to 301 Core, given the blinded nature of these events, a causality cannot be assigned.

In the applicant provided 301 OLE Table 16.2.7.1 which lists SAEs outside of ARIA or hypersensitivity reactions the following dictionary derived terms for SAEs during the OLE period were noted: pneumonia (b) (6) myocardial infarction (b) (6) hip fracture (b) (6) COVID pneumonia (b) (6) severe depression (b) (6) agitation atrial fibrillation (b) (6) Non ST elevation myocardial infarction (b) (6) hypertensive encephalopathy (b) (6) altered mental status (b) (6), peptic ulcer (b) (6) respiratory tract infection (b) (6) left femoral neck fracture (b) (6) cardiac failure (b) (6) and coronary artery stenosis (b) (6) and GI symptoms (b) (6)

Participants (b) (6) had SAEs that led to death (see Section 12.1.3 for narratives)
No narratives were provided for the other SAEs above as they were not ARIA or hypersensitivity related SAEs.

Study 303
SAEs listed in applicant Table 16.2.7.3 for study 303 for studies A3 and A45, not related to ARIA or infusion reactions are: dehydration and dyspnea/shortness of breath (b) (6), COVID 19 (b) (6) pulmonary embolus (b) (6), new onset atrial fibrillation (b) (6) acute ischemic stroke (b) (6) fall with right femur fracture (b) (6) pulmonary mass (b) (6) and advanced squamous cell carcinoma of the anal canal (b) (6)

7.4.0. Dropouts and/or Discontinuations Due to Adverse Effects

Study Withdrawal

A greater percentage of participants withdrew from the study because of TEAEs in the LEC10-BW group (7.5 %) compared to placebo (4.1 %) (Table 19). The higher TEAE discontinuation in the two highest doses of lecanemab (LE10-M and LEC10-BW) was driven by per protocol discontinuations for ARIA. Additionally, 25 participants who were ApoE4 carriers and who were on 10 mg/kg biweekly for less than 6 months were discontinued in accordance with European Health Authority request. This was the reason for the observed higher discontinuation rate captured under the "Other" category in Table 19.

Table 19 Study Withdrawals by Treatment Arm in Study 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Completed Study	**35 (67.3)**	**37 (72.5)**	**61 (66.3)**	**155 (61.3)**	**87 (54)**	**177 (72.2)**
Discontinued Study	**17 (32.7)**	**14 (27.5)**	**31 (33.7)**	**98 (38.7)**	**74 (46)**	**68 (27.8)**
Adverse Events	4(7.7)	2 (3.9)	5 (5.4)	23 (9.1)	12 (7.5)	10 (4.1)
Lost to Follow up	0	1 (1.9)	2 (2.2)	4 (1.6)	3 (1.9)	7 (2.9)
Other	7 (13.5)	4 (7.8)	4 (4.4)	20 (7.9)	31 (19.3)	13 (5.3)
Withdrawal by participant	6 (11.6)	7 (13.7)	20 (21.7)	51 (52)	28 (17.4)	38 (15.5)

Reviewer created using the ADDS dataset, Study ID= BAN2401-G000-201, SAFFL=Y, completers=Y for those who completed study, for non-completers: completers=N (those discontinued from the study), Epoch=Final, Phase= Treatment or Follow up, subcategory =primary reason

Study Drug Discontinuation

In the 201 Core study, participants were discontinued from study treatment if they developed any of the following features on MRI: vasogenic edema, cerebral hemorrhage (described as a single macrohemorrhage greater than 10 mm at greatest diameter), an area of superficial siderosis or a symptomatic microhemorrhage. Additionally, any participant who started on a prohibited medication long term was discontinued. Participants required to start chronic (> 4 weeks) anticoagulant treatment during the study for concomitant diseases were withdrawn from study drug. However, short-term (<4 weeks) treatment with anticoagulants was permitted for randomized participants who underwent procedures requiring anticoagulants for thromboembolic disease prophylaxis after approval by the applicant's medical monitor. While these participants were not discontinued, study drug was temporarily suspended during this anticoagulant therapy.

In Study 201 OLE safety related criteria for discontinuation of study drug are as follows:

- Infusion reactions associated with administration of study drug, of Grade 3 severity or above (as defined in the NCI-CTCAE) that do not lessen or resolve with treatment
- Clinical features which indicate meningoencephalitis (e.g., combination of 1 or more of the following: headache, worsening confusion, neck stiffness, impaired consciousness, focal neurological signs)
- Hypersensitivity reactions with clinical features of tissue injury (e.g., arthritis, glomerulonephritis, mononeuritis multiplex)

Overall, there were more discontinuations in all of the LEC arms combined (15%) compared to the placebo arm (6%) (Table 20).

Table 20 Study drug discontinuation due to TEAE by study arm in 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
	7 (13.5)	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)	14 (5.7)

Reviewer created using the ISS ADAE dataset Study ID=BAN2401-G000-201, SAFFL=Y, TRTEMFL =Y, Action taken with study treatment=drug withdrawn, grouped on dictionary-derived term, &actual treatment for period 01

In the placebo-controlled periods of Study 201, the most frequently reported TEAEs leading to treatment discontinuation by primary organ system were: nervous system disorders, cardiac disorders, injury, poisoning and procedural complications, psychiatric disorders and neoplasms. The incidence of nervous system disorders were almost five times higher in the LEC 10-BW arm compared to placebo (10.6 % versus 2%) (**Table 21**).

Table 21 Study drug discontinuation by primary organ system in > 1 participant receiving lecanemab and at greater frequency than placebo by study arm and primary organ system

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Nervous system disorders	2 (3.8)	3 (5.9)	7 (7.6)	31 (12.3)	17 (10.6)	5 (2)
Cardiac disorders	3 (5.8)	0	0	3 (1.2)	3 (1.9)	0
Injury, poisoning and procedural complications	0	1 (2)	0	7 (2.8)	4 (2.5)	3 (1.2)
Psychiatric disorders	1 (1.9)	0	1 (1.1)	5 (2)	0	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9)	0	0	1 (0.4)	0	3 (1.2)

Reviewer created using the ISS ADAE dataset, Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y , Action taken with study treatment = drug withdrawn, grouped on USUBJID, primary system organ class, and actual treatment for period 01

In the placebo-controlled period of Study 201, most frequently reported TEAEs leading to treatment discontinuation were ARIA-E, ARIA-H (cerebral microhemorrhages, superficial siderosis), infusion related reactions, atrial fibrillation. The AEs that fall under the submission specific safety issues, namely ARIA-E, ARIA-H, infusion related reactions, and all occurred in 7 or more individuals in the lecanemab treatment arms combined compared to placebo. AEs leading to treatment discontinuation were driven by per protocol discontinuations for ARIA-E in Study 201 Core. Selected narratives of these discontinuations will be discussed under Section 7.5.1 and 12.1.5. Other TEAEs that led to discontinuation in 2 or more participants in all lecanemab groups compared to placebo, including atrial fibrillation, hemorrhagic transformation of stroke, and hallucinations will be discussed below. (Table 22). Discontinuation of study treatment due to adverse reactions other than ARIA-E occurred in 5.0% (8/161) of participants treated with LEC10-BW compared to 5.3% (13/245) of placebo treated participants.

Table 22 Study Drug discontinuation 201 Core in more than one participant receiving lecanemab and at greater frequency than placebo by study arm and dictionary derived term

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Amyloid related imaging abnormality-oedema/effusion	1 (1.9)	1 (2)	3 (3.3)	25 (9.9)	16 (9.9)	1 (0.4)
Superficial siderosis of central nervous system	0	1 (2)	3 (3.3)	5 (2)	1 (0.6)	0
Cerebral microhemorrhage (ARIA-H)	0	2 (3.9)	0	8 (3.2)	2 (1.2)	0
Infusion related reaction	0	0	0	5 (2)	4 (2.5)	2 (0.8)
Atrial fibrillation	1 (1.9)	0	0	2 (0.8)	2 (1.2)	0
Hemorrhagic transformation stroke	1 (1.9)	1 (2)	0	0	0	0
Hallucination/Hallucination visual	1 (1.9)	0	1 (1.1)	1 (0.4)	0	0
Confusional state	0	0	0	2 (0.8)	0	1 (0.4)

Reviewer created using the ISS ADAE dataset, by Study ID= BAN2401-G000-201,SAFFL=Y, , TRTEMFL = Y, Action taken with study treatment = drug withdrawn, grouped on USUBJID, dictionary derived term, and actual treatment for period 01, and tabulated for actual treatment for period 01 and dictionary derived term.

Narratives of discontinuations by dictionary derived term that occurred in at least 2 participants in the LEC arm compared to the placebo arm are summarized below.:

ARIA

There were 56 discontinuations due to ARIA. There were 47 discontinuations due to ARIA-E (per protocol). One participant (b) (6) discontinued due to cerebral microhemorrhages with a concomitant cerebral hemorrhage > 1 cm). See Sections 12.1.2 and Section 7.5.2 for narratives.

Infusion Related Reactions and Drug Eruptions

Narratives for infusion related reactions and drug eruption are provided under Section 7.5.2 and 7.5.3.

Atrial fibrillation

Five participants on lecanemab who discontinued due to atrial fibrillation (b) (6) . Two (b) (6) are described under Section 7.4.2 SAEs. Discontinuations in majority of participants with TEAE of atrial fibrillation were due to starting prohibited medications (anticoagulation) in the Core study. Most participants had underlying risk factors for atrial fibrillation including cardiovascular disease and advanced age and I could not identify a clear role of study drug in these cases.

Hemorrhagic transformation stroke

Two participants discontinued due to dictionary derived term of hemorrhagic transformation of a stroke (b) (6) Participant (b) (6) discontinued due to being started on warfarin per protocol for stroke prevent (See Section 12.1.2 for narrative), and participant (b) (6) was discontinued per protocol due to superficial siderosis.

Hallucination/Hallucination visual

Three participants were discontinued due to dictionary derived term hallucination (b) (6) or hallucination, visual (b) (6) None had ARIA, and the events of hallucination appeared to be related to underlying AD rather than related to study drug.

Confusional state

Two participants experienced confusional state (b) (6) within days after the third dose of study drug. Both participants had an infusion related reaction after the first dose of study drug but not on the 2 subsequent doses. Participant (b) (6) also had episode of confusional state prior to starting study medication. Participants, who both happened to be at the same study site, were discontinued from study due to confusion. As confusion is commonly seen in participants with AD, and given that one of the participants had pre-existing confusion, I cannot identify a clear role of study drug in these cases. Neither had ARIA preceding the confusion.

Acute Kidney Injury (b) (6) and Complete AV block (b) (6) that led to study discontinuations are described under Section 12.1.2 Death and SAE Narratives for Study 201

Macrohemorrhage (Cerebral Hemorrhage > 1 cm in diameter)

(b) (6) had a cerebral hemorrhage > 1 cm and is described in Section 7.5.2.

Drug eruption

Participant (b) (6) on LEC5-BW, who was discontinued due to a drug eruption, is described under Section 7.5.4 Hypersensitivity Reactions.

Seizure

Participant (b) (6) on LE10-M was discontinued due to a seizure due to electrolyte abnormalities and brain surgery. I could not identify a role of study drug.

201 OLE

There were 9 discontinuations due to adverse events listed in the 120-Day updated narratives for 201 OLE. Two AEs occurred in the same participant. AEs in 7 participants occurred within 30 days of last study drug administration, and 2 occurred beyond 30 days of last dose of study drug administration.

The 7 (3.9%) AE-related study discontinuations occurring within 30 days of study drug administration were due to the dictionary derived terms: pancytopenia (b) (6), metastatic breast cancer (b) (6), road traffic accident and subdural hemorrhage (b) (6) cervical vertebral fracture (b) (6) infusion related reaction (b) (6), neuroendocrine carcinoma (b) (6) and aggression (b) (6)

I reviewed the narratives for the two discontinuations that occurred after 30 days after study drug administration. Both of these narratives (b) (6) which were deaths, are described under Section 7.4.1 Deaths. I could not identify a role of study drug in these cases.

Study 104
There were no discontinuations in Study 104. Study drug interruption occurred in two participants (b) (6) (described under Section 7.4.2) and participant (b) (6) who had had an event of atrial fibrillation and ECG ST segment elevation.

Study 101

There were 5 discontinuations from Study 101. Three due to participant choice (b) (6) and one lost to follow up (b) (6). One participant (b) (6) was diagnosed with unresectable pancreatic cancer approximately one month after completing all four doses of study drug. Given the short duration of exposure to study drug, I cannot identify a clear role of study drug in the diagnosis of pancreatic cancer.

Study 301
The applicant provided an updated listing of TEAEs by preferred term for all discontinuations in Study 301 Core and 301 OLE, blinded to study drug with the 120-Day update. I reviewed these listings and blinded narratives when available, and did not identify a new safety signal. Given that these listings and narratives are blinded to study drug, summaries and selected narratives for discontinuations for 301 CORE and OLE will not be discussed in more detail and can be found in Section 12.1.3.

Study 303
There have been no discontinuations in study 303 so far.

7.4.1.Significant Adverse Events

Overall, the evaluation of significant AEs did not identify a new safety signal. Most TEAEs were mild or moderate, with approximately 8-9 % considered severe in the combined lecanemab arms and placebo (Table 23)

In Study 201 Core, the preferred terms for the severe AEs with the highest frequency were

ARIA-E, cerebral microhemorrhage (ARIA-H) of central nervous system that each occurred in approximately 1.9 % of LEC10-BW treated participants and in none of the placebo-treated participants.

Of note is that none of the infusion reactions were rated as severe.

The applicant defined Adverse events for Study 201 Core as follows:

AEs were graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions were as follows:
Mild Discomfort noticed, but no disruption of normal daily activity
Moderate Discomfort sufficient to reduce or affect normal daily activity
Severe Incapacitating, with inability to work or to perform normal daily activity

Table 23 Incidence of a Participant Experiencing a TEAE by Severity in Study 201- Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Mild	43 (82.7)	43 (84.3)	76 (82.6)	222 (87.7)	123 (76.4)	190 (77.6)
Moderate	27 (51.9)	24 (47.1)	45 (48.9)	134 (53)	71 (44.1)	123 (50.2)
Severe	7 (13.5)	2 (3.9)	12 (13)	17 (6.7)	16 (9.9)	20 (8.2)

Reviewer created by the reviewer using ISS ADAE, Study ID=BAN2401-G000-201; SAFFL=Y; TRTEMFL=Y; Grouped by USUBJID, Severity/Intensity, Actual Treatment in Period01; Tabulate by Severity and Actual Treatment in Period 1 (Reassigned order of dose)

In the placebo-controlled period of Study 201, the most frequent severe TEAEs were ARIA-E (Table 24). The TEAE severity rating was based on the clinical judgement of the investigator based on the functional impact of the TEAE. The TEAE severity rating did not always match the radiographic severity rating of an ARIA event.

Table 24 Severe TEAEs occurring in > 2 participants in all LEC arms and at higher incidence compared to placebo in 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Amyloid related imaging abnormality-oedema/effusion	0	0	0	2 (0.8)	3 (1.9)	0
Cerebral microhemorrhage (ARIA-H)	0	0	0	0	2 (1.2)	0
Headache	0	0	0	0	2 (1.2)	0
Chronic obstructive pulmonary disease	0	0	0	1 (0.4)	1 (0.6)	0
Nephrolithiasis	0	0	0	1 (0.4)	1 (0.6)	1 (0.4)

Transient ischemic attack	0	0	0	1 (0.4)	1 (0.6)	0
Agitation	0	0	2 (2.2)	0	0	0
Dyspnea	1 (1.9)	0	1 (1.1)	0	0	0
Muscle spasms	0	1 (2)	0	1 (0.4)	0	0

Reviewer created using ISS ADAE, Study ID= BAN2401-G000-201,SAFFL=Y, TRTEMFL = Y; Severity/Intensity=Severe, Grouped by USUBJID, Dictionary Derived Term, Actual Treatment in Period01; Tabulate by Dictionary Derived Term and Actual Treatment in Period 1 (Reassigned order of dose).

During the OLE period, of the 908 TEAEs, 613 (65.5%) were mild, 268 (29.5%) were moderate and 27 (2.9%) were severe (Table 25)

Table 25 Severe TEAEs by Dictionary Derived Term in the 201 OLE Study

Dictionary Derived Term	Number of participants with severe TEAE N=180 (n)
Acute kidney injury	2
Cervical vertebral fracture	2
Hip fracture	2
Myocardial infarction	2
Acute myocardial infarction	1
Adenocarcinoma of colon	1
Aortic valve stenosis	1
Constipation	1
Craniofacial fracture	1
Decubitus ulcer	1
Fall	1
Gastroenteritis	1
Hiccups	1
Infusion related reaction	1
Nightmare	1
Post procedural hypotension	1
Product administration error	1
Small intestinal obstruction	1
Spinal cord injury	1
Spinal stenosis	1
Syncope	1
Tooth infection	1
Urinary tract infection	1

Reviewer created using the 120-day updated ISS ADAE dataset, Study ID= BAN2401-G000-201-OLE SAFFL=Y, TRTEMFL = Y, Severity/Intensity=Severe, grouped by USUBJID, dictionary derived term, tabulated by dictionary derived term.

7.4.2. Treatment Emergent Adverse Events and Adverse Reactions

In the placebo-controlled portion of the 201 Core Study, there was no imbalance in the incidence of TEAEs in the LEC10-BW group (86%) compared to placebo (87%). The most commonly reported TEAEs in the LEC10-BW (incidence at least 10% and at least 2% greater than placebo) were infusion related reactions (20% in LEC10-BW vs 3% in placebo), ARIA-E (10% in LEC10-BW vs 1% in placebo), and headache (14% in LEC10-BW vs 10% in placebo). The incidence of infusions reactions and of ARIA-E in the 201 OLE were comparable to the incidence of those reactions in the 201 Core Study.

Randomization of Apo ε4 carriers to the LEC10-BW group was halted due to the observed higher risk of ARIA-E in that group. Only 49/161 (30%) participants randomized to LEC-10 BW were ApoE 4 carriers, compared to 174/245 (71%) in the placebo group, and compared to an estimate of approximately 30-70 % in the general population in individuals with AD.[9] Additionally, duration of exposure to study drug was shorter for ε4 carriers in the LEC10-BW arm (on average 247 days for ApoE homozygotes (n=10), 1177 days for ApoE heterozygotes (n=39), and 7015 days for noncarriers (n=112)) which could also have influenced the TEAEs.

Therefore, the TEAEs observed in 201 Core at the proposed dose may not accurately represent what may be observed in the general population, particularly with respect to the risk of ARIA-E that may be underrepresented as a TEAE in the data below. Please refer to Section 7.5.1 of this review for a more detailed discussion of ARIA.

In calculation of the risk difference between the proposed dose arm and the placebo group in the incidence of TEAEs the approach in this review includes rounding up the incidence to no decimal points, and then obtaining the risk difference based on rounded up incidence.

Placebo-Controlled 201 Core Study

In the 201 Core Study there was no imbalance overall in the incidence of participants experiencing at least 1 TEAE in the LEC10-BW group compared to participants who received placebo.

There were a total of 762/854 (89.3%) participants who had at least one TEA during Study 201 Core (Table 26).

Table 26 Number of participants with at least 1 TEAE per treatment arm in Study 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
TEAEs	46 (88.5)	47 (92.2)	80 (87)	237 (93.7)	138 (85.7)	214 (87.3)
Severe	7 (13)	2 (4)	12 (13)	17 (7)	16 (10)	20 (8)

[9] Ward A, et al: Prevalence of Apolipoprotein E4 Genotype and Homozygotes (APOE ε4/4) among Patients Diagnosed with Alzheimer's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2012;38:1-17.

Serious Deaths	8 (15) 2 (4)	4 (8) 0	16 (17) 1	29 (11) 1	21 (13) 0	42 (17) 2
Discontinuations	7 (13)	4 (8)	10 (11)	47 (19)	24 (15)	14 (6)
Drug interruption	8 (15)	5 (15)	15 (10)	20 (8)	19 (12)	36 (15)

This table was created using the ISS ADAE dataset selecting for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y. Subsets were created separately for serious event=yes, subject death flag=yes, or action taken with study drug = drug withdrawn or drug interrupted, grouped by USUBJID and actual treatment for period 01 and then tabulated by treatment arm.

The most common TEAEs by primary organ system occurring at a higher incidence in the proposed arm vs the placebo arm was Injury, Poisoning and Procedural Complications (41 % vs 31 %) and Nervous System Disorders (41 % vs 36 %) (Table 27).

Table 27 Incidence of TEAEs occurring at least once by treatment arm based on primary organ system with frequency of ≥ 2 % in the proposed dose arm and ≥ 2 % higher than placebo[10]

Primary Organ System	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Injury, poisoning and procedural complications	14 (27)	21 (41)	37 (40.)	110 (44)	66 (41)	77 (31)
Nervous system disorders	22 (42)	15 (29)	45 (49)	106 (42)	66 (41)	88 (36)
Renal and urinary disorders	4 (8)	4 (8)	8 (9)	18 (7)	15 (9)	15 (6)
Blood and lymphatic system disorders	3 (8)	2 (4)	3 (3)	12 (5)	10 (6)	11 (4)

Reviewer created using the ISS ADAE dataset (submitted on 06/08/2022, which added one more number participant (b) (6) *with subdural hemorrhage under injury, poisoning and procedural complications compared to the originally submitted ADAE dataset) Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y, grouped on USUBJID, Primary Organ System, and actual treatment for period 01.*

The most commonly reported TEAEs in Study 201 Core observed greater than 10 % incidence on the LEC10-BW arm compared to placebo were infusion related reactions, ARIA-E and headache (**Table 28**).

[10] *When creating TEAE tables, TEAEs are first selected for having an incident of > 2 % in the LEC10-BW group without rounding up, then selected for having a 2 % higher frequency than placebo based on rounded up incidence.*

Table 28 TEAEs by Preferred Term with an incidence ≥ 2% in the proposed dose arm and ≥2% greater than placebo in 201 Core[10]

Dictionary Derived Term	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Infusion related reaction	3 (6)	4 (8)	11 (12)	59 (23)	32 (20)	8 (3)
Amyloid related imaging abnormality-edema/effusion	1 (2)	1 (2)	3 (3)	25 (10)	16 (10)	2 (1)
Headache	8 (15)	4 (8)	17 (19)	41 (16)	22 (14)	25 (10)
Cough	1 (2)	2 (4)	4 (4)	11 (4)	14 (9)	12 (5)
Diarrhea	5 (10)	7 (14)	12 (13)	16 (6)	13 (8)	12 (5)
Cerebral microhemorrhage (ARIA-H)	2 (4)	7(14)	10 (11)	18	9 (6)	11 (4)
Atrial fibrillation	1 (2)	0	2 (2)	3 (1)	6 (4)	3 (1)
Hematuria	1 (2)	1 (2)	1 (2)	6 (2)	6 (4)	5 (2)
Paresthesia	0	1 (2)	0	2 (1)	5 (3)	1 (<1)
Dental caries	1 (2)	0	1 (1)	1 (<1)	5 (3)	1 (<1)
Lymphopenia	0	0	1 (1)	4 (2)	4 (2)	1 (<1)
Tooth fracture	1 (2)	0	0	2 (1)	3 (2)	0
Dysuria	0	1 (2)	1 (2)	0	3 (2)	0
Orthostatic hypotension	0	0	1	2 (1)	3 (2)	1 (<1)
Myalgia	0	0	0	5 (2)	3 (2)	1 (<1)
Infusion site extravasation	1 (2)	1 (2)	3 (3)	1 (<1)	3 (2)	1 (<1)
Glycosuria	0	1	0	1 (<1)	3 (2)	1 (<1)
Asthma	2 (4)	0	0	2 (0)	3 (2)	1 (<1)

Reviewer created using the ISS ADAE dataset, selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y, grouped on USUBJID, Dictionary derived term, and actual treatment for period 01, then tabulated by Actual treatment for period 01 and dictionary derived term.

When analyzing the frequency of TEAEs in those without ARIA or cerebral hemorrhage in 201 Core, the majority of the TEAEs occurred with an incidence similar to that of the entire group, suggesting that most of the TEAEs captured in **Table 29** are not related to ARIA or cerebral hemorrhage.

Table 29 TEAEs by Preferred Term in participants without ARIA or cerebral hemorrhage greater than 1 cm with an incidence of ≥ 2 % in the LEC10-BW arm and 2 % higher than placebo in 201 Core[10]

	LEC10-BW N=140 N (%)	Placebo N=232 N (%)
Infusion related reaction	31 (22)	8 (3)
Headache	18 (13)	24 (10)
Cough	14 (10)	12 (5)
Diarrhea	10 (7)	11 (5)
Hematuria	6 (4)	5 (2)
Dental caries	5 (3)	1 (<1)
Paresthesia	5 (3)	1 (<1)
Atrial fibrillation	5 (3)	3 (1)
Lymphopenia	4 (3)	1 (<1)
Orthostatic hypotension	4 (3)	1 (<1)
Herpes Zoster	3 (2)	1 (<1)
Glycosuria	3 (2)	1 (<1)
Myalgia	3 (2)	1 (<1)
Infusion site extravasation	3 (2)	1 (<1)
Tooth fracture	3 (2)	0
Dysuria	3 (2)	0

Reviewer created using the ISS ADAE dataset selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y, excluding participants with dictionary derived terms of amyloid related imaging abnormality edema/effusion, brainstem, cerebellar or cerebral microhemorrhage, cerebral hemorrhage, and superficial siderosis of the nervous system. Grouped on USUBJID, Dictionary derived term, and actual treatment for period 01, and tabulated by Actual treatment for period 01 and dictionary derived term. Denominator reflects number of participants without ARIA or cerebral hemorrhage.

The reason for higher incidence of cough, diarrhea, dental carries, atrial fibrillation, hematuria and lymphopenia in those receiving study drug is not clear. Some of the difference in risk was driven by very small numbers, such as TEAEs occurring in one or two participants and the clinical significance of these findings is unclear. However, I note that while 2 % (4/161) of participants had a PT of Lymphopenia compared to 0 in the placebo arm, another 1 % (2/151) in the proposed dose arm had a PT of Lymphocyte Count Reduced (data not shown). Additionally, in those receiving the proposed dose a post-infusion decrease in lymphocytes after the first infusion was observed (See Section 7.4.3 Laboratory Findings).

Using applicant provided tables in the 201 Core Clinical Study Report, I examined baseline imbalances which may have led to some of the observed differences in these TEAEs between placebo and the LEC10-BW arm for TEAEs that that had a risk difference of 4 % or higher in table 28. For the TEAE of cough, while the prevalence of participants on medications that could cause cough, and prevalence of System Organ Class Respiratory, Thoracic and Mediastinal disorders was comparable between the placebo and LEC10-BW arm, the LEC10 BW arm had a slightly higher incidence of those with a history of asthma, chronic obstructive pulmonary disease and cough, at baseline which may have contributed to the higher incidence of cough in the LEC10-BW group. I could not identify any notable baseline differences that could lead to the

observed differences in the incidence of atrial fibrillation and diarrhea between the placebo and the proposed dose arm.

Additional analysis using medical query groups, confirmed some of the above observations (Table 30). For example, higher incidence of lymphopenia in the study drug group compared to placebo was confirmed when using a medical query term that combined lymphopenia and lymphocyte count decreased with an incidence rate in proposed dose and placebo arms of 6/161 (3.7 %) vs 1/161 (0.4 %). (Table 30). This also is observed during analyses of laboratory data and will be discussed under the Laboratory Findings Section 7.4.3. Similarly, in review of chemistry values, I also noticed a slightly higher incidence of high post-baseline glucose values in the proposed dose arm compared to placebo. Findings consistent with this are observed in the Medical Query Group analysis of TEAEs (Table 30) showing a higher incidence of the Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones ODE-1 MQG in the proposed dose arm compared to placebo.

Table 30 TEAEs by Medical Query Groups occurring at least once in a participant with an incidence of 2% or higher in the LEC10-BW arm 2 % or higher compared to placebo in Study 201 Core[10]

FDA Medical Query Group	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Local administration reactions FDA N	5 (10)	5 (10)	18 (20)	66 (26)	36 (22)	12 (5)
Cough FDA N	1 (2)	2 (4)	4 (4)	13 (5)	16 (10)	13 (5)
Hemorrhage FDA N	12 (23)	14 (27)	21 (23)	50 (21)	29 (18.6)	37 (16)
Lymphopenia MQG	0 (0)	1 (2)	1 (1)	4 (2)	6 (4)	1 (<1)
Paresthesia FDA N	(0)	1 (2)	1 (1.1)	6 (2)	6 (4)	2 (1)
Diarrhea FDA N	5 (10)	7 (14)	12 (13)	16 (6)	13 (8)	13 (5)
Irritability FDA N	3 (6)	2 (4)	7 (8)	10 (4)	8 (5)	6 (2)
Headache FDA B	9 (17)	4 (8)	18 (20)	43 (17)	23 (14)	30 (12)
Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones ODE-1	1 (2)	1 (2)	0 (0)	1 (<1)	8 (5)	3 (1)
MQG: infection, viral	3 (6)	5 (10)	8 (9)	19 (8)	10 (6)	10 (4)
Supraventricular tachycardia ODE-1	1 (2_	3 (6)	1 (1)	8 (3)	8 (5)	6 (2)
Myalgia FDA B	1 (2)	1 (2)	8 (9)	14 (5)	10 (6)	11 (4)
Hematuria-ODE-1	1 (2)	1 (2)	1 (1)	7 (3)	6 (4)	5 (2)
Bronchospasm	2 (2)	0	0	2 (1)	3 (2)	1 (<1)

Created by reviewer using ISS ADAE dataset, selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL = Y and joined with FDA Medical Query Groups (MQG) , grouped by USUBJID, MQG, and actual treatment for period 01, and tabulated by Actual treatment for period 01 and MQG See Table 82 *for a list of preferred terms and number of participants that fall under each MQG.*

The preferred terms under the FDA Hemorrhage N that had a higher incidence in the LEC10-BW arm and were driving the increased incidence under this MQG in the LEC10-BW arm compared to the placebo arm were cerebral microhemorrhage (ARIA-H) (5.6 % vs 4.5 %), contusion (4.9 % vs 2.9 %), hematuria (3.7 % vs 2 %), ecchymosis (1.2 % vs 0.4 %), hematoma (0.6 % vs 0.4 %) and the following preferred terms which had an incidence of 0.6 % in the LEC10-BW compared to 0 in the placebo arm: blood loss anemia,, cerebral hemorrhage, diverticulum intestinal hemorrhagic, hemorrhoidal hemorrhage, infusion site bruising, petechiae, vessel puncture site bruise. The incidence of having PTs that fall under the Hemorrhage FDA N MQG, excluding ARIA-H (brainstem microhemorrhage, cerebellar microhemorrhage and, cerebral microhemorrhage) and cerebral hemorrhage, was 21/161 (13 %) at the proposed dose, versus 26/245 (11 %) in the placebo arm.

There were only 2 preferred terms under FDA Irritability N both of which had a 2 % or higher incidence at the LEC10-BW arm and together were driving the increased incidence in the LE10BW arm compared to placebo; these were agitation 5/161 (3%) at the proposed dose vs 4/245 (2%) on placebo, and irritability 3/161 (2%) at the proposed dose vs 2/245 (0.8 %) on placebo.

The Infection Viral MQG, included the following preferred terms that had a higher incidence in the LEC10-BW arm compared to placebo, influenza (2. 5 % vs 0.8 %), herpes zoster (1.2 % vs 0.4 %), and viral pharyngitis (0.6 % vs 0).

The difference in incidence for myalgia, hematuria and bronchospasm was driven by small number of participants in each group.

The incidence of having one or more participant having a PT falling under the “Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones” MQG was higher in those receiving the proposed dose arm compared to placebo. This may have been driven by the fact that a higher percentage of participants in the full analysis set in the LEC10-BW arm compared to placebo had Type 2 Diabetes (13 % % vs 8 %) and obesity (3 % vs 1 %) at baseline. This potential signal for hyperglycemia will be evaluated in the 301 Core study with a larger dataset.

The incidence of Designated Medical Events (Table 31) were too small to reach any conclusions, but did not appear to occur at a consistently higher incidence in the drug arms. Of those that had narratives (see section 7.4.2 SAE), I did not identify a clear role of the study drug.

Table 31 Designated Medial Events by dictionary derived term occurring at least once in a participant with an incidence of 2% or higher in the LEC10-BW arm and 2 % or higher compared to placebo in Study 201 Core[10]

Designated Medical Events by preferred term	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Bilateral deafness	0	0	0	1 (0.4)	0	0
Unilateral blindness	0	0	1 (0.6)	0	0	1 (0.4)
Hepatic failure	0	0	1 (0.6)	0	0	0
Prolonged QT syndrome	1 (2)	0	0	0	1 (0.6)	2 (0.8)
Seizure/ Focal dyscognitive seizure	0	0	1	1 (0.4)	0	1 (0.4)
Acute kidney injury	0	1 (2)	1 (1.1)	0	0	0

Reviewer created table using the MedDRA Based Adverse Event (MAED) program to analyze the ISS ADAE dataset, selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL =Y. A participant who had a seizure in the setting of ARIA-E in the LEC10-BW group is not captured in this table, as the applicant did not include clinical symptoms of ARIA-E as separate TEAEs in the Adverse Events Dataset.

201 OLE

In Study 201 OLE 170/180 (94.4%) participants experienced a treatment emergent AE. Infusion related reactions were reported in 37 (20.6 %) of the participants, and ARIA-E in 14 (8 %) (**Table 33**), both of which are comparable to the incidence of 20 % and 10 % respectively for infusion related reactions and ARIA in the 201 Core study. Falls occurred in 20% of participants in Study 201 OLE; a greater incidence of falls was not observed in 201 Core for LEC10-BW (9%) compared with placebo (13%), and the incidence of falls in Study 201 OLE is within the 29% of adults at least 65 years old in the general population reporting at least 1 fall in the previous year.[11]

Table 32 TEAEs by Primary Organ System occurring at a frequency of ≥ 5 % in Study 201 OLE

Primary Organ System	N=180 n (%)
Injury, poisoning and procedural complications	89 (49)
Infections and infestations	87 (48)

[11] Bergen G, Stevens MR, Burns ER. Falls and Fall Injuries Among Adults Aged ≥65 Years — United States, 2014. MMWR Morb Mortal Wkly Rep 2016;65:993–998. DOI: http://dx.doi.org/10.15585/mmwr.mm6537a2external icon

Nervous system disorders	79 (44)
Gastrointestinal disorders	49 (27)
Musculoskeletal and connective tissue disorders	47 (26)
Psychiatric disorders	47 (26)
General disorders and administration site conditions	36 (20)
Respiratory, thoracic and mediastinal disorders	33 (18)
Vascular disorders	32 (18)
Renal and urinary disorders	26 (14)
Investigations	25 (14)
Metabolism and nutrition disorders	25 (14)
Skin and subcutaneous tissue disorders	23 (13)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (12)
Cardiac disorders	19 (10)
Blood and lymphatic system disorders	16 (9)
Eye disorders	15 (8)
Reproductive system and breast disorders	9 (5)

Reviewer created by using the ISS ADAE dataset, selecting for Study ID= BAN2401-G000-201-OLE, SAFFL=Y, TRTEMFL =Y., grouping by unique subject ID, and primary organ system, and then tabulating by primary organ system.

Table 33 TEAEs by Dictionary Derived Term at a frequency of ≥ 5 % in Study 201 OLE

Dictionary Derived Term	N (%)
Fall	36 (20)
Infusion related reaction	37 (21 %) *
Urinary tract infection	26 (14)
Cerebral microhemorrhage (ARIA-H)	21 (12)
Nasopharyngitis	18 (10)
Headache	16 (9)
Upper respiratory tract infection	15 (8)
Amyloid related imaging abnormality-oedema/effusion (ARIA-E)	14 (8)
Hypertension	14 (8)
Anxiety	13 (7)
Arthralgia	13 (7)
Back pain	12 (7)
Dizziness	11(6)
Skin laceration	11 (6)
Basal cell carcinoma	10 (6)
Contusion	10 (6)
Depression	9 (5)
Nausea	9 (5)

Reviewer created using the 120-day updated ADAE dataset selected for Study-ID= BAN2401-OLE, SAFFL=Y, TRTEMFL =Y., grouping by unique subject ID and dictionary derived term and tabulating by dictionary derived term.

** This total includes 2 additional participants that the applicant identified as not being coded to the PT of "infusion related reactions" but were categorized as infusion related reactions in the AE case report from (CRF) from the investigator (PTs were pyrexia and injection site joint erythema).*

Table 34 TEAEs occurring in > 10 % in the 201 OLE by Medical Query Group

Medical Query	N (%)
Hemorrhage FDA N	43 (24)
Intracranial hemorrhage (includes hemorrhagic stroke, SAH, SDH)	25 (14)
Local administration reactions FDA N	39 (22)
Arthritis FDA B	26 (14)
Anxiety FDA B	23 (13)
Arrhythmia FDA B	22 (12)
Arthralgia FDA B	22 (12)
Dyspepsia FDA B	21 (12)
Nasopharyngitis FDA N	21 (12)
Syncope FDA B	20 (11)
Systemic hypertension FDA N	19 (11)
Back pain FDA B	18 (10)
Malignancy FDA N	18 (10)

Reviewer Created Table using 120-day updated ISS-ADAE dataset selected for Study ID= BAN2401-G000-201-OLE, SAFFL=Y, TRTEMFL =Y., joined with FDA created medical query groups (MQG). See Table 82 for preferred terms captured in each MQG.

Additionally the following TEAEs of interest were noted in 6/180 participants: visual field defect in 3/180 ((b) (6) had visual field deficit secondary to a cerebral hemorrhage (see section 7.4.2), (b) (6) had a cerebral infarction as cause of visual field deficit, and there was no clear cause identified for visual field deficit in participant (b) (6) .), drug eruption in 1/180 (participant (b) (6) had multiple episodes of drug eruption related to study drug see Section 7.5.3), urticaria 1/180 ((b) (6) -one time occurrence of urticaria 12 days after 22nd dose with no recurrence thereafter despite continued dosing), acquired epileptic aphasia in 1/180 ((b) (6) -see narrative under SAEs, likely due to cerebrovascular disease), brain stem hemorrhage in one (verbatim term was pons microhemorrhage, and this was included in the ARIA-H microhemorrhage count), lymphopenia in 1/180 ((b) (6) -mild nonserious) and pancytopenia 1/180 ((b) (6) -serious event, see section 7.4.2 for narrative).

According to the clinical study report for Study 104, the TEAEs occurring in at least 2 participants and more frequently in the BAN2401 treatment group than in the placebo group were increased blood pressure (15.8% [3 participants] in the BAN2401 treatment group and 0% in the placebo group), atrial fibrillation (10.5% [2 participants, (b) (6)] in the BAN2401 treatment group and 0% in the placebo group), and cerebral microhemorrhage (10.5% [2 participants] in the BAN2401 treatment group and 0% in the placebo group). Of these, increased incidence of atrial fibrillation and cerebral microhemorrhages in the proposed dose arm compared to placebo were also observed in the 201 Core study. I reviewed the medical history for any risks for atrial fibrillation for (b) (6) in Study 201 Core.

I could not identify any clear risk factors for participant (b) (6), but participant (b) (6) had a past medical history of hypertension which increases risk of atrial fibrillation.

Reviewer Comment: It is notable that similar to the observation in the 201 Core study, in the 104 study, atrial fibrillation was also observed at higher frequency in the study drug arms compared to placebo, although the numbers are small.

7.4.3. Laboratory Findings

The main finding related to laboratory assessments in Study 201 Core is that those receiving lecanemab are more likely to experience a decrease in lymphocytes, and an increase in neutrophils after the first infusion. In 201 Core, laboratory assessments were conducted on blood collected 4 hours following the first infusion, but in subsequent assessments were conducted on blood collected prior to infusion, so it is not known if the observed changes occur after each infusion.

While for the majority of participants this normalizes, in subsequent infusions, a small percentage of participants still had lower lymphocyte counts at the end of the study. I reviewed participants who had a TEAE of lymphopenia, and did not identify a higher incidence of infections, or other clinical symptoms or complications related to these hematological changes.

For the analysis of laboratory findings, I reviewed the mean and mean change from baseline by visit, outlier shift analysis by visit provided by the applicant, and outlier analyses of potentially clinically significant changes in the applicant's response to an IR dated August 23, 2022, limiting findings to within 30 days after the last dose (week 79, early termination visit if terminating early or at an unscheduled visit if within 30 days of last dose). I also reviewed TEAEs belonging to the system organ classes (SOC) investigation related to laboratory findings.

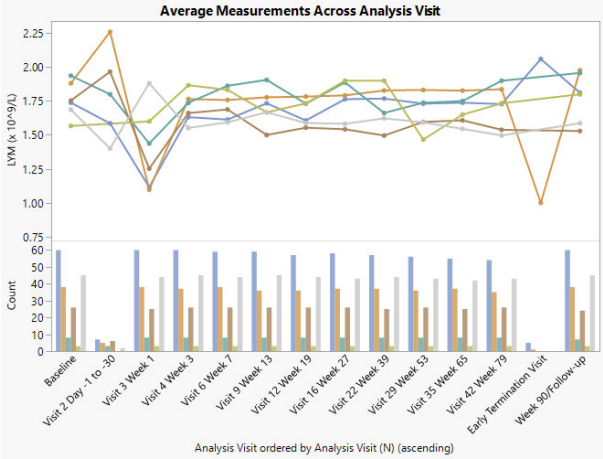
Hematology

Although not associated with clinically adverse outcomes, there were transient, dose-dependent decreases in lymphocytes and increases in neutrophil and leukocyte counts in lecanemab treated groups compared to placebo that were noted after the first infusion. These changes may be related to an infusion reaction.

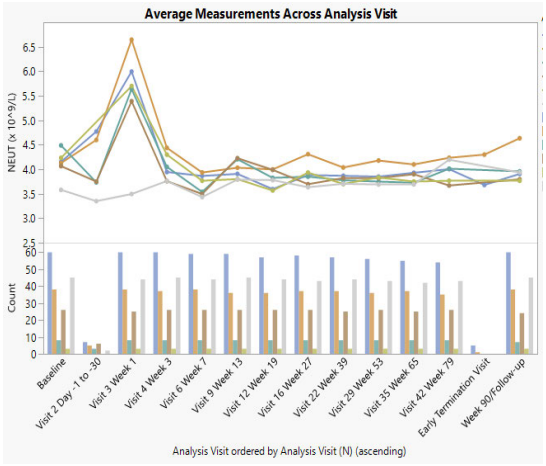
At baseline the mean hematology values appeared to be comparable between groups. Four hours after the first infusion, there appeared to be a dose dependent decline in all lecanemab arms in lymphocyte count, and an increase in neutrophil count and leukocyte count compared to placebo (Figure 1A and 1B, Visit 3/week 1) The neutrophil/leukocyte ratio increased at this time point (data not shown) suggesting that the increase in the neutrophil count is not merely a result of increase in leukocyte count.

Figure 1A and 1B. Mean hematology values by analysis visit by treatment arms in 201 Core

1A, Lymphocyte Count



1B. Neutrophil Count



Based on applicant Table 14.3.4.1.1 Mean and Mean Change from Baseline by Visit, the absolute mean change from baseline at week 1 for the proposed LEC10-BW compared to placebo was -0.7 vs 0.2 (x 10^9/L) for mean lymphocyte count, 2 vs -0.1 (x 10^9/L) for neutrophil count and 1.1 vs 0.1 (x 10^9/L) for leukocyte count. (Table 34, Figure 1). Smaller transient declines in monocyte count and platelet count compared to placebo were observed as well. Most of these changes were transient and the mean values normalized for the majority of participants at subsequent visits.

Based on applicant Table 14.3.4.1.2.1 Laboratory Hematology Results - Shift from Baseline to Postbaseline Visits, of the participants in the LEC10-BW arm who had assessments for lymphocytes at visit 3 (week 1) post-infusion, 59/155 (38 %) had a value that was less than 0.9 $x10^9$/L (reference lower limit) at that visit compared to 4/233 (1.7%) in the placebo arm. Similarly, based on the same applicant table of the total 156 participants in the LEC10-BW arm who had a hematology assessment for absolute neutrophil count at visit 3, post infusion 35/156 (22 %) had an elevated neutrophil count value that was higher than 7.9 x $x10^9$/L (reference upper limit) compared to 0.9% (2/233) in the placebo arm although hematologic parameters fluctuated throughout the study, the changes were transient and were observed primarily after the first infusion.

In the LEC10-BW arm the lowest observed lymphocyte count was 0.1x10^9/L (reference lower limit: 0.9 x10^9/L), platelet was 92x10^9/L (reference lower limit 125x10^9/L), Hgb was 86 g/L (reference lower limit 110 g/L) and the highest recorded neutrophil count was 12.8 x10^9/L (Reference upper limit: 7.9x10^9/L).

Since the hematology values were only measured pre-dose at subsequent visits in the 201 Core study, whether there were transient changes in hematology values within hours after each subsequent infusion is unknown.

Based on applicant Table IR39-4-2 submitted on September 6, 2022, the proposed dose arm (LEC10-BW) had a higher incidence of participants with normal baseline values who at postbaseline assessments had high leukocyte and neutrophil counts, and low lymphocyte and platelet counts, based on reference range values. The changes were mostly driven by the changes observed right after the first infusion and seemed dose dependent. The most robust difference in incidence between the proposed dose arm and placebo was observed in lymphocyte and neutrophil values; the incidence of low lymphocytes was 41.5 % for the LEC10-BW arm compared to 9.2 % for placebo. The incidence of high neutrophils was 24.4 % for the LEC10-BW arm compared to 9.2 % for placebo (Table 34).

Table 34 Abnormal Laboratory Post-Baseline with Normal Baseline Hematology values at higher incidence in the proposed arm versus placebo in the 201 Core - Safety Analysis Set

	LEC10-BW N=161 N (%)	Placebo N=245 N (%)
Lymphocyte Count Low (<0.9 x10^9/L)	66/159 (41.5)	22/240 (9.2)
Neutrophil Count, High (>7.9 x x10^9/L)	38/156 (24.4)	22/239 (9.2)
Leukocytes High (>11 x10^9/L)	15/156 (9.6)	12/239 (5.0)
Platelet, Low (< 125x10^9/L)	11/156 (7.1)	9/236 (3.8)
Hemoglobin, Low (< 110 g/L)	25/154 (16.2)	33/233 (14.2)
Hematocrit, Low (<37 %)	20/158 (12.7)	29/237 (12.2)

Reviewer created based on sponsor Table IR39-4-2 which includes laboratory collected at any postbaseline visit during the period starting after the first dose of study drug and within 30 days after the last dose. Subjects with at least one postbaseline laboratory measurement meeting cut point criteria are counted only once for each row. Low is any value <Lower Limit of Normal. High is any value > Upper Limit of Normal. denominator for each value indicates the number of subjects with normal baseline and at least one postbaseline data; this number is used to calculate percentages within each laboratory parameter. Program: ./ban2401/iss/biostats/fda/dev/pg/tables/T_ir39_4_2.sas

In response to an IR dated October 17, 2022, the applicant repeated the analysis for abnormal laboratory values post-baseline with normal baseline hematology values this time excluding the week 1 post infusion time point. With this analysis, at the proposed dose arm 6.3 % of participants at the LEC10-BW had a low lymphocyte count, compared to 8.4 % in the placebo group. The incidence of high neutrophil count was 4.5 % at the proposed dose arm and 8.4 % in the placebo arm suggesting that the original findings in Table 34 may be driven by the reduced lymphocyte count and increased neutrophil count observed after the first infusion. This said, the higher incidence of postbaseline low platelet and hemoglobin values at the proposed dose arm versus placebo persisted after excluding the first visit: 5.8 % vs 3.8 % for low postbaseline platelets, this reduction did not appear to be dose dependent anymore after excluding the first visit, and 16.2 % versus 13.9 % for hemoglobin values, which did not appear to be dose dependent both with and without including the first visit.

In the 201 Core Study the last dose of study drug administration was at week 77. Of the participants who had normal lymphocyte count at baseline, at week 1 post infusion 3/234 (1 %) of the placebo arm had low lymphocytes compared to 58/155 (37 %) at the proposed dose arm. At week 79 (2 weeks after the last study dose), 2/181 (1 %) placebo participants, and 4/87 (5 %) in the LEC10-BW group had low lymphocyte counts, and at the week 90 follow up visit, 7/197 (4 %) in the placebo group, and 2/131 (1%) in the LEC10-BW had low lymphocyte counts. These findings suggest that the higher incidence of low lymphocyte counts normalized in a majority of participants by the end of the study. Based on applicant Table IR 39-3-2, submitted in response to an IR from the agency, at the last treatment emergent hematology value, there were 5 participants in the PBO group, 1 in the LEC2.5 BW group, 3 in the LEC5-M group, 5 in the LE10-M, and 1 in the LEC10-BW group who a lymphocyte value < 750 cells/uL.

Of the TEAEs of laboratory abnormalities (Table 36) the highest incidence occurred for reduction in lymphocyte count (Preferred Term: Lymphopenia or Lymphocyte Count Reduced). In the LEC10-BW there were 6 participants (4%), followed by 4 participants (2%) in the LE10-M arm, 1 participant (2%) in the LEC5-M arm, 1 participant (1%) in the LEC5 BW arm, and 1 participant (0.6%) in placebo and no participants in the LEC2.5 BW arm.

I reviewed the narratives of the 12 participants who had a TEAE of Lymphopenia or reduction in Lymphocyte Count.

9/12 participants had a single occurrence of lymphocyte count that was below the lower limit of normal (LLN), post-infusion on Study Day 1 which normalized on ~ Study Day 15 and did not recur with continued study drug administration during 201 Core. Three participants had fluctuating levels of lymphocyte counts, with recurrence of lymphocyte count lower than the lower limit of normal at different time points during the study, but all normalized either by the end of study or at the follow up visit after the end of study. The majority of participants with a TEAE involving reduced lymphocyte count had elevation of neutrophils post infusion on Study Day 1 compared to baseline as well. These values remained in the normal range for the majority of the participants but was above the upper limit of normal (ULN) for 3 participants. One of these participants (b) (6) had both elevated neutrophil count and leukocyte count above the ULN, both of which remained elevated after week 1 (b) (6). Participant (b) (6) also had elevation above the ULN in leukocyte count which normalized on Study Day 15.

Three participants (b) (6) had a TEAE of lymphopenia and an infusion reaction, and one participant (b) (6) had a TEAE of lymphocyte count decreased and infusion reaction. Three had an infusion related reaction and low lymphocyte counts on Study Day 1 after the first infusion. In all 4 participants the infusion related reaction resolved on Study Day 1, and low lymphocytes resolved by Study Day 15. Participants (b) (6) and (b) (6) completed the study without recurrence of lymphopenia or infusion related reaction, and participant (b) (6) continued until she discontinued per protocol after the 9th dose of study drug due to ApoE genotype. One participant, (b) (6), had TEAE of lymphocyte count

reduced on the first Day after the first dose, and experienced an infusion related reaction on Study Day 29 with chills, rigors and lethargy. On Study Day 30 the infusion related reaction resolved with paracetamol. He withdrew consent and discontinued from the study on Study Day 37 and lymphopenia resolved on Study Day 43.

I reviewed the narratives and the ADAE datasets for the participants with a TEAE of lymphopenia to assess whether the reduction in lymphocyte count was associated with an increased risk of infection or other clinical effects. In almost all cases, the lymphocyte count returned to normal within 2 weeks, and no infection occurred within that period, with the exception of one participant, (b) (6), in whom lymphopenia occurred on (b) (6), and resolved by (b) (6) and the narrative listed an "influenza like illness" as an AE without further narrative provided that occurred on (b) (6). I also could not identify an increased risk of infection during the period of ongoing lymphopenia for the three participants in whom levels were not normalized in 2 weeks. In terms of those with low platelet count, there was one participant (b) (6) in 201 Core who had a TEAE of platelet count decreased on (b) (6), with resolution of this on (b) (6). No AEs related to this were reported. In 201 OLE one participant (b) (6) had blood loss anemia listed as an AE on (b) (6), with resolution on (b) (6) and had an AE listed of thrombocytopenia on (b) (6) Thus, it is unlikely that the event of blood loss anemia was related to the thrombocytopenia. Currently there is no evidence that the change in hematology values led lead to clinical adverse effects such as infections, higher risk of bleeding or other complications

In a response to an IR dated October 4, 2022, the applicant posited that the high neutrophil counts and low lymphocyte count observed after the first infusion are a subclinical manifestation of an infusion reaction. The applicant provided citations to support that these changes have been observed with other monoclonal antibodies.[12,13,14]. Of these studies, only one study[13]. measured the lymphocyte count post-infusion of IVIG and observed a decrease in both lymphocyte and neutrophil count. The timing of blood collection was not clear in one of the studies [14], and in another study[12] blood collection was prior to the weekly infusion, making it unclear if the decrease in lymphocyte count observed is indeed related to an infusion related reaction or not. The applicant additionally provided the following information: At any time during the study, the incidence of symptomatic infusion-related reactions was 20 % and the incidence of high neutrophils was 24 % and low lymphocytes was 42 %. On Day 1 (day of first dose) the incidence of symptomatic infusion related reactions among participants with high

[12] Sikic et al. First-in-Human, First-in-Class Phase I Trial of the Anti-CD47 Antibody Hu5F9-G4 in Patients With Advanced Cancers. Journal of Clinical Oncology. Volume 37, Issue 12.
[13] Koffman et al. Effect of high-dose intravenous immunoglobulin on serum chemistry, hematology, and lymphocyte subpopulations: Assessments based on controlled treatment trials in patients with neurological diseases. Muscle & Nerve, September 1997
[14] Glade-Bender et al. Phase I Trial and Pharmacokinetic Study of Bevacizumab in Pediatric Patients With Refractory Solid Tumors: A Children's Oncology Group Study. J Clin Oncol, 2008: 26:399-405

neutrophils was 24 % and low lymphocytes was 31 %. Conversely, on Day 1 (day of first dose) among participants with symptomatic infusion-related reactions, the incidence of high neutrophils was 31 % and low lymphocytes was 69 %.

Reviewer Comment: It is plausible, as the applicant suggested that the changes in lymphocytes and neutrophil counts observed right after the infusion are related to a transient reaction to the infusion. Whether this occurs on subsequent infusions however is unknown, as blood for analysis was not collected post dose for the remainder of 201 Core after week 1, and also not collected post dose in 201 OLE.

In the 201 OLE study, the schedule for collection of laboratory measures differed from the 201 Core. In Study 201 OLE blood collection occurred at screening, and then at weeks 3, 7, 13, 19, 27, 53, 79, 105, 131, 157, 183, 209, 235, 261 or early termination visit and follow up visit. Blood for laboratory tests was taken predose at all visits Due to this difference in laboratory value testing schedule it is unknown if participants in 201 OLE experienced the transient changes in lymphocytes, neutrophils and leukocytes similar to what was observed in 201 Core at week.

Based on the Shifts from Baseline to Lowest Post Baseline visits Table in 201 OLE of those that started with a normal baseline lymphocyte count, 29 (16%) had a low post-baseline visit at any time compared to 63 (43.8%) in the LEC10-BW group in the 201 Core Study. The lower incidence in the OLE may have been due to the later timing of the first postbaseline laboratory assessment.

The Mean at Baseline and Mean Change by Visit and Change from Baseline by Visit Tables did not show any notable decrease in the mean lymphocyte count and no notable increases in the neutrophils count, leukocyte count, or other hematology values over time.

Comparing the Shift from Baseline to Postbaseline visits for OLE and 201 Core, the percentage of individuals who started with a normal lymphocyte count, but had a low lymphocyte count at any time point between visits week 3-week 39 (inclusive) were higher in the OLE group (ranging from 5%-9%) compared to those receiving LEC10-BW in the 201 Core study (ranging from 1%-3%). The incidence was 2% at week 53 for both OLE and the LEC10-BW group, and at week 79 was 3 % in the OLE, 5 % in the LEC10-BW group and 1% in the placebo group in 201 Core. At the week 90 follow up visit (13 weeks after last dose), in 201 Core, 2 % in the LEC10-BW group, and 4% in the placebo group had low lymphocyte counts.

With the exception of those who had normal values at baseline having a higher neutrophil and leukocyte count compared to placebo at the week 1 visit post infusion in 201 Core, I could not identify any trends on follow up visits, in leukocyte or neutrophil counts in 201 Core or OLE. In the OLE study, those with normal baseline and high neutrophil count at postbaseline visits ranged from 0-3% starting at week 3, while in the 201 Core study 21 % of participants with

normal baseline had elevated neutrophil count at week 1, which after week 3 became comparable to placebo and ranged from 0-3 % for the remaining postbaseline visits.

Reviewing the hematology shift tables from baseline to the highest and lowest post baseline values (Applicant Table 14.3.4.1.2.3 and Table 14.3.4.1.2.3) in 201 OLE, the following were observed post baseline at an incidence > 10 %: high, low erythrocyte value, low hematocrit values, low hemoglobin values, low lymphocyte values. It is difficult to interpret these findings without a comparator group.

In Study 104, which is a repeated dosing study of 3 dose cohorts where 19 participants were exposed to study drug, of the participants that had normal baseline values, 2 had low lymphocyte count and low lymphocyte/leukocyte ratio, and 2 had elevated neutrophil/leukocyte ratio at day 99 all which normalized by day 155. While the blood collection schedule suggests that collection occurred 3 hours after drug administration, Table 14.3.4.1 only shows baseline, followed by visits starting with visit 43 collection time point (second drug administration), and does not include Study Day 1. I could not identify any clear trends in the mean and mean change from baseline by visit table 14.3.4.1, due to the small number of individuals in each group, and blood collection schedule that did not include assessment of post infusion blood draw on first day of infusion, which was when most hematology abnormalities were observed in the 201 Core study.

In Study 101, there was a transient reduction in lymphocyte count and increase in neutrophil count in most of the lecanemab arms on day 1, most notably in the highest two dose groups of 10 mg/kg and 15 mg/kg. These changes seemed dose dependent and became comparable to other groups by day 2. There was also a reduction in platelet count on day 1, which normalized by day 10.

Similar trends in lymphocyte and neutrophil count, and lymphocyte/leukocyte and neutrophil/leukocyte ratio were observed in the 101 MAD study, though the timing of the changes were slightly later, and these changes persisted longer at the highest dose of 10 mg/kg in the MAD study and became comparable to placebo around week 84 to 98.

One of the participants in the 101 SAD/MAD study receiving lecanemab at 10mg/kg, experienced an infusion reaction with chills, fever, tachycardia along with increased leukocyte count, and neutrophil values and reduced lymphocyte values.

Chemistry

I performed analysis of the 201 Core data using JMP Clinical Version 8 and examined average measurements across analysis visits for each Chemistry Value by study arm. I also reviewed the applicant tables for Chemistry Values for the Safety Analysis Set including, Table 14.3.4.2.1

Mean and Mean Change from Baseline by Visit, Table 14.3.4.2.2.1 Shift from Baseline to Postbaseline Visits, Table 14.3.4.2.2 Shift from Baseline to Highest Post-Baseline Value at Any Visit and Table 14.3.4.2.2.3 Laboratory Chemistry Results shift from baseline to lowest post baseline value at Any Visit. I also reviewed Table IR 39-4, and Table IR39-2-1 submitted on September 6, 2022, by the Applicant, in response to an IR by the Division sent on August 23, 2022.

I selected the following laboratory values from Table IR39-2-1 as the incidence of abnormal chemistry values were higher in the proposed arm group compared to placebo (Table 35). The interpretation of these findings is limited by the fact that the participant may have had an elevated value at one or more time point, and relatively small differences between groups.

Table 35 Participants with One or More Laboratory Value Exceeding Specified High or Low Laboratory Chemistry Values in the 201 Core - Safety Analysis Set occurring at ≥2% incidence in the proposed dose arm versus placebo

	LEC10-BW N=161 N (%)	Placebo N=245 N (%)
Potassium level > 5.5 mEq/L	28 (17.4)	35 (14.3)
Potassium level < 3.6 mEq/L	12 (7.5)	11 (4.5)
Fasting glucose level ≥ 126 mg/dL or Random ≥ 200	15 (9)	16 (6)
Calcium level <8.4 mg/dL	8 (5.0)	6 (2.4)
Protein level < 6 g/dL	39 (24.2)	38 (15.5)
Triglyceride levels > 150 mg/dL	108 (67.1)	154 (62.9)

Based on applicant table IR39-2-1. Includes laboratory tests collected at any postbaseline visit during the period starting after the first dose of study drug and within 30 days after the last dose. Subjects with at least one postbaseline laboratory result meeting specified high or low value criteria are counted only once for each lab parameter, using the worst high or worst low value.

Similar observations to Table 35 were seen in participants who started out with normal baseline values, and had values that were above ULN or below LLN at any postbaseline visit (Table 36).

Table 36 Abnormal Laboratory Post-Baseline with normal Baseline-Laboratory Chemistry Results occurring at an incidence of ≥2 % in the proposed dose arm versus placebo, 201 Core - Safety Analysis Set

	LEC10-BW N=161 N(%)	Placebo N=245 N (%)
Calcium, Low	10/159 (6)	10/236 (4)
Cholesterol, Low	12/94 (13)	14/137 (10)
Globulin (g/L), low	68/112 (61)	84/174 (48)
Protein, Low	34/158 (22)	34/239 (14)

Glucose High	13/248 (8)	13/244 (5)
Lactate Dehydrogenase, high	14/232 (10)	16/145 (7)
Triglyceride High	47/133 (35)	63/208 (30)

Based on applicant Table IR39-4-1. Includes laboratory collected at any postbaseline visit during the period starting after the first dose of study drug and within 30 days after the last dose. Subjects with at least one postbaseline laboratory measurement meeting cut point criteria are counted only once for each row. Los is any value <LLN. High is any value > ULN. Denominator indicates the number of subjects with normal baseline and at least one postbaseline data; this number is used to calculate percentages within each laboratory parameter.

When examining graphs of average chemistry values at each analysis visit, by treatment arms, while there were some points of divergence between the placebo arm and the proposed dose arm, but there was no clear trend for one group having persistently lower or higher chemistry values, except for globulin, protein and glucose levels. The significance of the mildly lower protein and globulin, and higher glucose values is unclear. The possible signal for elevated glucose at the proposed dose arm was also noted in an MQG analysis of TEAEs for the MQG ODE-1 diabetes (including preferred terms, glucose intolerance, hyperglycemia, HbgA1C, glycosuria, and ketones) showing an incidence of 5 % in the proposed dose arm versus 1 % in placebo However these differences were small and the clinical significance of these changes is not known.

Based on 201 OLE Study Report Table 14.3.4.2.2.3 summarizing chemistry shifts from baseline to lowest postbaseline visits, of the participants who started out with normal baseline globulin and protein values, 45 % had one or more low globulin value and16 % had one or more low protein value at any postbaseline visit. This is similar to the observation in the 201 Core where low globulin and protein were observed. In 201 OLE, 25 % of participants who started out with a normal baseline glucose level, had one or more high value of glucose at any postbaseline visit. These differences in chemistry changes are of unclear clinical significance.

The number of participants with abnormal chemistry values were too small in the placebo and drug arms in the mean change from baseline, shifts from baseline to post-baseline visits and treatment emergent markedly abnormal laboratory results in Study 104, and Study 101 to identify any consistent trends laboratory values in the drug versus placebo arms.

Hepatic-Related Events

I did not identify a safety signal for hepatic related events on treatment in an analysis of maximum post baseline liver enzyme values, hepatic related adverse events in Study 201 Core. There were no Hy's Law cases found based on alanine transaminase (ALT) or aspartate transaminase) AST ≥ 3ULN and bilirubin (BIL) ≥ 2 ULN within 30 days of ALT/AST elevation. Table 37 shows average ALT, AST, ALP, BIL values by analysis visit for each treatment arm.

Table 37 Maximum Post Baseline Liver Enzymes

Lab Test	Cut Point	Placebo (N = 245)	2.5mg/kg bi-Weekly (N = 52)	5 mg/kg Monthly (N = 51)	5 mg/kg bi-Weekly/ (N = 92)	10 mg/kg Monthly (N = 253)	10 mg/kg bi-Weekly (N = 161)
ALT	> 3*ULN	2 / 245 (0.8)	0 / 52 (0.0)	1 / 51 (2.0)	0 / 92 (0.0)	3[#] / 253 (1.2)	2 / 161 (1.2)
	> 5*ULN	1 / 245 (0.4)	0 / 52 (0.0)	1 / 51 (2.0)	0 / 92 (0.0)	0 / 253 (0.0)	1 / 161 (0.6)
	> 10*ULN	0 / 245 (0.0)	0 / 52 (0.0)	0 / 51 (0.0)	0 / 92 (0.0)	0 / 253 (0.0)	0 / 161 (0.0)
AST	> 3*ULN	1 / 245 (0.4)	0 / 52 (0.0)	1 / 51 (2.0)	1 / 92 (1.1)	2 / 253 (0.8)	1 / 161 (0.6)
	> 5*ULN	0 / 245 (0.0)	0 / 52 (0.0)	0 / 51 (0.0)	0 / 92 (0.0)	0 / 253 (0.0)	1 / 161 (0.6)
	> 10*ULN	0 / 245 (0.0)	0 / 52 (0.0)	0 / 51 (0.0)	0 / 92 (0.0)	0 / 253 (0.0)	0 / 161 (0.0)
ALP	> 1.5*ULN	7 / 245 (2.9)	0 / 52 (0.0)	2 / 51 (3.9)	1 / 92 (1.1)	4 / 253 (1.6)	0 / 161 (0.0)
BILI	> 2*ULN	0 / 245 (0.0)	0 / 52 (0.0)	0 / 51 (0.0)	0 / 92 (0.0)	3 / 253 (1.2)	0 / 161 (0.0)

Safety population, inclusive of last follow up visit at week 90 or early termination visit.
[#]If limited to 30 days after last dose (week 79, early termination visit or unscheduled visit) this number is 2.
[tliver1.rtf] [tliver1.sas] 31JUL2022, 19:04

I did not identify any participants meeting Hy's Law criteria in the 201 OLE, Study 101 or Study 104. In the 201 OLE study there was one participant who had an AST level > x3 ULN, and 4 participants with bilirubin level > 1.5 ULN. In Study 104 one participant had an AST level > x3 ULN, and one participant with bilirubin level > 1.5 ULN.

TEAEs of abnormal laboratory results

In my review of TEAEs belonging to the system organ classes (SOC) Investigations related to laboratory findings, LEC10-BW did not have an excess of TEAEs compared to placebo in Study 201 Core (incidence of 9 % versus 10%, respectively).

TEAEs related to the same system were captured under different preferred term (i.e., "lymphopenia" captured under the SOC of investigations, "lymphocyte count decreased" captured under the SOC of Blood and Lymphatic Disorders). I searched the following SOC's for potential treatment emergent laboratory changes: Investigations, Renal and Urinary Disorders, Metabolism and Nutritional Disorders, and Blood and Lymphatic Disorders. Laboratory abnormalities related preferred terms that occurred in 2 or more participants at the proposed dose included anemia/ blood loss anemia, lymphopenia/ lymphocyte decreased, neutrophil count increased, glucose urine present/glycosuria, hyperglycemia and hematuria (**Table 38**).

Table 38 Incidence of a participant experiencing at least one TEAE related to laboratory findings in Study 201 Core occurring in 2 or more participants at the proposed dose

Preferred Term	LEC10-BW N=161 N (%)	Placebo 245 (n (%)
Lymphopenia/ lymphocyte decreased	6 (4)	1 (<1)
Hematuria	6 (4)	5 (2)
Anemia/ blood loss anemia	7 (4)	7 (3)
Glucose urine present/glycosuria	4 (2)	1 (<1)
Neutrophil count increased	2 (1)	0 (0)
Hyperglycemia	2 (1)	1 <10)

Reviewer created using the ISS ADAE dataset selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL =Y. Subset of all dictionary derived terms related to laboratory values was created. This subset table was grouped by USUBJID, actual treatment for period 01, and dictionary derived term, and then tabulated by dictionary derived term and actual treatment for period 01.

There were 15 lecanemab treated participants who experienced hematuria. There were 6 each in the LE10-M and LEC10-BW groups, and one each in the LEC5-M, LEC5-BW and LEC2.5-BW groups.

I reviewed these narratives and could not identify a clear role of the study drug in the majority of the cases. In some participants, hematuria occurred once, resolved on subsequent testing and did not occur again during the study treatment. In other participants there was another clear cause of hematuria such as UTI, bladder cancer, benign prostate hyperplasia, or use of anticoagulation. I could not rule out a role of the study drug in hematuria in one participant (b) (6)

Briefly this participant is a 71-year-old woman randomized to receive LEC5-BW. At the time of the 7th dose of study drug (Study Day 85) she experienced pyrexia. On Study Day 179, ten days after the 13th infusion, she experienced itching in the right arm followed by the occurrence of 3 vesicles in the right arm. On Study Day 323, thirteen days after the 24th dose of study drug, she experienced diarrhea, vomiting and pyrexia which resolved the next day with ibuprofen. On Study Day 366, 15 days after the 26th dose of study drug, she experienced hematuria. No action was taken with the study drug and this resolved by the next day. On Study Day 456, on the day she received the 33rd dose of study drug she developed erythema in the left cubital fossa which resolved the next day. She completed the study as planned.

Reviewer Comment: Given the constellation of symptoms occurring after some of the infusions, I cannot rule out that the hematuria was related to study drug, and represented a form of hypersensitivity reaction.

I reviewed the applicant's markedly abnormal Laboratory Results Table 14.3.4.4.1 for Study 201 Core. The following markedly abnormal laboratory values occurred with an incidence of more

than 2 % greater in the proposed dose arm compared to placebo: markedly abnormal high glucose (fasting > 160 mmol/L) occurring in 14 participants (9 %) in the LEC10-BW vs 12 (5%) in placebo, markedly abnormal high potassium (> 5.5mmol/dL) occurred in 11 participants (7%) in LEC10-BW vs 9 (4 %) in the placebo group, markedly abnormal low lymphocytes (< 0.8 x 10^9/L) occurred in 55 (34 %) participants in the LEC10-BW arm compared to 12 (5%) in placebo.

Most common TEAES related to laboratory abnormalities reported in the 201 OLE study are summarized in **Table 39**. While hematuria is consistent with the observation in 201 Core, it is difficult to interpret the other observations without a comparator group.

Table 39 TEAEs of abnormal laboratory values occurring in more than 5 % of participants in Study 201 OLE

Dictionary Derived Term	N (%)
Hematuria	11 (17%)
Hyperkalemia	6 (9 %)
Asymptomatic bacteriuria	3 (5 %)
Hypokalemia	3 (5 %)
Thrombocytopenia	3 (5 %)

Reviewer created using the ISS ADAE dataset selected for Study ID= BAN2401-G000-201-OLE, SAFFL=Y, TRTEMFL =Y. Subset of all dictionary derived terms related to laboratory values was created. This subset table was grouped by USUBJID, and dictionary derived term, and then tabulated by dictionary derived term.

There were 2 participants who had a TEAE of lymphopenia, and one with neutrophil count decreased in 201 OLE. One participant had an SAE of pancytopenia (b) (6), narrative of this participant is described under Section 7.4.2 Serious Adverse Events.

In the applicant's markedly abnormal laboratory table for the 201 OLE study (markedly abnormal as defined by the applicant as having a CTCAE grade 2 or higher), while the majority of abnormalities occurred in a small number of participants, those occurring above 5 % incidence were: abnormal high glucose levels (fasting glucose > 160) occurring in 20 (17 %), abnormal high potassium (>5/5mmol/L) in 13 (7 %), abnormal low lymphocyte count (<800 /mm^3) in 16 (9 %), and abnormal low neutrophil count (< 1.5 10^9/L in 10 (6 %) of participants, abnormal triglycerides in (>300mg/dL) in 11 (6%).

Urine analysis

I reviewed the applicant's Shift from Baseline to Postbaseline Visits, and Shift from Baseline to Postbaseline visits for Laboratory Parameters without Normal Ranges for Study 201 Core.

I noted there was a higher percentage of participants with urine glucose at the week 1 visit in the proposed dose 9 (6 %) in LEC10-BW compared to 5 (2 %) in placebo. This trend was not observed consistently at every visit. At the 79-week visit (2 weeks after the last dose of study drug), urine glucose was present in 5 (6 %) in the LEC10-BW group, compared to 2 (2%) in the placebo group. There was no difference in abnormal protein or occult blood observed in the urine in proposed dose arm versus placebo in the 201 Core Study.

The significance of small differences in urine glucose levels at the proposed dose arm versus placebo is unclear.

In the 201 OLE study, of those with normal Urine Analysis at baseline, 20-26 % of participants had bacteria in their urine at any time during post baseline visits 11 % had abnormal glucose, 27 % had leukocyte esterase in urine abnormal, 13 % had occult blood and 36 % abnormal protein in urine at any postbaseline visit.

7.4.4. Vital Signs

For Study 201 Core, I reviewed the applicant's Table 14.3.4.5. 1 Mean and Mean Change form Baseline By Visit, the applicant's Table 14.3.4.5.2 Abnormal Vital Signs Results by Visit in the Study 201 Core Clinical Study Report, trajectory of the mean of vital signs per study drug arm by analysis visit using JMP Clinical Version 8, and Table IR39-1 which was submitted by the applicant on September 6, 2022, in response to a request from the agency showing shifts from normal baseline to the following potentially clinically significant (PCS) postbaseline abnormal values: systolic blood pressure < 90 mmHg, or > 140 mmHg, Diastolic Blood Pressure < 50mmHg or > 90 mmHg, respiratory rate < 12 breaths/minute or > 20 breaths per minute, pulse < 60 bpm, or > 100 bpm, and temperate < 36 Cor > 38 C. Overall, there were no clinically significant trends showing persistent differences in vital signs between the proposed dose arm and the placebo group.

After the first infusion at week 1, 7/604 (1.2 %) participants receiving lecanemab had an elevated temperature compared to 0 participants in placebo arm. No participants in the LEC2.5 BW, or LEC5-M had an elevated temperature, 1/ 92 (1.1 %) in the LEC5-BW, 5/249 (2 %) in the LE10-M arm, and 1/160 (0.6 %) in the LEC10-BW arm had elevated temperature after the first infusion. This was likely consistent with an infusion reaction (See section 7.5.2 Infusion Related Reaction). At any postbaseline visit the difference in incidence of increased temperature between all lecanemab and placebo arms was small (3 % vs 2 %).

Applicant Table 14.3.4.5.2 Abnormal Vital Signs Results by Visit and Timepoint was reviewed. Abnormal High and Abnormal Low vital sign at any post baseline visit obtained from this table are summarized in Table 40 below. Overall, the proposed dose arm had a slightly higher

incidence of individuals with abnormal low diastolic blood pressure. The significance of these small differences in incidence is unclear.

Table 40 Abnormal Vital Signs at any postbaseline time point

	Placebo N=245	LEC10-BW N=161
Diastolic blood pressure abnormal low	25 (10.2)	69 (11.3)
Diastolic blood pressure abnormal high	5 (2.0)	2 (1.2)
Systolic blood pressure abnormal low	11 (4.5)	7 (4.3)
Systolic blood pressure abnormal high	67 (27.3)	27 (16.8)
Pulse abnormal low	58 (23.7)	35 (21.7)
Pulse abnormal high	7 (2.9)	5 (3.1)
Temperature abnormal high	4 (1.6)	4 (2.5)
Temperature abnormal low	148 (60.4)	82 (50.9)

Based on applicant Table IR39-1 Abnormal thresholds: pulse- abnormal low <50 bpm, abnormal high: > 100 bpm, temperature-abnormal low < 36 C, abnormal high >38 C, systolic blood pressure abnormal low < 90 mmHg, abnormal high > 160 mmHg, and diastolic blood pressure abnormal low < 50 mmHg, and abnormal high > 100 mm Hg.

I reviewed applicant prepared Table IR39-1 Abnormal Vital Signs Postbaseline with Normal Baseline in 201 Core Safety Analysis Set submitted on September 6, 2022, per FDA request This table shows abnormal shifts in vital signs to potentially clinically significant (PCS) values: systolic blood pressure < 90 mmHg, or > 140 mmHg, Diastolic Blood Pressure < 50mmHg or > 90 mmHg, respiratory rate < 12 breaths/minute or > 20 breaths per minute, pulse < 60 bpm, or > 100 bpm, and temperate < 36 Cor > 38 C. Overall, most of the abnormal shifts occurred at a higher frequency in the placebo arm compared to proposed dose arm of LEC10-BW, with the exception of high temperature. which occurred in 4 (3%) at the proposed arm, and 4 (2%) in the placebo arm. Otherwise, there appeared to be no other trends that differed between the proposed dose arm and the placebo arm in other clinically notable vital sign measurements.

When I reviewed the mean vital sign trends in treatment arms by visit in JMP clinical, there appeared to be a pattern of a slight decrease in heart rate by ~ 2-beats/minute post-infusion after each infusion compared to pre-infusion in the lecanemab arms which was not observed in the placebo arm. However, the mean heart rates pre and post infusion for each treatment arm remained in the normal range, despite the persistent pattern of mild decrease in heart rate post-infusion.

Given this observation to better understand whether the shift from baseline to post baseline abnormal visits could show differences between drug and placebo arms when separated by pre-infusion and post-infusion postbaseline visits, in an IR dated November 9, 2022, the Agency requested the applicant to provide tables for shifts to abnormal postbaseline visits separately for pre-infusion and post-infusion post baseline visits.

Based on applicant Table IR58-1 abnormal vital signs at any post-baseline post infusion visit the number of participants with at least 4 abnormal low heart rate measurements (< 50 bpm), was 18/161 (11.2 %) in the LEC10-BW group, compared to 21/245 (8.6 %) in placebo. When limiting analysis to only those with a normal baseline value (Table IR58-3), the incidence was 12/151 (7.9 %) in the LEC10-BW arm versus 16/238 (6.7 %) in placebo arm. When looking at abnormal vital signs at postbaseline pre-infusion measurements (Table IR58-2) the incidence of having 4 or more heart rate measurements <50 bpm, was 17/245 (6.9 %) in the placebo arm compared to 13/161 (8.1 %) in the LEC10-BW. When limiting this to those with normal baseline values (Table IR58-4), 12/238 (5%) of placebo, and 6/151 (3.9 %) of those in the LEC10-BW arm had at least 4 heart rate measurements < 50bpm.

Reviewer Comment: Taken together these findings suggest that, in those who had normal baseline values, a higher incidence of placebo participants compared to participants in the proposed dose arm had 4 or more heart rate measurements < 50bpm, pre-infusion, but more participants in the LEC10-BW arm compared to placebo had 4 or more heart rate measurements < 50BPM post-infusion. This is consistent with the observation of transient drop in heart rate post-infusion in the lecanemab arms. However, the numbers are too small to draw any firm conclusions.

While there was a higher incidence in the LEC10-BW arm compared to placebo noted in the following vital sign shifts, the difference was based on a small number of participants making it difficult to draw conclusions: The incidence of having one or more heart rate measurement postbaseline post-infusion above 100 bpm was 1.2 % in the LEC10B arm compared to 0 in placebo. The incidence of having one or more temperature above 38 C was 1.9 % in the LEC10-BW arm compared to 0.8 % in the placebo arm. When limiting this to those with a normal baseline, these numbers did not change. Additionally, when just including those with a normal baseline, the incidence of those with at least 2 or more diastolic blood pressure readings > 90mm Hg was 7.5 % in the LEC10-BW arm compared to 6.6 % in the placebo. It is difficult to draw conclusions given the small changes in small numbers of participants.

When I examined the TEAEs under the Primary Organ System Investigations related to vital signs in the 201 Core Study, I did not identify any TEAEs that occurred in the LEC10-BW arm at an incidence of 2% or higher. Additionally, there was not a higher incidence of TEAEs of bradycardia, hypotension or syncope in the proposed dose arm compared to placebo. The incidence of orthostatic hypotension was higher in the proposed dose arm compared to placebo (1.8 % vs 0.4 %), and was driven by a small number of participants.

In the 201 OLE study, I reviewed applicant Table 14.3.4.5.1 Mean and Mean Change from Baseline by Visit, and Table 14.3.4.5.3.1 Clinically Notable vital Sign Results by Visit. I also reviewed the mean trends in vital signs using JMP Clinical. I did not identify clinically significant trends in vital sign mean and mean change from baseline by visit. I did note however that similar to the 201 Core study, in participants receiving lecanemab the heart rate dropped by a

few beats/minute post-infusion after most of the doses compared to pre dosing, the mean values remained in the normal range, mostly between 60-70 beats/ minute.

Table 14.3.4.5.3.1 in the 201 OLE Clinical Study Report lists clinically notable vital signs results by visit in 201 OLE. From this table it appeared that there was a trend towards higher number of participants having pulse rates < 50 bpm post infusion compared to pre-infusion at some of the infusions occurring later during the course of the study, however this was not consistently observed after each infusion. In the absence of a control group it is difficult to interpret whether any changes noted in this table are related to study drug.

There were no clear dose dependent trends noted in vital signs in the drug arms compared to placebo in studies 101 and 104. Table 41 below from the Study 104 Clinical Study Report -Table 32 shows clinically notable vital sign results in the safety analysis in Study 104. Only abnormally low diastolic blood pressure and abnormally low systolic blood pressure was observed at a higher incidence at the proposed dose arm compared to placebo. However, given the relatively small number of participants the significance of these findings are unclear.

Table 41 Clinically Notable Vital Signs in Study 104

Parameter Category	Placebo (N=5) n (%)	BAN2401			
		2.5 mg/kg (N=6) n (%)	5 mg/kg (N=6) n (%)	10 mg/kg (N=7) n (%)	Total (N=19) n (%)
Systolic blood pressure					
Low	2 (40.0)	3 (50.0)	2 (33.3)	3 (42.9)	8 (42.1)
High	2 (40.0)	5 (83.3)	4 (66.7)	2 (28.6)	11 (57.9)
Diastolic blood pressure					
Low	2 (40.0)	4 (66.7)	5 (83.3)	4 (57.1)	13 (68.4)
High	4 (80.0)	5 (83.3)	4 (66.7)	4 (57.1)	13 (68.4)
Pulse rate					
Low	2 (40.0)	0	1 (16.7)	1 (14.3)	2 (10.5)
High	2 (40.0)	1 (16.7)	2 (33.3)	2 (28.6)	5 (26.3)

For pulse, criterion for low was <50 or change from baseline ≤ –20 bpm and criterion for high was >100 or change from baseline ≥ 20 bpm; for systolic blood pressure, criterion for low was <90 or change from baseline ≤ –20 mmHg and criterion for high was >160 or change from baseline ≥ 20 mmHg; for diastolic blood pressure, criterion for low was <50 or change from baseline ≤ –10 mmHg and criterion for high was >100 or change from baseline ≥10 mmHg.

Percentages were based on the number of subjects with nonmissing postbaseline data. Subjects were counted only once for each row.

7.4.5. Electrocardiograms (ECGs)

Overall, I did not find an imbalance in abnormal not clinically significant ECGS or in abnormal clinically significant ECGs between the proposed dose arm and placebo in 201 Core. There were several events of atrial fibrillation (AF) across all trials. In the 201 Core study, TEAEs of atrial fibrillation occurred in 6 participants (4 %) in the LEC10-BW arm vs 3 participants (1%) in placebo Core. 50 % of participants with AF were ≥ 80 years old, and 25 % in the placebo group were ≥ 80 years old. As age is a known risk factor for AF it is not possible to determine whether the study drug played a role in these events.

Single-lead ECGs were obtained at baseline visit, and then on weeks 9, 17,27,39, 53,65, 79, and early termination visit of follow up visit at week 90.

Abnormal ECG (QTcF; QT interval corrected by Fridericia's formula) results, if not otherwise considered part of a clinical symptom that was being reported as an AE, were considered an AE if (1) the QTcF interval was more than 450 msec and there was an increase of more than 60 msec from Baseline, or (2) the QTc interval was more than 500 msec. Any ECG abnormality that the investigator considered as an AE was reported as such. If a QTc was found to be out of range, 2 additional ECGs were recorded to allow evaluation of triplicate ECGs. The participant was withdrawn if: (1) the absolute value of the QTc was greater than 500 msec; or (2) if the QTc increased by more than 60 msec from Baseline and the QTc was greater than 450 msec.

In Studies 101, 104, 201 Core and 201 OLE, qualitative ECG findings (normal; abnormal, not clinically significant; abnormal, clinically significant) as evaluated by the investigator were collected. The incidence of participants who had shifts from normal to abnormal ECGs at each visit was reported in the respective Clinical Study Reports (CSRs) in the BLA. As noted in the Integrated Safety Summary (ISS).

Quantitative ECG parameters were not captured in Studies 101 and 201 Core, but were captured in Studies 104 and 201 OLE, as follows:

- For Study 104, ECG parameters (RR, QT, QTcF, and QRS) were collected
- For Study 201 OLE, ECG parameters (HR, QT, QTcF, QTcB, QRS, and PR) were collected

I reviewed the applicant's Table 14.3.4.6.1 showing shifts from baseline to post-baseline by visit results. There did not appear to be a trend towards higher incidence of abnormal clinically significant, or abnormal clinically nonsignificant values in the lecanemab arms versus placebo, in those participants who had a normal baseline ECG finding. Overall, in participants who had a normal baseline ECG, there were no participants in the proposed dose arm of LEC10-BW who had an abnormal clinically significant ECG, in the placebo arm this ranged between 0-1%. The incidence of abnormal not clinically significant ECGs during the duration of the study between week 9 and week 79 ranged between 11%- 19% in the placebo arm compared to 9 %-17 % in the LEC10-BW arm.

When I examined the ECG related abnormalities selecting ECG related dictionary derived terms, only TEAEs of atrial fibrillation occurred with an incidence of more than 2 % in the LEC10-BW arm [6 (4 %)] vs placebo [3(1 %)].

In Study 201 OLE, I did not note any significant changes in the mean and mean change from baseline by visit tables for heart rate, QT Duration, QTcF, QTcB, QRS Duration, PR Duration. Based on the Shift from Baseline to Post-Baseline Visits, of those that started with a normal baseline ECG, the incidence of abnormal clinically significant ECG changes ranged from 0-0.6 %, and the abnormal clinically not significant changes ranged between 20-27 %.

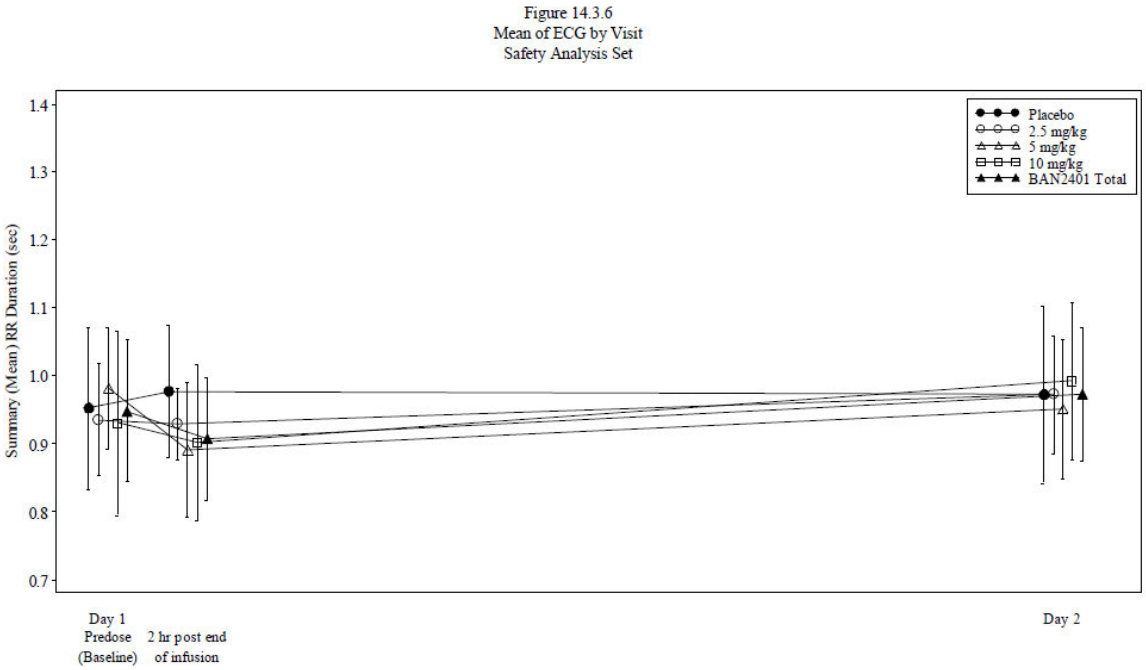
For Study 104 I reviewed the Table 14.3.6.1 for shifts from baseline to normal, abnormal clinically significant or abnormal not clinically significant, I did not identify a trend for higher incidence of abnormal clinically significant findings for the study drug group compared to placebo. I reviewed applicant's

In Study 104, one participant (b) (6) in the 5 mg/kg group and 2 participants (b) (6) in the 10 mg/kg group experienced treatment-emergent clinically significant abnormal ECG findings in at least 1 postbaseline assessment. These participants had an abnormal, not clinically significant baseline ECG. Clinically significant abnormal ECG findings were reported as an AE.

Participant (b) (6) (5 mg/kg) had QT prolongation beginning on Day 149, which occurred over 30 days after the last (6th) dose of study drug was administered. Participant (b) (6) (10 mg/kg) experienced atrial fibrillation beginning on Day 99 (day of the 6th and last study dose), and Participant (b) (6) (10 mg/kg) experienced atrial fibrillation beginning on Day 44, after which she continued with study drug. She had electrocardiogram ST segment elevation beginning on Day 114 which occurred 4 days after she received the 5th (last) dose of study drug. All of these events were considered recovered or recovering.

Examining Figure 14.3.6 in the Study 104 Clinical Study Report provided by the applicant, there appears to be a transient dose dependent decline in the RR interval post -infusion in the study drug arms compared to baseline and compared to placebo, on Day 1. The shorter RR interval in the Lecanemab arms returns to being comparable to the placebo arm on day 2. This may be related to the finding of a nonsignificant drop in HR observed post infusion during 201 Core.

Figure 2 Study 104,change in RR duration after first dose



In Study 101 the incidence of abnormal clinically significant ECG findings was comparable between the placebo and study arms both in the SAD and MAD study. One participant (b) (6) who received a single dose of LEC15 mg/kg had an abnormal ECG finding related to a clinical event of acute coronary artery syndrome which was considered to be clinically significant. She had QT prolongation prior to receiving the infusion, and continued to have QT prolongation post infusion, with nonspecific T-Wave abnormalities. These were considered clinically nonsignificant by the PI. On Study day 2 the participant had T-wave changes in Leads II and a VF. She remained asymptomatic and was discharged home. She returned on study day 21, and was still asymptomatic. Her ECG on study day 21 showed Q waves in leads II and aVF consisted with a completed inferior MI. On study day 40 (39 days after last study drug) she was admitted for chest pain and dyspnea and work up at the time was normal including unremarkable ECG, and troponins. On her return visit on study day 180, ECG was again interpreted as consistent with an inferior MI. The participant followed up with a cardiologist who considered that the ECG changes post-dose from Study Day 1 to Study Day 180 were likely due to transient occlusion of a small branch of the right coronary artery, which subsequently re-perfused. The cardiologist diagnosed the ECG changes as being due to a silent coronary event (acute coronary syndrome) and not due to an inferior MI, as was originally suspected. The investigator considered this event of acute coronary syndrome to represent an SAE and assessed it as mild in severity and unrelated to the study drug. This participant's risk for cardiovascular disease included medical history of hypertension and age of 87 years old. One

participant (b) (6) who received a single dose of 1 mg/kg arm study drug, had baseline ECG abnormality of first degree atrioventricular block. On day 2 of the study this participant experienced transient atrial fibrillation which lasted for 24 hours and resolved without any treatment. The participant did not experience any symptoms. Risk factors were age (87 years old) and pre-existing cardiovascular disease as evidenced by abnormal ECG at baseline.

7.4.6. QT

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. Only studies 104 and 201 OLE collected quantitative ECG data. In Study 104 which was the only study that had a placebo group and collected quantitative ECG data, I did not identify a higher incidence of QTc prolongation in the study drug arms compared to placebo.

In Study 201 Core, there were 4 participants that had electrocardiogram prolonged QT listed as a treatment emergent AE. Two were on placebo (b) (6) one on LEC10-BW (b) (6) and one on LEC2.5-BW (b) (6) In only one of them (b) (6) on LEC10-BW arm) did the QT prolongation resolve. There were no clinical symptoms identified as a treatment-emergent AE in any of these participants. Drug was interrupted in one placebo participant (b) (6) and dose not changed, and drug not interrupted in the rest.

In Study 104 there was not a higher incidence of QTc prolongation in the study drug arms compared to placebo. No participant had a QTcF value of > 500ms. The incidence of QTc prolongation both post baseline increases over > 30msec and > 60msec, and post baseline value > 450msec were more frequent in the placebo arm compared to the drug arms (Applicant Table 14.3.6.3 Abnormal QTc Results Safety Analysis Set).

In the 201 OLE study, there were 15 participants who had a postbaseline increase in QTcF > 30 msec. Of these 5 had an increase of > 50 ms. There were 20 (12 %) participants who had a postbaseline QTcF value of > 450 ms, of these 4 (2 %) were > 480, 1 (1 %) > 500. Four (2 %) participants had at least one post-baseline value of > 450 which also was an increase from baseline of > 60 ms.

One participant in the OLE had a QTcF value of >500 ms (participant (b) (6)) at Visit 57 in the OLE, QTcF=517 ms). The subsequent QTcF values for this participant became <500 ms at the remaining visits.

7.4.7. Immunogenicity

In Study 201 Core, the applicant conducted ADA sampling at predose in a blinded fashion from all participants during the treatment period at Weeks 1, 13, 27, 39, 53, 65, 79 and at the Early Termination Visit (if applicable) and the Follow-up. Limited number of participants had baseline samples.

Treatment emergent anti-lecanemab antibodies (ADA) were reported in at least 1 sample in approximately 41% (63/154) participants treated with LEC10 BW and according to Dr. Yifei Zhang's Clinical Pharmacology review, these were generally characterized by low titers. Of these participants, treatment emergent anti-lecanemab neutralizing antibodies (Nab) were positive in at least 1 sample in 25% (16/63). However, Dr. Zhang notes that the plasma concentrations of lecanemab exceed the drug tolerance level of the ADA and Nab assays. In that case, the presence of lecanemab in the sample interferes with the ADA assay, so that a negative result of an ADA sample is considered inconclusive. Dr. Zhang's review notes that this may result in an underestimation of ADA and Nab positivity. The assay limitations preclude definitive conclusions regarding the impact of ADA on lecanemab safety.

7.5. Analysis of Submission-Specific Safety Issues

7.5.1. ARIA

Executive Summary of ARIA

Amyloid related imaging abnormalities (ARIA) have been observed in clinical trials with therapeutics aimed at lowering amyloid-β burden in AD. ARIA refers to changes on magnetic resonance imaging (MRI) of the brain that includes signal hyperintensities on fluid attenuation inversion recovery (FLAIR) sequences and are thought to represent "vasogenic edema" and/or sulcal effusion (ARIA-E), and signal hypointensities on GRE/T2∗ thought to represent hemosiderin deposits (ARIA-H), including microhemorrhage and superficial siderosis.[15] Carrying one or more ApoE ε4 allele is associated with a higher risk of ARIA, based on observations from aducanumab, and studies of other monoclonal antibodies.

The observance of MRI changes consistent with ARIA-E or ARIA-H in the absence of treatment with an anti-amyloid monoclonal antibody, have been reported in participants with cerebral

[15] *Sperling et al. Amyloid Related Imaging Abnormalities in Amyloid Modifying Therapeutic Trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement.2011; (7):367-385*

amyloid angiopathy (CAA) and in the general population.[16] [17] In two phase 3 studies of aducanumab, ARIA-E was reported to occur at an incidence of 2.7 % in the placebo group.[18] Microhemorrhages overall have a prevalence of ~ 5 % in older individuals in the absence of anti-amyloid treatment, with a higher prevalence in those with cerebrovascular risk factors such as hypertension and those with underlying CAA.[19] The prevalence of microhemorrhages in memory clinic and AD cohorts is reported to be 17% or higher.[20] Superficial siderosis is reported to occur at a prevalence of 0.43 % in the general population (based on Framingham and Rotterdam studies)[21] and in ~ 5 %in participants with AD.[22]

The risk for ARIA-E during treatment with anti-amyloid treatments has been reported to be higher at treatment initiation, in ApoE ε4 carriers, with higher dosage , and in those with pretreatment microhemorrhages.[23] Additionally ARIA incidence has been reported to be higher with mAbs that bind the N- versus C-terminus and target aggregated-versus-soluble forms of Aβ.[24] While the majority of ARIA-E remains asymptomatic, ARIA-E may present with a wide array of symptoms including headache, confusion, visual changes, seizures, malignant hypertension, psychiatric symptoms or focal neurologic symptoms. ARIA-H is defined by the occurrence of cerebral microhemorrhages (hemorrhages less than 1 cm) or superficial siderosis which may be seen on GRE images. The inclusion of cerebral hemorrhages greater than 1 cm in diameter the definition of ARIA-H is variable. While the applicant included cerebral hemorrhages > 1 cm in the definition of ARIA-H, in this review they are not included as part of ARIA-H and are analyzed separately.

The evidence presented by the applicant supports that lecanemab treatment is associated with an increased risk of ARIA. In the placebo-controlled portion of Study 201 Core, where 161 participants were randomized to receive the proposed dose for 79 weeks, any occurrence of

---

[16] Ryan et al. Spontaneous ARIA (amyloid-related imaging abnormalities) and cerebral amyloid angiopathy related inflammation in presenilin 1-associated familial Alzheimer's disease. (J Alzheimer's Dis. 2015;44(4):1069-74.,
[17] Raman et al, Spontaneous amyloid-related imaging abnormalities in a cognitively normal adult. Neurology 2014;83;1771-1772
[18] Salloway et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease. Jama Neurology. JAMA Neurol. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161
[19] Viswanathan et al. Cerebral microhemorrhage. Stroke. 2006;37:550–555).
[20] Cordonnnier et al. Prevalence and Severity of Microbleeds in a Memory Clinic Setting. . Neurology May 09, 2006; 66 (9)
[21] Shoamenesh et al. Cortical superficial siderosis in the general population. The Framingham Heart and Rotterdam studies. International Journal of Stroke. Volume 16, Issue 7.
[22] Zonneveld et al. Prevalence of cortical superficial siderosis in a memory clinic population. Neurology. February 25, 2014; 82 (8)
[23] Withington CG, et al. Amyloid-Related Imaging Abnormalities With Anti-amyloid Antibodies for the Treatment of Dementia Due to Alzheimer's Disease. Front Neurol. 2022;13:862369. doi:10.3389/fneur.2022.862369
[24] Cogswell et al. Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice. American Journal of Neuroradiology Sep 2022, 43 (9) E19-E35; DOI: 10.3174/ajnr.A7586 6

ARIA was observed in 12.4 % (20/161) of participants who received LEC10-BW- and in 5.3 % (13/245) of participants who received placebo.

ARIA-E was observed in 9.9 % (16/161) of participants receiving LEC10-BW and 0.8 % (2/245) in placebo. ARIA-H occurred in 6% of participants on LEC10-BW vs 5% in participants on placebo.

There were no deaths due to ARIA-E in 201 Core or in the 201 OLE. SAEs of ARIA in Study 201 Core occurred in 2% (3/161) of participants in the LEC10-BW arm, compared with 0 of participants on placebo; all of these SAEs were ARIA-E related.

In the LEC10-BW arm in 201, Core 5/20 participants with ARIA had at least 1 treatment emergent clinical symptom compared to none of the placebo participants who had ARIA in 201 Core. The most common symptoms reported in participants with ARIA at the proposed dose arm were headache (3/5 participants), confusion or altered mental status (2/5 participants), visual disturbance (2/5 participants), agitation (2/5 participants), followed by the following, occurring in 1 participant each: paresthesia, labile affect, aphasia, hallucinations, vomiting, transient ischemic attack, confabulation, homonymous hemianopia. One possible seizure was reported but could not be confirmed by the applicant. Clinical findings that were reported included clonus, hyperreflexia, and abnormal EEG in 1 participant each who had ARIA-E and/or -H. Cases of symptomatic serious ARIA were too few to fully characterize the extent, duration, outcomes. 4/5 participants who had clinical symptoms with ARIA recovered during the course of the study.

At the proposed dose, most ARIA-E was radiographically mild or moderate, 44% (7/16) for each, and 12.5 % (2/16) was radiographically severe. Most ARIA-H was classified as radiographically mild; of the number of participants with ARIA-H microhemorrhage at the proposed dose in 201 Core, a radiographically severe finding occurred in 1% (2/161) of participants.

At the proposed dose in 201 Core, the majority, 12/16 (75 %), of ARIA-E events occurred before the 7th dose. At the proposed dose, ARIA-E occurred on average 8.6 days (SD 4.7, range: 1-20) after a dose and on average lasted for 89 days (SD 58, range 37-258) before it resolved in participants receiving lecanemab.

In three instances, all in the LEC10-M, ARIA-E occurred 136-169 days after last dose.

Similar to other monoclonal antibodies, in the placebo controlled 201 Core study of lecanemab, the risk of ARIA-E was related to ApoE status. An observation of higher risk of ARIA-E in ApoE ε4 carriers, early in the study led to protocol amendments that did not allow further enrollment of ε4 carriers and required discontinuation of the already enrolled ε4 carriers from the proposed dose. This resulted in only 30 % of the participants in the proposed dose arm being carriers of the ε4 allele, compared to 69-89 % in other study arms, and ~30-70 % in individuals with AD in the general population. Therefore, interpretation of ARIA related analyses by ApoE ε4 carrier

status should consider the limitations of the unbalanced subgroups and the small number of ApoE ε4 carriers in the proposed dose. In the 201 Core, for participants treated with LEC10-BW, ARIA-E occurred more frequently in ApoE ε4 homozygotes compared to heterozygotes and noncarriers (50 % in homozygotes, 5% in heterozygotes and 8 % in noncarriers). ApoE ε4 homozygotes also had an increased frequency of ARIA-H microhemorrhage (30 % in homozygotes, 8 % in heterozygotes, and 3 % in noncarriers).

Females treated with LEC10-BW had a higher incidence of ARIA-E compared to men (13 % vs 8 %). The incidence of ARIA-E was slightly higher in those between age 65-80 years (11 %) relative to those age < 65 years (7 %), and those over age 80 years (9 %). However, the numbers were too small to reach any conclusions.

While use of only short-term anticoagulation (< 4 weeks) was permitted in Study 201 Core; use of antiplatelets were allowed. In 201 Core, participants who were on antithrombotics (antiplatelets or anticoagulants) during the period preceding an ARIA-H event (microhemorrhage or superficial siderosis), had a slightly higher incidence of ARIA-H events compared to those who were not (5/85 (6%) vs 3/76 (4%)), which was also seen in the placebo arm (6/127 (5%) vs 5/118 (4%)). This was also observed in the 201 OLE study (ARIA-H incidence 18/103 (17%) on antithrombotic vs 7/77 (9%) without an antithrombotic).

The determination of potential benefit of treatment with lecanemab should be made with consideration of the risk of ARIA. In the 201 Core study, at the proposed dose arm, 5/16 (31 %) of participants with ARIA-E, (5/20 [25%]) with ARIA), had symptoms. While the majority of ARIA-E is asymptomatic, symptomatic ARIA-E can cause significant morbidity in older individuals with a neurodegenerative disease. In the 201 Core study, ARIA, including symptomatic ARIA, occurred even with the trial's 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.

Because ARIA management decisions for lecanemab are mainly based on 16 participants with ARIA-E at the proposed dose of LEC10-BW in Study 201 Core, where ApoE ε4 allele carriers were underrepresented, I recommend an approach to ARIA monitoring and management, combining the limited experience from the 201 Core and OLE studies, the Division's approach to monitoring and managing ARIA for aducanumab and considering the published expert recommendations on appropriate use for aducanumab.[25]

I recommend safety MRIs for detection of ARIA-E prior to the 5th infusion, 7th infusion, and 14th infusion, which is consistent with the timing of MRIs performed during the first 6 months in Study 201 CORE. This approach is based on the fact that at the proposed dose in 201 Core majority of ARIA-E occurred before the 7th dose: 3/16 (19%) of the ARIA-E events occurred

[25] Cummings et al. Aducanumab: Appropriate Use Recommendations Update. J Prev Alz Dis 2022;2(9):221-230

between the 3rd and 5th doses, 9/16 (56%) were between the 5th and 7th dose (8/16 occurring between the 6th and 7th dose), 1/16 (6.3%) occurred between the 11th and 12th doses, and 1/16 (6.3%) occurred between the 26th and 27th doses, and 2/16 (12%) between the 32nd and 33rd doses. In 201 OLE, 5/14 of ARIA-E occurred between the 4th and 5th dose, 5/14 between the 5th and 7th dose, 3/14 between the 12thth and 14th dose, and 1/14 between the 22nd and 23rd dose. In 4 participants who were new exposures in 201 OLE and had ARIA-E , ARIA-E events occurred between the 4th and 5th, 5th and 6th, 6th and 7th, and between the 13th and 14th doses.

Of those participants who had serious ARIA-E events at the proposed dose (all of which also had clinical symptoms and were ApoE ε4 homozygotes), one occurred 7 days after the 3rd dose, two occurred between the 6th and 7th doses. Of the 6 radiographically severe ARIA-E events in all participants receiving lecanemab, one occurred between the 3rd and 4th dose, 4 occurred between the 6th and 7th doses, and one occurred between the 13th and 14th doses. In three participants in the LE10-M arm only, ARIA-E occurred 34-199 days after last dose. Therefore, I recommend continued clinical monitoring during the course of treatment and up to 6 months after treatment, and obtaining unscheduled MRIs for any emerging clinical symptoms suggestive of ARIA.

Because risk factors and clinical presentation of ARIA appear similar across anti-amyloid monoclonal antibody products, a standardized approach to management of ARIA for different anti-amyloid monoclonal antibody products is reasonable. As there may be differences between products in incidence and timing of ARIA, MRI monitoring schedule will remain specific for each anti-amyloid monoclonal antibody product. The following Dosing Recommendations for Participants with ARIA-E (Table 42) and ARIA-H (Table 43), reflect the Divisions' approach to management of ARIA updated on April 2022 (Aducanumab Label). In general, I agree with these dosing recommendations. I note that there is insufficient data from studies, submitted as part of this BLA, on the safety of continued dosing through radiographically mild ARIA-E with mild clinical symptoms. In the aducanumab label, it is recommended that, in radiographically mild ARIA-E with mild symptoms, dosing may be continued based on clinical judgment. The rationale for this recommendation is that some symptoms, such as nausea or dizziness, may be vague and there may be uncertainty regarding the relationship of these symptoms to ARIA. There were also a few instances where patients were treated with aducanumab through mild symptomatic ARIA-E without adverse outcomes. Therefore, it was determined that prescribers should use clinical judgment in determining if the presence of mild symptoms are of clinical concern and should preclude dosing with aducanumab. During the 201 Core study dosing was discontinued for any ARIA-E whether clinically symptomatic or not. During 201 OLE, dosing was discontinued for any ARIA-E that was symptomatic regardless of the radiographic severity of ARIA-E. Given the lack of safety data for lecanemab on continued dosing in radiographically mild ARIA-E with mild clinical symptoms due to study design, reliance on the clinical judgement of the treating physician, whether to continue dosing appears reasonable.

Table 42 Division's Dosing Recommendations for Participants with ARIA-E

Clinical Symptom Severity	ARIA-E Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[1]	Suspend dosing[1]
Mild	May continue dosing based on clinical judgment	Suspend dosing[1]	
Moderate or Severe	Suspend dosing[1]		

1. Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment.

Table 43 Division's Dosing Recommendations for Participants with ARIA-H

1. Clinical Symptom Severity	1. ARIA-H Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

1. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment.
2. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue Lecanemab.

The Division's approach for management of cerebral hemorrhage greater than 1 cm in diameter occurring in the context of treatment with anti-amyloid monoclonal antibody is suspending dose until MRI demonstrates radiographic stabilization and symptoms if present resolve (Aducanumab Label). Clinicians should use clinical judgment in considering whether to continue or permanently discontinue treatment. The rationale for this recommendation was that intracerebral hemorrhages can occur in an older population and may have an etiology that is unrelated to cerebral amyloid angiopathy or treatment with an anti-amyloid monoclonal antibody, such as a hypertensive hemorrhage or trauma. Clinicians should consider the potential etiology of the hemorrhage and also the individual risk factors for a patient when deciding whether to continue or permanently discontinue treatment. In Study 201 Core participants were discontinued if they had a cerebral hemorrhage > 1 cm. In the 201 OLE study, in participants with a single asymptomatic cerebral hemorrhage (greater than 1 cm at greatest diameter) study drug would continue uninterrupted with safety MRIs obtained at approximately every 30 days until the asymptomatic ARIA-H stabilized radiographically. For

symptomatic cerebral hemorrhage > 1 cm, the study drug was temporarily stopped until ARIA-H is stabilized and participant was no longer symptomatic.

Due to the small exposure numbers in Study 201 Core and 201 OLE, there is insufficient data in in this BLA application to determine the safety of continued dosing with lecanemab after a cerebral hemorrhage because there was only one participant in 201 Core who had an asymptomatic cerebral hemorrhage and one participant in 201 OLE who had a symptomatic cerebral hemorrhage. Until more data becomes available from the phase 3 studies, I recommend clinical judgement be used whether to continue treatment after a period of dose suspension until radiographic stabilization and resolution of clinical symptoms after a cerebral hemorrhage or permanently discontinue study drug. Clinical judgement should take into consideration the individual risk of a participant including the size and location of the cerebral hemorrhage, concomitant antithrombotic use, degree of ARIA-H burden, ApoE ε4 status, and the etiology of the hemorrhage (e.g., hypertensive bleed, spontaneous, trauma) and the possibility of having underlying diagnosis of cerebral amyloid angiopathy.

All participants should have a screening MRI obtained within 1 year prior to initiation. The safety of lecanemab in participants with history of seizures, TIA or stroke within 12 months prior to study drug initiation, and pretreatment presence of more than 4 microhemorrhages (less than1 cm at greatest diameter), a single cerebral hemorrhage greater than 10 mm, an area of superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease has not been established.

In Study 201 Core, those taking antiplatelets or anticoagulants had a slightly higher incidence of ARIA-H (microhemorrhage or superficial siderosis) compared to those who were not, both in the LEC10-BW arm (6% vs 4%) and placebo arm (5% vs 4%). This suggests that the use of antithrombotics may increases the risk of ARIA-H but the increase is similar in the LEC10-BW and placebo arms. In 201 OLE, the incident of ARIA-H was 17% in those on antiplatelet or anticoagulants and 9% in those not taking antiplatelets or anticoagulants. This also suggests that antithrombotics may increase the risk of ARIA-H but the absence of a placebo arm does not allow for assessment of any potential impacts of lecanemab. Of the two participants who had a cerebral hemorrhage in 201 Core and OLE, both were taking aspirin. Additionally, there were two participants (b) (6) in 301 OLE, who had one or more cerebral hemorrhage resulting in death while on lecanemab and concomitant antithrombotic or thrombolytic medication (See Section 7.5.2 for Narratives). Both received placebo during 301 Core. One of these participants (b) (6) received apixaban, and thrombin prior to the cerebral hemorrhage. The other participant (b) (6) received tPA for an acute stroke, and sustained bilateral multiple hemorrhages and subarachnoid bleed which led to death. Overall, the numbers are too small to draw any firm conclusions whether the risk of ARIA-H or cerebral hemorrhage while on lecanemab and antithrombotic is higher than antithrombotic alone. This

is further complicated by the fact that almost half of participants with AD have underlying CAA based on neuropathological exam,[26] and are at higher risk for ARIA-H and cerebral hemorrhage. A statement in the label, that prescribers should exercise caution and consider the potential increased risk of ARIA-H or cerebral hemorrhage when using antithrombotics or thrombolytics during treatment with lecanemab should be considered. The risk benefit considerations should take into account the individual risk of a participant (such as duration of treatment with lecanemab, history of ARIA-H or cerebral bleed, other co-morbidities that may further increase risk of bleeding) and a thorough discussion of the risk versus benefit with the patient and caregiver (as applicable).

The limited exposure to lecanemab in 201 Core, and the small numbers of participants with ARIA preclude drawing firm conclusions regarding characterization of ARIA after administration of lecanemab. If lecanemab is approved, I recommend that enhanced post marketing pharmacovigilance be requested for ARIA-E and ARIA-H (microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 cm, to include an evaluation of CNS hemorrhage in participants with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. This should also include evaluation of participant characteristics, including ApoEε4 genotype, if available. Additional information from Study 301 of lecanemab, as well as post marketing pharmacovigilance are expected to assist in more fully characterizing ARIA associated with lecanemab in the future.

ARIA-E and ARIA-H Definitions in Study 201 Core
In the original submission the applicant provided the following (Table 44) in the ISS to define ARIA-H and ARIA-E based on MedDRA Terms:

[26]Jäkel, Lieke et al. "Prevalence of Cerebral Amyloid Angiopathy: A Systematic Review and Meta-analysis." Alzheimer's & dementia: the journal of the Alzheimer's Association. 18.1 (2022): 10–28. Web.

Table 44 MedDRA Terms for ARIA-E and ARIA-H described in applicant table

Category Subcategory	Preferred Term	Lower Level Term
ARIA-E	Amyloid related imaging abnormality-oedema/effusion	ARIA-E, Asymptomatic ARIA-E, Symptomatic ARIA-E
ARIA-H		
Macrohemorrhage	Cerebral haemorrhage	Cerebral hemorrhage
Cerebral microhemorrhage	Cerebral microhaemorrhage	Cerebral microhemorrhage, Cerebral microhaemorrhage
Superficial siderosis	Superficial siderosis of central nervous system	Superficial siderosis of central nervous system

ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-hemorrhage.
MedDRA Version 24.0
Source: Table 4.1.5.9.

Reviewer Comment: In May 2022 in response to an IR from the Agency, the applicant revised their definition of ARIA-H to include Dictionary Derived Terms of cerebellar microhemorrhage. As a result, two participants who had cerebellar microhemorrhages were included as having ARIA-H.

To be consistent with the approach to classification of ARIA-H across anti-amyloid monoclonal antibody programs, including aducanumab, the Division classified ARIA-H as follows:

<u>MedDRA TERMS for ARIA-H by the Division of Neurology</u>
Cerebral microhemorrhage
Cerebellar microhemorrhage
Brainstem microhemorrhage
Superficial Siderosis

Cerebral macrohemorrhage or intracerebral hemorrhage or cerebral hemorrhage > 1 cm was not included under ARIA-H but presented as a separate category.

ARIA Monitoring

ARIA monitoring in the clinical trials included safety MRIs which included sequences that adequately capture the MRI findings associated with ARIA. The safety MRI had to be reviewed by the imaging vendor and a local reader, with agreement that none of the abnormalities on MRI which require discontinuation of study drug are present, prior to a participant receiving the next dose of study drug. In 201 Core, after the protocol revision that took place on July 9, 2014 (version 5 to version 6), MRI imaging for ARIA was performed during screening, prior to the 4th (European sites only), 5th, 7thth, 14th, 20th, 27th, the 33rd dose, and 2 weeks after the last dose of study drug in 201 Core.

Follow-up brain MRIs at approximately 30 days after the visit at which MRI features of ARIA were first identified were performed for all participants in whom ARIA was detected. Additional visits for safety could be arranged if clinically indicated in the opinion of the investigator, including after 90 days since the final dose of study drug.

ARIA-E and ARIA-H Radiographic Classification in Study 201
The applicant's radiographic severity for ARIA-E is described in Table 46 (revised per Amendment 12).

During the review process, it was noted that radiographic severity assessments for ARIA-H events were missing. An IR was sent to the applicant on April 12, 2022, to inquire about the applicant's approach to describe the radiographic severity of ARIA-H events. In their response the applicant clarified that there was no radiographic severity rating for ARIA-H events. The applicant stated that investigators were provided with the radiographic report for each participant's MRI, and the investigator would provide a severity grading based on the protocol defined severity grading for other AEs (mild: discomfort noticed, but no disruption of normal daily activity, moderate: discomfort sufficient to reduce or affect normal daily activity, severe: Incapacitating, with inability to work or to perform normal daily activity). Because all 68 participants with ARIA-H were asymptomatic, the applicant hypothesized that the investigators likely determined ratings of severity based on radiographic evidence as described in the radiographic report.

Use of a clinical symptom-based severity rating scale for asymptomatic radiographic findings was not consistent with Division analyses of other monoclonal antibodies targeting Aβ. On April 20, 2022, the Division requested that the applicant provide missing ARIA-E severity ratings as well as provide radiographic ARIA-H severity ratings using the Division proposed ratings Table 45, consistent with ARIA classification criteria as agreed upon with the Agency in the aducanumab prescribing information. The applicant provided an updated ADAE dataset on April 25, 2022, which included ARIA-H severity ratings based on radiographic findings, and ARIA E radiographic severity ratings that were previously missing. The classification of the radiographic severity of ARIA is presented in the table below.

Table 45 Radiographic Severity Assessment of ARIA-E and ARIA-H in 201 Core and OLE

ARIA Type		Radiographic Severity		
	Questionable	**Mild**	**Moderate**	**Severe**
ARIA E	Subtle sulcal or cortical FLAIR hyperintensity , most likely artifactual.	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5-10 cm in single greatest dimensions, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H * microhemorrhage	N/A	≤ 4 new incident microhemorrhages	5-9 new incident microhemorrhages	≥ 10 new incident microhemorrhages
ARIA-H Superficial siderosis*	N/A	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

**Radiographic severity classifications for ARIA-H were not part of the original protocol for 201 Core and OLE, and were retroactively applied as per the FDA's request.*

In addition, any cerebral hemorrhage > 1 cm (also referred to as macrohemorrhage) will be reviewed under a separate heading and will be analyzed separately and not part of ARIA-H.

ARIA Management

201 Core

Management of ARIA in 201 Core, shown in the table below, required discontinuations for all cases of ARIA except for asymptomatic cerebral microhemorrhage (Table 46)

Table 46 Management of ARIA in 201 Core

Clinical Symptoms	**ARIA-E**	**Cerebral Microhemorrhage**	**Superficial Siderosis**	**Cerebral Macrohemorrhage***
Asymptomatic	Discontinue dosing	Continue dosing	Discontinue dosing	Discontinue dosing
Symptomatic	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

**A macro-hemorrhage was defined as a cerebral hemorrhage that was greater than 10 mm (1cm) at greatest diameter*

201 OLE

In the ongoing 201-OLE study, safety MRIs are performed at Extension Baseline and at Extension Weeks 9, 13, and 27, (prior to the 5th dose, the 7th dose, and the 11th dose) and every 6 months thereafter. Management of ARIA-E in the 201-OLE is shown in the table below.

Table 47 Management of ARIA-E in 201 OLE

Clinical Symptoms	ARIA -E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Continue dosing	Continue dosing [a]	Temporarily stop dosing until radiographic resolution
Symptomatic (any severity)	Temporarily stop dosing until radiographic resolution and resolution of symptoms	Temporarily stop dosing until radiographic resolution and resolution of symptoms	Temporarily stop dosing until radiographic resolution and resolution of symptoms

[a] Dosing is temporarily stopped in Japan for asymptomatic, radiographically moderate ARIA-E until radiographic resolution.

Once the ARIA-E resolved both radiologically and clinically, participants could resume treatment for the study duration and study assessments on the Schedule of Assessments. Resumption of treatment following symptomatic and/or radiographically moderate or severe ARIA-E could only occur twice, after which the participant was to be discontinued from the study. (Revised per Amendment 13)

Management of ARIA-H in 201-OLE is shown in Table 48below.

Table 48 Management of ARIA-H in 201 OLE

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Continue dosing	Continue dosing	Continue dosing
Symptomatic	Temporarily stop dosing until ARIA-H is stabilized and participant is no longer symptomatic	Temporarily stop dosing until ARIA-H is stabilized and participant is no longer symptomatic	Temporarily stop dosing until ARIA-H is stabilized and participant is no longer symptomatic

Resumption of treatment following symptomatic ARIA-H could only occur twice, after which the participant was discontinued from the study (Revised per Amendment 12).

Participants who developed asymptomatic ARIA-H, could continue on the study and did not require additional MRI follow up outside the regularly scheduled assessment) with the following exceptions: participants who developed multiple (> 10) asymptomatic cerebral microhemorrhages, superficial siderosis, or a single cerebral hemorrhage (greater than 10 mm at greatest diameter) could continue on the study uninterrupted per the Schedule of Assessments, with an unscheduled safety visit (with MRI) at approximately 30 days after the MRI features were first identified and further safety visits (with MRI) at approximately every 30 days until the asymptomatic ARIA-H stabilized radiographically.

Participants who discontinued study treatment because of ARIA-E or ARIA-H, were to undergo the Early Termination Visit within 7 days of discontinuation and undergo the 3 month Follow Up Visit per protocol. These participants would continue to be followed with safety MRIs on a monthly basis thereafter, until the finding either resolved or stabilized.

Reviewer Comment: The approach in 301 Core (see 301 protocol) is similar to that taken in 201 core, while the 201 OLE approach to management is less stringent allowing for any radiographic severity ARIA-E to resume treatment if it is asymptomatic.

Analysis of ARIA

Incidence of ARIA in 201 Core

Because 10 mg/kg biweekly is the proposed maintenance dose of lecanemab, the analyses in this review will largely focus on that dose. **Table 49** presents the incidence of Treatment Emergent ARIA in 201 Core, including ARIA-E or ARIA-H which may occur in isolation or concurrently.

Table 49 Number of participants with one or more Treatment Emergent ARIA Events in Study 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
ARIA	4 (7.7)	7 (13.7)	16 (17.4)	38 (15)	20 (12.4)	13 (5.3)
ARIA-E	**1 (2)**	**1 (2)**	**3 (3.3)**	**25 (9.9)**	**16 (9.9)**	**2 (0.8)**
Isolated ARIA-E	0	0	2 (2.2)	11 (4)	9 (5.6)	1 (0.4)
Co-occurrence of ARIA-E and ARIA H	1 (2)	1 (2)	1 (1.1)	12 (4.7)	7 (4.3)	1 (0.4)
Not co-occurring concurrent ARIA-E with ARIA-H	0	0	0	2 (0.8)	0	0

ARIA-H	**3 (5.8)**	**7 (13.7)**	**13 (14.1)**	**25 (9.9)****	**10 (6.2)**	**12 (4.9)**
Isolated ARIA-H	3 (5.8)	6 (11.8)	13 (14.1)	13 (5.1)	4 (2.5)	11 (4.5)
Superficial Siderosis	0	1(2)	3 (3.3)	6 (2.4)	1 (0.6)	1 (0.4)
ARIA-Microhemorrhage	3 (5.8)	7 (13.7)	10 (19.6)	19 (7.5)	9 (5.6)	11 (4.5)

Co-occurrence of ARIA-E with ARIA-H is defined by this reviewer as incident ARIA-H that occurs while ARIA-E is radiographically present, this includes participants with a late occurring ARIA-H (beyond 30 days after last dose of study drug) while a treatment emergent ARIA-E was radiographically present.

Not co-occurring concurrent ARIA-E with ARIA-H refers to participants that either had an ARIA-H preceding the ARIA-E, or had an ARIA-H after the ARIA-E was radiographically resolved.

Isolated ARIA-E describes ARIA-E occurrence in a participant who had no ARIA-H during the duration of the study.
Isolated ARIA-H describes ARIA-H occurrence who had no ARIA-E during the duration of the study
ARIA-H includes the following preferred terms: cerebellar microhemorrhage, cerebral microhemorrhage, brainstem microhemorrhage

* (b) (6) *in the LE10-M arm had a cerebral microhemorrhage that was discovered during data reconciliation by the applicant, and this information was provided to the Agency on August 12, 2022. This cerebral microhemorrhage event was not added to the ADAE dataset by the applicant because other information such as symptoms, severity, and outcome were not known. This participant is included in the table for total number of ARIA-H events.*

Reviewer created using ISS ADAE dataset (submitted 08/12/2022) selected for Study ID= BAN2401-G000-201,, SAFFL=Y, TRTEMFL =Y.. A subset was created using dictionary derived term= amyloid related imaging abnormality-edema/effusion, brainstem microhemorrhage, cerebellar microhemorrhage, cerebral microhemorrhage, cerebral hemorrhage and superficial siderosis. Cerebellar microhemorrhage, brainstem microhemorrhage and cerebral microhemorrhage were all included in ARIA-H microhemorrhage. For All ARIA events, data was grouped by USUBJID and Actual Treatment for Period 01, and tabulated by Actual treatment for Period 01. The analyses were repeated with and without the treatment emergent flag.

The incidence of ARIA was greater in the LEC10-BW group compared to placebo treated participants (12.4 % versus 5.3 %), as well as across all doses Table 49. ARIA-E, as well as co-occurring ARIA-E and ARIA-H, had a higher incidence in the lecanemab-treated participants than in participants on placebo. Most participants on placebo who experienced ARIA had isolated ARIA-H. Isolated ARIA-H occurred less frequently in the LEC-10 BW arm than in the placebo group.

The overall incidence of ARIA-H associated with the use of LEC10-BW was observed in 6.2 % of participants treated with LEC10-BW compared to 4.9% of participants on placebo. This appeared to be largely influenced by co-occurrence with ARIA-E; ARIA-H in the setting of ARIA-E associated with the use of LEC10-BW was observed in 4% of participants treated with LEC10BWI compared to 0.4% of participants on placebo.

On November 7, 2022, the applicant submitted topline results from Study 301 Core. In the 301 Core ARIA-H was reported in 9 % in placebo and 17.3 % in the LEC10-BW arm. The incidence of ARIA-E was reportedly 1.7 % in placebo and 12.6 % the LEC10-BW arm. The primary data have

not been submitted or evaluated by the Agency in detail as of the present review and no conclusions can be made.

Similar observations have been noted in studies of other monoclonal antibodies. For example, in participants receiving bapineuzumab about half of those who developed ARIA-E also had incident ARIA-H, which occurred at the same time and location in majority of the cases.[27] In two phase 3 studies of aducanumab, the incidence of brain microhemorrhages and localized superficial siderosis was increased in participants with ARIA-E compared with participants without ARIA-E. In participants without ARIA-E, the incidence of brain microhemorrhage and localized superficial siderosis was lower and similar between the aducanumab and placebo groups.[18]

These findings suggest that ARIA-E and ARIA-H are related phenomena, and likely are related to changes in vascular permeability, resulting from the processes leading to removal of amyloid during treatment with anti-amyloid antibodies. As described by Sperling et al, it is possible that depending on the location of the vessel, in the parenchyma versus meninges, leakage of proteinaceous fluid could give rise to an increased signal detected on FLAIR images (ARIA-E) in the brain parenchyma (vasogenic edema) and leptomeningeal spaces (sulcal effusions), while leakage of red cells would result in ARIA-H, seen on T2*GRE MRI as cerebral microhemorrhages and hemosiderosis. [27]

Isolated ARIA-H (ARIA-H in participants who did not also experience ARIA-E) occurred more frequently (4.5%) in the placebo group than in in the LEC10-BW group (2.5%) in 201 Core. The prevalence of isolated ARIA-H in the placebo population appears to be consistent with the background rate of microhemorrhages in older individuals in the absence of anti-amyloid treatment.[19] The incidence of ARIA-H in general and specifically isolated ARIA-H was highest in the LEC5-M and LEC5 BW groups. It is possible that this is due to these groups having high percentage of ε4 carriers (78% and 91 % respectively compared to 30 % at the proposed dose LEC10-BW). However, the rate of isolated ARIA-H was not as high in the LE10-M arm which also had a high percentage of e4 carriers (89 %) arms. Current management of ARIA is not based on whether ARIA-E and ARIA-H events occurred concurrently or in isolation.

ARIA-E events and some of the ARIA-H events which were late-occurring, and occurred after more than 30 days after the last dose of study drug, were not considered treatment-emergent and were not included in Table 49 with the exception of the following: any ARIA-H that occurred while the ARIA-E was radiographically present, in some cases this included an ARIA-H event which was not treatment emergent and may have occurred more than 30 days after the last dose of study drug. Table 50 shows the incidence of late-occurring, nontreatment emergent ARIA events.

[27] Sperling et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol. 2012 March; 11(3): 241–249

Table 50 Incidence of one or more ARIA-E or ARIA -H occurring in Study 201 Core 30 days after the last dose of the study drug

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
ARIA	**1 (2)**	**0**	**6 (6.5)**	**10 (3.9)**	**6 (3.7)**	**2 (0.8)**
ARIA-E	0	0	0	3 (1.2)	0	O
ARIA-H	**1 (1.2)**	**0**	**6 (6.5)**	**10 (3.9)**	**6 (3.7)**	**2 (0.8)**
ARIA-H microhemorrhage	1 (2)	0	4 (4.3)	9 (3.6)	6 (3.7)	2 (0.8)
ARIA-H superficial siderosis	0	0	2 (2.2)	3 (1.2)	0	0

Reviewer created using ISS ADAE dataset (submitted 08/12/2022) selected for Study ID= BAN2401-G000-201,SAFFL=Y, TRTEMFL =N.. A subset was created using dictionary derived term= amyloid related imaging abnormality-edema/effusion, brainstem microhemorrhage, cerebellar microhemorrhage, cerebral microhemorrhage, cerebral hemorrhage and superficial siderosis. The dataset was grouped by dictionary derived term, USUBJID and Actual treatment for period 01, then tabulated by actual treatment for period 01.

Of ARIA occurring beyond 30 days after the last dose, most events, (including all events in LEC10-BW) were ARIA-H microhemorrhage. Late-occurring ARIA beyond 30 days after the last dose of study drug occurred at a mean duration of 93 days (range 34-177, median 84). The majority were carriers of one or more ApoE ε4 allele: 9/10 of participants in the LE10-M arm, all of the participants in the LEC2.5-BW (1/1), and the LEC5-BW arm (6/6) and, 4/6 in the LEC10-BW group arm.

I reviewed the narratives of the participants who had ARIA-E that occurred beyond 30 days after last dose of study drug administration in 201 Core. Participant (b) (6), with ApoE ε4/ε4 genotype, on LE10-M, had two ARIA-H microhemorrhages during Study 201 Core, and two additional ARIA-H microhemorrhages 107 days after the last dose of study drug and a first time ARIA-E, which was radiographically mild, that occurred 136 days after the last dose of the study drug. This participant also had ARIA-H superficial siderosis at the same time. The participant remained asymptomatic. Participant (b) (6), on LE10-M, with ApoE ε3/ε4 genotype, had radiographically moderate ARIA-E event that occurred 14 days after the 6th dose of study drug, and ARIA-H microhemorrhage 55 days after the last dose of study drug, and a radiographically mild ARIA-E event 113 days after last dose. This participant had mild headaches after the first ARIA-E occurrence. Participant (b) (6), on LE10-M, with ApoE ε4/ε4 genotype, had a radiographically mild ARIA-E and superficial siderosis identified on the day of the 26th dose of study drug administration and remained asymptomatic. Study drug was discontinued. ARIA-E radiographic severity worsened from mild to moderate 169 days after the study drug was discontinued.

The following are representative summaries of ARIA-H events which occurred beyond 30 days after last dose of study drug. Participant (b) (6), on LE10-M had new ARIA-H microhemorrhage occurring 40 days after last study dose and 23 days after first occurrence of ARIA-E. The ARA-E was still radiographically present at the time of the new ARIA-H and it is

possible that the ARIA-H microhemorrhages are due to the mechanisms underlying amyloid removal that led to ARIA-E. This participant also experienced intermittent dizziness during this period that the investigator attributed to changes in escitalopram dose, but which also may have been related to ARIA. Participant (b) (6), on LE10-M had the first occurrence of ARIA-E and ARIA-H microhemorrhage occurring 7 days after the 6th study dose on Study Day 77. On Study Day 133 (60 days after last study drug administration), the participant had new ARIA-H microhemorrhage and ARIA-H superficial siderosis. It is possible in this case that the ARIA-H was not related to study drug; participant' s main risk for nondrug related ARIA-H was being an ε4 homozygote. Participant (b) (6), with ε2/ε3 genotype, on LEC10-BW had bi-occipital ARIA-E and ARIA-H 9 days after the 11th dose, but continued to have new cerebral microhemorrhages, up to day 331 (162 days after last dose of study drug).

Reviewer Comment: Whether the study drug plays a role in these late-occurring, nontreatment emergent ARIA events that occur on average 84 days after last dose of study drug is unclear. ARIA-H in older people is not uncommon, and it is possible that these late-occurring ARIA-H events are unrelated to study drug. These did occur at a higher incidence in participants who have received the study drug compared to placebo, and at higher incidence in ApoE ε4 carriers Whether study drug contributed to the two new ARIA-E events, and radiographic worsening in one ARIA-E over 100 days after the last dose is unclear. Until these late-occurring events are better characterized in larger studies, continued clinical vigilance in monitoring participants for 6 months after study drug discontinuation may be considered.

Incidence of ARIA in Study 201 OLE

The overall rate of ARIA in Study 201 OLE was slightly higher compared to the rate in the LEC10-BW group in Study 201 Core (18 % versus 12 %) (Table 49 &Table 51).

The overall incidence of ARIA-E in the OLE period was comparable to the ARIA-E incidence in the LEC10-BW group in Study 201 Core (8 % vs 9.9 %). On average there was a gap period of 2 years between a participant's completion of the 201 Core Study and participation in the 201 OLE study. Examination of the Amyloid positron emission tomography (PET) Standardized uptake value ratio (SUVR) suggests that those receiving the proposed dose during the 201 Core had lower amyloid PET SUVR after completion of Study 201 Core compared to placebo, which was mostly sustained during this gap period. Thus, the incidence of ARIA-E in the overall 201 OLE population may be slightly lower, because the amyloid burden for a subgroup of participants was already significantly reduced through their participation in 201 Core. The incidence of ARIA-E in the 45 participants who received placebo during their participation in the 201 Core, was 4/45 (9 %), a similar incidence as in the 201 Core study. The incidence of ARIA-E in the 135 OLE patients who received lecanemab during their participation in 201 Core was 10/135 (7.4%).

The overall incidence of ARIA-H was twice as much during the OLE period compared to the LEC10-BW arm in 201 Core (13 % vs 6 %). This was also true for isolated ARIA-H 10 % in 201 OLE, and 2.5 % at the proposed dose arm in 201 Core. The incidence of ARIA-H in the 45 placebo treated participants during the OLE period was also higher 5/45 (11 %). Of the 5 ARIA-H events in the drug naive OLE participants, 5 had one or more cerebral microhemorrhages and one participant had one or more superficial siderosis. One of the participants who received placebo during the 201 Core study, had a cerebral hemorrhage in the 201 OLE study. The longer duration of exposure, allowing participants to be on anticoagulants (see Table 66), combined with continued dosing after an ARIA event (which was per protocol not allowed in 201 Core but allowed in 201 OLE), may have led to more ARIA-H events in the OLE period. The limited exposures and absence of a placebo group limit the interpretation of these findings.

Table 51 Participants with one or more Treatment Emergent ARIA event in Study 201 OLE

	N=180 N (n%)
ARIA	32 (18)
Total ARIA- E	14 (8)
Isolated ARIA-E without ARIA-H	6 (3)
Co-occurring ARIA E and ARIA-H	8 (4)
Total ARIA H	26 (14)
Isolated ARIA H	18 (10)
All ARIA-H superficial siderosis	8 (4)
Superficial siderosis with ARIA-E	3 (2)
Isolated Superficial siderosis	5 (3)
All ARIA-H Microhemorrhage	22 (12)
ARIA-H microhemorrhage with ARIA-E	6 (3)
Isolated ARIA-H microhemorrhage	16
Cerebral hemorrhage > 1 cm	1 (1)
Cerebral hemorrhage with ARIA-E	0
Isolated Cerebral hemorrhage	1 (1)

Reviewer created using ISS ADAE dataset submitted on 08/12/2022, based on inclusion of newly recognized ARIA-H cases. Dataset was selected for Study ID= BAN2401-G000-201-OLE, ,SAFFL=Y, TRTEMFL =Y and dictionary derived terms for amyloid related imaging abnormality-edema/effusion, cerebral microhemorrhage, cerebral hemorrhage, and brainstem hemorrhage Then grouped by dictionary derived term, and USUBJID, and tabulated by dictionary derived term. The PT of brainstem hemorrhage had a verbatim term of pons microhemorrhage and thus was included under the ARIA-H microhemorrhage count. There were no cerebellar microhemorrhages in this dataset.

Impact of ApoE ε4 Allele Status on Frequency of ARIA

Study 201 Core

As a result of changes in study protocol, only 49/161 (30%) participants in the LEC10-BW arm were carriers of the ApoE ε4 allele carriers whereas, in other dose groups, the prevalence of ε4 carriers ranged from 69 % to 89 % (Table 7). Therefore, interpretation of ARIA related analyses

by ApoE ε4 carrier status should consider the limitations of the unbalanced subgroups and the small number of ApoE ε4 carriers in the proposed dose.

As shown in the table below (**Table 52**) there is an increased risk of ARIA-E and of ARIA-H microhemorrhage in ApoE ε4 carriers compared to non-carriers; the risk is greater in ApoE ε4 homozygotes than in heterozygotes. The increased risk of ARIA in ApoE ε4 carriers is consistent with findings previously reported for aducanumab. [28]

Table 52 Participants with one or more Treatment Emergent ARIA event by ApoE status in LEC10-BW (n=161) vs Placebo (n=245) in Study 201 Core

	Homozygote		Heterozygote		Noncarriers	
	LEC10-BW (n=10) N (%)	PBO (N=40) N (%)	LEC10-BW (N=39) N (%)	PBO (N=134) N (%)	LEC10-BW (N=112) N (%)	PBO (N=71) N (%)
ARIA	5 (50)	2 (5)	4 (10)	8 (6)	11 (10)	3 (4)
ARIA-E	5 (50)	1 (2)	2 (5)	1 (1)	9 (8)	0
ARIA-H microhemorrhage	3 (30)	1 (2)	3 (8)	7 (5)	3 (3)	3 (4)
Superficial Siderosis	0	0	0	1 (1)	1 (1)	0
Cerebral Hemorrhage > 1 cm	0	0	0	0	1 (1)	0

Reviewer created using the ISS ADAE dataset selected for Study ID= BAN2401-G000-201,SAFFL=Y, TRTEMFL =Y, dictionary derived terms ARIA E, cerebellar/brainstem/ cerebral microhemorrhage, superficial siderosis, cerebral hemorrhage. Subsets for ApoE genotype created and each, grouped by unique subject ID, dictionary derived term and actual treatment in period 1, and tabulated by dictionary derived term and actual treatment in period 01.

201 OLE

In the 201 OLE study, 28 (16 %) of the participants were homozygotes for the ε4 allele, 97 (54 %) were heterozygote, and 55 (31%) were noncarriers. ARIA-E was more commonly observed in carriers of the ApoE ε4 allele compared to noncarriers (observed in 14 % homozygotes, 9 % heterozygotes and 2 % in noncarriers (Table 53).

Table 53 Incidence of Treatment Emergent ARIA events by ApoE status in 201 OLE

Dictionary Derived Term	**Homozygote (n=28) N (%)**	**Heterozygote (n=97) N (%)**	**Noncarriers (n=55) N (%)**
ARIA	12 (42)	18 (19)	2 (1)
ARIA-E	4 (14)	9 (9)	1 (2)
ARIA-H microhemorrhage	9 (32)	11 (11)	2 (4)
Superficial Siderosis	3 (11)	5 (5)	0
Cerebral Hemorrhage > 1cm	0	0	1 (2)

Reviewer created using ISS ADAE dataset (submitted on 08/12/2022 to include newly identified ARIA-H cases), selected for study ID= BAN2401-G000-201 OLE, SAFFL=Y, TRTEMFL =Y, Dictionary derived Terms: ARIA E, cerebellar microhemorrhage,

[28] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process).

cerebral microhemorrhage, brainstem hemorrhage, superficial siderosis, cerebral hemorrhage. Subsets for ε4/ε4, ε3/ε4 (no ε2/ε4 genotype), and ε3/ε3 (no ε2/ε3 in this cohort) were created. These were grouped by unique subject ID, dictionary derived term and tabulated by dictionary derived term. Each participant was represented once under each dictionary derived term.
** Participants included in table 37 had multiple events and therefore, the sum of the cells in a column do not add up to the total number participants with the genotype in the column heading. For example, participant* (b) (6) *who was an ε3/ε4 carrier had 3 ARIA-E events, two cerebral microhemorrhage events and 2 superficial siderosis events (this participant was counted once under the dictionary derived terms ARIA-E, cerebral microhemorrhage and superficial siderosis).*

In the 45 who received placebo in 201 Core and participated in the 201 OLE study, the overall incidence of ARIA-E was 4/45 (9 %). Four were homozygotes, 27 were heterozygotes, and 14 were noncarriers of the ε4 allele. The incidence of ARIA-E was 1/4 (25 %), in homozygous participants, and 3/27 (11%) in heterozygotes. None of the noncarriers had ARIA-E in this group. ARIA-H microhemorrhages were observed in 2/4 (50%) homozygotes, and in 3/27 (11 %) heterozygotes. Superficial siderosis was only observed in 1/27 heterozygotes, and not in the other groups.

Severity of ARIA

See Table 45 for the definitions used to rate the severity of ARIA-E and ARIA-H based on radiographic findings. Radiographic severity of ARIA in the core study is shown in the table below (Table 54). There were too few ApoE ε4 carrier participants to evaluate severity by ApoE ε4 status.

Table 54 Participants with one or more Treatment Emergent ARIA Events, by Maximum Radiologic Severity, in the Study 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	All LEC groups N=609 (N%)	Placebo N= 245 N (%)
All ARIA							
Questionable	0	0	0	3 (1.2)	0	3 (0.5)	1 (0.4)
Mild	3 (5.8)	6 (11.8)	12 (13)	20 (7.9)	11 (6.8)	39 (6.4)	11 (4.5)
Moderate	0	1 (2)	4 (4.3)	12 (4.7)	7 (4.3)	20 (3.3)	1 (0.4)
Severe	1 (1.9)	0	0	3 (1.2)	2 (1.2)	6 (1)	0
ARIA-E							
Questionable	0	0	0	3 (1.2)	0	3 (0.5)	1 (0.4)
Mild	0	1 (2)	1 (1.1)	9 (3.6)	7 (4.3)	18 (3)	1 (0.4)
Moderate	0	0	2 (2.2)	10 (4)	7 (4.3)	19 (3.1)	0
Severe	1 (1.9)	0	0	3 (1.2)	2 (1.2)	6 (1)	0
ARIA -H microhemorrhage							
Questionable	0	0	0	0	0	0	0
Mild	3 (5.8)	6 (11.8)	9 (9.8)	14 (5.5)	7 (4.3)	39 (6.4)	10 (4.1)
Moderate	0	1 (2)	1 (1.1)	3 (1.2)	0	5 (0.8)	1 (0.4)
Severe	0	0	0	1 (0.4)	2 (1.2)	3 (0.5)	0
ARIA-H superficial siderosis							
Questionable	0	0	0	0	0	0	0
Mild	0	1 (2)	2 (2.2)	5 (2)	1 (0.6)	9 (1.5)	1 (0.4)
Moderate	0	0	1 (1.1)	1 (0.4)	0	2 (0.3)	0
Severe	0	0	0	0	0	0	0
Cerebral hemorrhage > 1 cm							
Questionable	0	0	0	0	0	0	0
Mild	0	0	0	0	1 (0.6)	1 (0.2)	0
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0

Reviewer Created using ISS ADAE (submitted on 08/12/2022) selected for Study ID= BAN2401-G000-201 = SAFFL=Y, TRTEMFL =Y,: dictionary derived term for ARIA, then creating subgroup datasets for ARIA subtypes, and grouping by unique subject ID, maximum derived radiological severity and actual treatment in period 1, and then tabulating by actual treatment during period 01, and maximum radiological severity. Brainstem hemorrhage (verbatim term pons microhemorrhage) in a participant in the placebo arm did not have a maximum severity rating and was not included in this table.

In Study 201 OLE, radiographical severity classification in the majority of ARIA-E events were moderate (50%) or severe (20 %). The majority of ARIA-H events were classified as mild (77 %). (Table 55)

Table 55 Participants with Treatment Emergent ARIA Events, by Maximum Radiologic Severity, in the 201 OLE study

ARIA	n=180 N (%)
Questionable	0
Mild	15(8.3)
Moderate	10(5.6)
Severe	6 (3.3)
Missing	1 (0.6)
ARIA-E	
Questionable	0
Mild	3 (1.7)
Moderate	7 (3.9)
Severe	4 (2)
Missing	0
ARIA -H microhemorrhage	
Questionable	0
Mild	15 (8.3)
Moderate	4 (2.2)
Severe	1(0.6)
Missing	1 (0.6)
ARIA-H superficial siderosis	
Questionable	0
Mild	4 (2.2)
Moderate	2 (1.1)
Severe	2 (1.1)
Cerebral hemorrhage > 1 cm (n=1)	
Questionable	0
Mild	0
Moderate	1 (0,6)
Severe	0

Reviewer Created using ISS ADAE (submitted on 08/12/2022) selected for Study ID= BAN2401-G000-201-OLE, SAFFL=Y, TRTEMFL =Y,: dictionary derived terms for ARIA, then creating subgroup datasets for ARIA subtypes, and grouping by USUBJID and maximum derived radiological severity, and then tabulating by maximum radiological severity. Brainstem hemorrhage (verbatim term pons microhemorrhage) in a participant in the placebo arm did not have a maximum severity rating and was not included in this table.

Incidence of SAEs, discontinuations and TEAEs attributed to ARIA

201 Core

The incidences of SAEs, discontinuations, and TEAEs attributed to ARIA in 201 Core are shown in the table below. Of note, an SAE was considered to be any untoward medical occurrence that:

- Resulted in death.

- Was life-threatening
- Required in participant hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug).

Other important medical events that may have not been immediately life-threatening or resulted in death or hospitalization but, when, based on appropriate medical judgment, may have jeopardized the participant or may have required intervention to prevent one of the outcomes in the definition of SAE listed above were also considered SAEs.

There were a total of 4/609 participants who had an SAE ARIA-E occurrence across all lecanemab arms: three (b) (6) were in the LEC10-BW arm, and one (b) (6) in the LE10-M arm (Table 56). (b) (6) all had radiographically severe ARIA-E with severe clinical symptoms associated with the ARIA-E. In participant (b) (6), radiographic severity of ARIA -E was mild and clinical symptoms were deemed moderate. The SAE designation was due to this being an important medical event. These cases are further described under the Narratives in this section.

Table 56 Incidence of Treatment Emergent SAEs, discontinuations and TEAEs attributed to ARIA in 201 Core

		LEC10-BW N=161 N (%)	Placebo N=245 N (%)
ARIA Overall *	SAES Discontinuations TEAEs	3 (2) 17 (11) 20 (14)	0 1 (<1) 13 (5.3)
ARIA-E	SAES Discontinuations TEAEs Symptomatic ARIA-E	3 (2) 16 (10) 16(10) 5 (3)	0 1 (<1) 2 (1) 0
ARIA-H microhemorrhage	SAES Discontinuations TEAEs	2 (1) 2 (1) 9 (6)	0 0 11 (4)
ARIA-H superficial siderosis	SAES Discontinuations TEAEs	0 1 (1) 1 (1)	0 0 1 (<1)
Cerebral hemorrhage > 1 cm	SAES Discontinuations TEAEs Symptomatic	0 1 (1) 1 (1) 0	0 0 0 0

**** Does not include cerebral hemorrhage > 1 cm***

201 OLE

Discontinuation for ARIA-E was not required per protocol in the 201 OLE study. Overall, there were no discontinuations due to ARIA. Study drug was interrupted in 9 participants due to an ARIA event, and dose was not changed in response to an ARIA event in 28 participants in Study 201 OLE. One participant with a cerebral hemorrhage > 1 cm also had study drug interrupted (not included under the ARIA count).

There was 1 participant who had a Serious ARIA event and one that had a serious cerebral hemorrhage in 201 OLE (detailed narratives provided under narratives in this section) (Table 57). One participant had ARIA-E and ARIA-H superficial siderosis (b) (6) which were identified as serious by the investigator as they were medically important events, but were asymptomatic, and the participant received 3 doses through the ARIA-E event. The participant chose to discontinue the study for other reasons unrelated to ARIA. Participant (b) (6) who was assigned to placebo during 201 Core, experienced an occipital lobe hematoma (cerebral hemorrhage > 1 cm) with edema and mass effect measuring 3.8x2.8 cm. after the third dose during her participation in the 201 OLE study. Study drug was held and restarted after 81 days once serial follow up MRI showed decreased in size of cerebral macrohemorrhage, and her participation in 201 OLE is ongoing.

Table 57 Incidence of Treatment Emergent SAEs, discontinuations and TEAEs attributed to ARIA in 201 OLE

		N=180 N (%)
ARIA Overall	SAES Discontinuations TEAEs	1 (1)* 0 33 (18)
ARIA-E	SAES Discontinuations TEAEs	1 (1) 0 14 (8)
ARA-H microhemorrhage	SAES Discontinuations TEAEs	0 0 22 (12)**
ARIA-H superficial siderosis	SAES Discontinuations TEAEs	1 (1) 0 8 (4)
Cerebral Hemorrhage	SAES Discontinuations TEAEs	1 (1) 0 (0) 1 (1)

** This participant had ARIA-E and superficial siderosis both of which were assigned as serious events by the investigator as these were designated medical events, but the participant remained asymptomatic and radiographic severity was mild for both ARIA-E and ARIA-H superficial siderosis.*
***Included in this number are 21 cerebral microhemorrhages and one PT of brainstem hemorrhage (with a verbatim term of pons microhemorrhage).*

Clinical Symptoms Associated with ARIA

201 Core

In Study 201 Core in all lecanemab arms, 7/46 (15%) participants with ARIA-E and/or-H experienced associated clinical symptoms. Neither of the 2 participants with ARIA-E in the placebo arm (both of mild radiographic severity) had associated symptoms. No participants with isolated ARIA-H had symptoms.

At the proposed dose of lecanemab, 5/20 (25%) of participants who had ARIA-E and/or-H experienced associated clinical symptoms (Table 58). The overall incidence of having an ARIA-E and/or -H event with clinical symptoms was 5/161 (3%) in the proposed dose arm. Of the 5 patients with symptoms in the proposed dose arm, 4 were ApoE ε4 homozygotes and 1 was a noncarrier. Clinical symptoms resolved in the majority of participants [4/5 (80 %)] receiving the proposed dose during the period of observation.

Table 58 Participants with clinical symptoms associated with Treatment Emergent ARIA-E in the placebo-controlled portion of Study 201 Core

Participant ID Age ApoE genotype	Dose	Last dose taken prior to ARIA	Serious event	ARIA-E radiographic severity	Concurrent Treatment Emergent ARIA-H with ARIA-E	Symptoms Severity of Symptoms	Outcome
(b) (6) 54, M, E3/E4	LEC2.5 BW	13th dose	No	Severe	No	Visual field deficit Moderate	Recovered with sequela
(b) (6) 79, M, E3/E4	LE10-M	6th dose	Yes	Mild	No	Burning sensation on head, headache Moderate; SAE of ARIA-E (moderate clinical severity, mild radiographic severity); considered medically significant	Recovered
(b) (6) 56, F, E4/E4*	LEC10-BW	3rd dose	Yes	Severe	Micro-hemorrhages Severe	Headache, confusion, vomiting, visual field deficit Severe	Recovered after steroid treatment
(b) (6) 65, M, E4/E4	LEC10-BW	6th dose	No	Moderate	No	Headache Mild	Recovered
(b) (6) ** 69, M, W E4/ε4	LEC10-BW	6th dose	Yes	Moderate	No	Aphasia, Right hand tingling TIA	Recovered

						Severe	
(b) (6) ** 72, M, E4/E4	LEC10 -BW	6th dose	Yes	Severe	Micro-hemorrhages Severe	Agitation, confusion, fluctuating status with delusion/lethargy/incoherence, significant frontal EEG slowing, confabulation, instability, hallucinations, possible generalized seizure Severe	Was treated with steroids and improving at last visit, with final clinical outcome unknown.
(b) (6) 69,M E3/E3	LEC10 -BW	5th dose	No	Moderate	No	Blurred vision in left eye, mild pressure left side of head Moderate	Recovered

Clinical symptoms associated with ARIA s obtained from the updated ISS ADAE sequence submitted with sequence 044 on June 8, and participant narratives.

**Participant (b) (6) also had severe subdural hemorrhage with ARIA-E and microhemorrhages that were both severe*

***Participant (b) (6) had TIA listed in the ADAE dataset. The Agency does not agree with this determination as the symptoms of transient aphasia and right-hand tingling were less likely to be due to a transient ischemic attack (cerebrovascular ischemic event) but were related to ARIA event in this participant, which was in the bilateral posterior parietal lobes, enlargement of sulci consistent with mass effect, and some white matter changes in bilateral posterior parietal lobes along with few subtle areas of temporal lobe and occipital lobe.*

For participant (b) (6) during the re-review of the narratives in response to an IR from the agency, the applicant revisited the original records to determine whether the participant truly had a seizure or not. In the original narrative, it was stated that "the participant had a generalized seizure" as part of the ARIA event. In the CIOMS the seizure event was described as follows: "On route to the hospital, the participant had a generalized seizure (not reported as event), based on the description provided by the participant's wife." No seizures were reported during the participant's hospital stay, and his EEG showed frontal slowing. The applicant requested further clarification from the site investigator whether based on their clinical judgement this was a seizure event. The PI sent written documentation via email in June 2022, to the applicant stating that based upon re-review of all available records, it was the PIs clinical judgement that there was no seizure event. The applicant updated the CIOMS for participant (b) (6) to include this information.

As there was no new information provided to re-adjudicate this event, I will continue to consider that this participant had a possible seizure event in this review.

The most commonly reported symptoms in participants with ARIA in the 201 Core study occurring in more than 2 participants were headache/head pressure/head discomfort,

agitation, confusion/mental status change, blurred vision, and burning sensation/paresthesia. The following occurred in one person each: visual field defect, labile affect, aphasia, confabulation, vomiting, possible seizure, transient ischemic attack, hallucination. Clinical findings reported were abnormal electroencephalogram, hyperreflexia, clonus, homonymous hemianopsia

Of the 7 participants receiving lecanemab who had symptomatic ARIA-E across all lecanemab doses in 201 Core, the radiographic severity of ARIE- E was mild in 1, moderate in 3, and severe in 3 participants.

When reviewing all ARIA-E events by radiographic severity in Study 201 Core, none of the 3 participants who had an ARIA-E radiographic severity rating of questionable were symptomatic. Of the 18 participants with radiographic severity rating of mild ARIA-E, only one participant was symptomatic with moderately severe symptoms. Of the 19 ARIA-E events with radiographic severity rating of moderate, 3 were symptomatic (with moderate or severe clinical symptoms). Of the 6 ARIA-E events which had a radiographic severity rating of severe, 3 were symptomatic (one with moderately severe symptoms, and 2 with severe clinical symptoms).

In 201 Core, there were no isolated ARIA-H microhemorrhage or ARIA-H superficial siderosis that were associated with clinical symptoms in the treatment or placebo arms. However, 4 (b) (6) of the 7 participants with symptomatic ARIA-E had co-occurring ARIA-H events.

201 OLE

In Study 201 OLE, 3 of the 14 participants with ARIA had clinical symptoms (incidence of 21 %). The overall incidence of having an ARIA event with clinical symptoms was 2 % (3/180) . Two of these participants had multiple ARIA-E events (Table 59).

Table 59 Symptoms associated with ARIA in the 201-OLE study

Subject Identification	Last dose taken before ARIA	Serious event	ARIA-E radiographic severity	Concurrent Treatment Emergent ARIA-H with ARIA-E	Symptoms	Action taken with study drug	Outcome
(b) (6) * 79, F, W E3/E3	13th dose	No	Moderate	Microhemorrhage Mild	Intermittent Left occipital headaches Mild	Temporarily interrupted (2 doses), then restarted	Recovered
(b) (6) * 72m M, W E4/E4	7th dose symptomatic ARIA-E)	No	Severe (steroid treatment)	Microhemorrhage Severe	Worsening dizziness Moderate	Study drug held-; participant withdrew	Not recovered
(b) (6) * 83, F, W E3/E3	5th dose	No	Moderate	Superficial siderosis Severe	Intermittent headaches	Study drug temporarily interrupted	Recovered

All of the participants in this table had other ARIA-E and ARIA-H events during their participation in Study 201 OLE, only ARIA-E that was closest to the onset of clinical symptoms and identified by the applicant as symptomatic were included in the table.
(b) (6) *had discontinued 201 core due to ARIA*

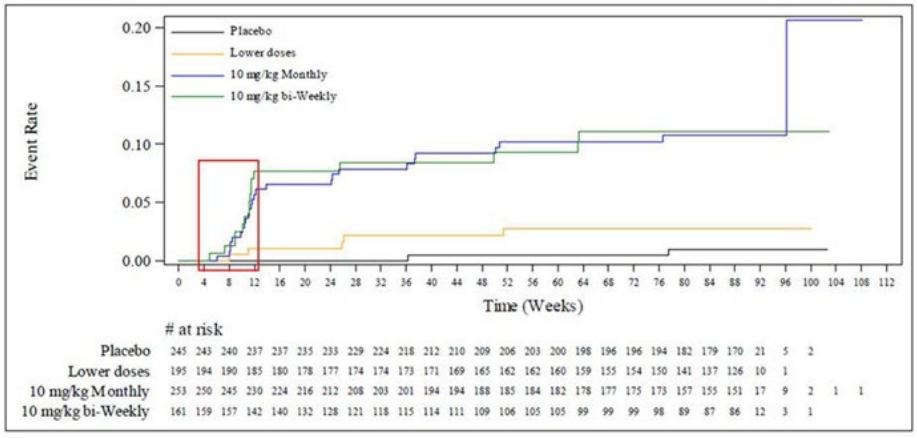
Narratives of all symptomatic ARIA participants can be found under the Narrative heading in this section.

Timing of ARIA

201 Core

In Study 201 Core the majority of ARIA-E in those receiving LEC10-BW was observed within the first 3 months (Figure 1).

Figure 1 Kaplan-Meier Plot of Time to First ARIA-E Event – Study 201 Core (Safety Analysis Set) (obtained from applicant document summary of clinical safety)



	Time (Weeks)				
Event rate of ARIA-E (%)	12	24	48	52	76
Placebo	0	0	0.5	0.5	0.5
Lower doses	1.1	1.1	2.2	2.8	2.8
10 mg/kg Monthly	5.7	6.5	9.2	10.2	10.2
10 mg/kg bi-Weekly	7.7	7.7	8.4	9.3	11.1

ARIA-E = amyloid-related imaging abnormality-edema/effusion. Source: Figure 4.1.5.1.

At the proposed dose in 201 Core, the majority, 12/16 (75 %), of ARIA-E events occurred before the 7th dose at the week 13 MRI (Table 60). The timing of first ARIA events in the 201 OLE is generally consistent with that observed in the 201 Core Study.

In 201 Core, treatment emergent ARIA-E occurred on average 8 days (SD 7, range: 1-34) after a dose and on average lasted for 82 days before it resolved in participants receiving lecanemab. In two instances (b) (6) radiographically mild, asymptomatic ARIA-E occurred in the range of 113-136 days after last dose. In participant (b) (6) asymptomatic ARIA-E that occurred during treatment, worsened from radiographically mild to moderate 169 days after the last dose of study drug. In all cases participants remained asymptomatic, and MRIs were done as per protocol to follow up with existing ARIA. ARIA H microhemorrhage occurred on average 30 days after the last dose (median 9, range 1-198), ARIA-H superficial siderosis occurred on average 28 days after last dose (range 1-170, median 8.5 days).

Table 60 Timing of first ARIA-E events in LEC10-BW group in Study 201 Core

Number of doses received prior to ARIA-E	Days Since Last Dose to ARIA-E Onset # of days or range of days	# of Participants experiencing a first ARIA-E	Cumulative frequency of first ARIA-E N (%)
3	7	1	1 (6)
4	10-20	2	3 (19)

5	6	1	4 (25)
6	1-14	8	12 (75)
11	10	1	13 (81)
26	2	1	15(94)
32	8-9	2	16 (100)

In Study 201 OLE time to first ARIA-E event is shown in Table 61. The highest number of ARIA-E events occurred after the 4th and 6th doses (weeks 6 and 8). ARIA-E beyond the first event in 10 participants who had multiple ARIA-E events were not counted in this table but are discussed in the paragraphs below.

Table 61 Timing to First ARIA-E event in 201 OLE

Lecanemab infusion number/dosing week	Days Since Last Dose to AE onset # of days or range of days	# of Participants experiencing a first ARIA-E	Cumulative frequency of first ARIA-E N (%)
4	1-12	5	5 (36)
5	1	1	6 (42)
6	1-4	4	10 (71)
12	19	1	11 (79)
13	13-15	2	13 (93)
22	2	1	14 (100)

Participants with Multiple ARIA Events

201 Core

In Study 201 Core, participants who had ARIA-E, superficial siderosis, or cerebral hemorrhage were to be discontinued from study drug. However, there were 5 participants (b) (6) who were dosed through an ARIA-E event. In four of these participants, there were no further ARIA-E events despite further dosing, the ARIA-E did not worsen radiographically, and the participants remained asymptomatic. Participant (b) (6) had an increase in ARIA-E size, with worsening in radiographic severity from mild to severe, though the participant remained asymptomatic.

In 201 Core, 25 participants (2 (0.8%) in placebo, 23 (3.8 %) across all lecanemab doses, and 6(4%) in LEC10 BW) continued to have new onset ARIA events, which occurred beyond 30 days after the study drug was discontinued (Table 50). On average these occurred 92 days after the last dose (range 34-177, median 84 days). These were mostly ARIA-H events, but there were three participants, all in the LE10-M arm, who had had new ARIA-E (b) (6) 113 days, 169 days, and 136 days after the last dose, respectively. All were carriers of the ε4 allele and had ARIA-H. Participants (b) (6) had treatment emergent

ARIA-E event that led to study drug discontinuation and had additional ARIA-E events. Participant (b) (6) did not experience a treatment emergent ARIA-E (did experience a treatment emergent ARIA-H microhemorrhage), with the first ARIA-E event occurring 136 days after the last dose of study drug. These will be described under the ARIA-E narratives. While both ARIA-E and ARIA-H can occur in the absence of lecanemab; and the relationship to study drug in these cases is not clear, more participants receiving lecanemab had late-occurring ARIA events compared to placebo.

201 OLE

Since dosing through ARIA-E was permitted for asymptomatic radiographically mild or moderate ARIA-E, and any asymptomatic ARIA-H (regardless of radiographic severity) in the 201 OLE study, some continued to be dosed after an ARIA-E and had multiple ARIA-E events. There is no experience in the OLE with continued dosing through symptomatic, radiographically mild ARIA-E.

Of the 14 participants with ARIA-E events in the OLE, 3/14 participants' dose was interrupted after the first ARIA-E occurrence; two were radiographically moderate (b) (6) and one radiographically severe (b) (6). One (b) (6) was symptomatic with occipital headache. In all participants, dosing continued after resolution of radiographic ARIA-E and symptoms (b) (6). None had recurrent ARIA-E. Participants (b) (6) withdrew from study prior to completion, and (b) (6)'s participation was ongoing at the time of the 120-Day Update. In 11/14 participants dosing continued after the first ARIA-E. Four out of 11 participants who were all asymptomatic and had radiographically mild (b) (6) and moderate (b) (6) ARIA-E were dosed without interruption, remained asymptomatic, and did not have any further ARIA-E events. Two of these prematurely discontinued from study due to other reasons prior to completion (b) (6) and participation was ongoing at the time of the 120 Day Update for two participants (b) (6) (b) (6) without any further ARIA-E events. Seven out of 11 participants (b) (6) (b) (6) in whom dosing was continued after the first ARIA-E event developed subsequent ARIA-E events or increase in size or worsening of the radiographic severity of the original ARIA-E event with or without ARIA-H or became symptomatic. None of these first ARIA-E events were deemed serious; 6/7 were moderately severe. Of these participants all but two (b) (6) also had ARIA-H occurring during the duration of the extension phase. Three participants became symptomatic after continued dosing after the first ARIA-E event (b) (6) See Appendix Section 12.1.5 for narratives and Table 83 in the Appendix regarding details for these participants.

10 participants (b) (6) who had one or more isolated treatment emergent ARIA-H event without ARIA-E during the Core continued to participate in the OLE study. Seven had no

further ARIA-H events; 2 participants (b) (6) had additional ARIA-H events. One participant (b) (6) who received LEC5 -M in Core and had a cerebral microhemorrhage in the Core study, had 3 ARIA-E, 2 ARIA-H microhemorrhage, and one ARIA-H superficial siderosis occurrence during the OLE.

Whether an event of ARIA predicts the occurrence of future events is not known, particularly given the gap period ranging from 9-56 months between the Core and OLE for lecanemab.

Radiographic Duration of ARIA in 201 Core

The mean duration of ARIA-E in the LEC10 BW arm was 89 days (~ 13 weeks), ranging between 37-251 days (5-35 weeks) (Table 62).

Radiographic recovery from ARIA-E in 201 Core occurred in approximately 62 % of participants by 12 weeks, and in approximately 75% of participants by 17 weeks, in approximately 79.1% by 21 weeks and in approximately 95.8 % overall after detection (Lecanemab Summary of Safety, Table 28). In the OLE, the mean time to radiographic resolution of ARIA E was approximately 4 months.

The following data were provided by the applicant in response to an IR from the Agency. This reviewer was able to replicate the numbers in this table. Duration is calculated as last visit date if not resolved.

Table 62 Duration (days) and Outcome of First Episode of Treatment-Emergent Radiographic ARIA in 201 Core

	ARIA-E	
	LEC10-BW n=16	Placebo n=2
Mean	89 days	102 days
SD	58 days	95 days
Range	37-258 days	35-170 days
Number Resolved	15	2

Table 63 Duration (days) and Outcome of First Episode of Treatment-Emergent Radiographic ARIA in 201 OLE

	ARIA-E
	LEC10-BW n=14
Mean	107 days
SD	90 days
Range	29-368 days
Number Resolved	14

The duration of ARIA-H cannot be reliably calculated because in most cases ARIA-H does not resolve on MRI.

Effect of Antithrombotic Medications on ARIA risk

In the 201 Core study, anticoagulants were not permitted starting 7 days prior to study entry. Participants who needed to start chronic (> 4 weeks) anticoagulant treatment during the study for concomitant diseases were withdrawn from study drug. However short term (< 4 week) treatment with anticoagulants was permitted for randomized participants who underwent procedures requiring anticoagulants for prophylaxis of thromboembolic disease. These participants had the study drug temporarily suspended during anticoagulant therapy. The protocol also excluded participants with an increased risk for hemorrhage: a bleeding disorder not under adequate control (including a platelet count less than 50,000 or an international normalized ratio greater than 1.5), uncontrolled hypertension with a history of blood pressure consistently above 165/100 mm Hg at screening, and evidence of multiple lacunar infarcts or stroke involving a major vascular territory.

In 201 OLE, there was no restriction on antiplatelet or anticoagulation use.

Whether use of antithrombotic medications increases risk of ARIA-H or increases the radiographic or clinical severity of ARIA-H is not known. Neither 201 Core or 201 OLE were designed to answer the above questions.

In response to an IR from the Agency on June 27, 2002, the applicant provided tables with incidence of antithrombotic use during 201 Core and OLE both for the period between the MRI at which ARIA-H was discovered and the previous MRI, and for any period of time during the study. Tables 68 and 69 were created using data from applicant provided Table IR29-2a and Table IR29-1a, both of which were updated with the submission on August 12, 2022, by the applicant after the applicant identified additional ARIA-H events which were not included in the dataset earlier.

Based on applicant Table 14.1.4.3.1, in 201 Core, 74/81 (91%) of participants with concomitant antithrombotic use in the LEC10-BW arm received aspirin, with a variety of other antithrombotics including clopidogrel (10%), enoxaparin (6%), apixaban (2.5%), heparin (4%), rivaroxaban (2%), warfarin (1%) and Asasantin (1%). Those who were on an antithrombotic at any time during the study or during the time preceding an ARIA-H event, had a higher incidence of having ARIA-H microhemorrhage or ARIA-H superficial siderosis, or ARIA-E with ARIA-H both in 201 Core and 201 OLE (Table 64 and Table 65). In the 201 OLE, 91/180 (51%) participants in the lecanemab 10 mg/kg arm had concomitant use of aspirin, with a variety of other antithrombotics including clopidogrel (6%), apixaban (3%), heparin (3%), rivaroxaban (2%), and

warfarin (1%). The incidence was higher in the 201 OLE study likely because during that study use of anticoagulant use was not limited to short term use.

Table 64 Incidence of ARIA-H in Study 201 Core with Anti-Thrombotic Use Preceding ARIA -H[29]

Anti-thrombotic * medication use during the study*	ARIA-H microhemorrhage or superficial siderosis		Intracerebral hemorrhage		ARIA-E with Concurrent ARIA-H***	
	LEC10-BW N (%)	Placebo N (%)	LEC10-BW N (%)	Placebo N (%)	LEC10-BW N (%)	Placebo N (%)
Not on antithrombotic preceding** the ARIA	3/76 (4)	5/118 (4)	0/76 (0)	0/118 (0)	2/76 (3)	1/118 (1)
On antithrombotic preceding the ARIA, and had ARIA after starting medication	5/85 (6)	6/127 (5)	1/85 (1)	0/127 (0)	4/85 (5)	0/127 (0)_

Table 65 Incidence of ARIA-H in Study 201 OLE with Anti-Thrombotic Use Preceding ARIA -H[29]

Anti-thrombotic medication during the study*	ARIA-H microhemorrhage or superficial siderosis N (%)	Intracerebral hemorrhage N (%)	Concurrent ARIA-E with ARIA-H
Not on antithrombotic preceding the ARIA	7/77 (9)	0/77 (0)	2/77 (3)
On antithrombotic preceding the ARIA, and had ARIA after starting medication	18/103 (17)	1/103 (1)	6/103 (6)

.

Because of the small numbers of exposures to antithrombotic medications and few events of ARIA-H and cerebral hemorrhage in Study 201, it is difficult to draw conclusions about the risk of ARIA-H or cerebral hemorrhage in participants exposed to antithrombotic medication while on lecanemab, or determine whether the risk of ARIA-H and cerebral hemorrhage while on lecanemab and antithrombotic is higher than antithrombotics alone. The Agency became aware of two additional cases of cerebral hemorrhage > 1 associated with use of antithrombotic or thrombolytics in 301 OLE during the review period. Please see Section 7.5.2 for further discussion of this topic.

MRI Monitoring

[29] *The term "anti-thrombotic" includes aspirin, other antiplatelet drugs, and anticoagulants.
** Preceding the ARIA refers to use of antithrombotic medication(s) for any duration during the period between the MRI at which the ARIA events (ARIA-E, ARIA-E concurrent with ARIA-H, and ARIA-H) were discovered and the previous MRI scan, and the incidents reflect events which occurred post the use of the medication.
*** Concurrent ARIA-E with ARIA-H is defined by the sponsor as follows; This flag identifies individuals who had a treatment emergent ARIA-E event ongoing at the time of the start of the ARIA-H event, or an ARIA-E event that starts while an ARIA-H event is ongoing.

The applicant amended the protocol, based on Data Safety Monitoring Board recommendations, on July 9, 2014 (Version 6) in order to allow early detection of ARIA-E, adding MRI scans prior to the 5th and 7th doses. Subsequently on July 30, 2015, based on a request from the European Regulatory Authorities, a safety MRI was added prior to the 4th dose in European sites only.

As a result, ARIA monitoring with safety MRIs was conducted during screening, prior to the 4th infusion (European sites only), 5th infusion, 7th infusion, 14th infusion, 20th infusion, 27th infusion, 33rd infusion and 2 weeks after the last dose of study drug during the 201 Core Study.

I recommend safety MRIs for detection of ARIA-E prior to the 5th infusion, 7th infusion, and 14th infusion, similar to MRI monitoring in Study 201 Core. I also recommend continued clinical monitoring during the course of treatment and up to 6 months after treatment, and obtaining unscheduled MRIs for any emerging clinical symptoms suggestive of ARIA.

This recommendation is based on the fact that at the proposed dose in 201 Core 3/16 (19%)of the ARIA-E events occurred between the 3rd and 5th doses, 9/16 (56%) were between the 5th and 7th dose (8/16 occurring between the 6th and 7th dose), 1/16 (6.3%) occurred between the 11th and 12th doses, 1/16 (6.3%) occurred between the 25th and 26th doses, and 2/16 (12%) between the 32nd and 34th doses. Of those participants who had serious ARIA-E events at the proposed dose, (all of whom also had clinical symptoms and were ε4 homozygotes), one occurred 7 days after the 3rd dose, two occurred between the 6th and 7th doses. In 201 OLE, 5/14 of ARIA-E occurred between the 4th and 5th dose, 5/14 between the 5th and 7th dose, 3/14 between the 12th and 14th dose, and 1/14 between the 22nd and 23rd dose. In three participants in the LE10-M arm only, ARIA-E occurred 34-199 days after last dose, suggesting utility of continued clinical monitoring up to 6 months after the last dose.

Narratives of participants with ARIA

Deaths

There were no deaths in studies, 101, 104, 004 and 201 Core and OLE phase due to ARIA.

The sponsor submitted the narrative of a death due to cerebral hemorrhage (b) (6) in 301 Core at the time of the 120-Day Update. On December 14, 2022 the sponsor replied to an IR informing the Agency that this participant was on placebo. Additionally, during the review, the Agency became aware of two deaths due to cerebral hemorrhage in the 301 OLE, one occurring on (b) (6) (participant (b) (6)) and one on (b) (6) (participant (b) (6)). See Section 7.5.2 Cerebral Hemorrhage for further discussion and narratives.

Serious Adverse Events Associated with ARIA

Illustrative narratives are provided below. Other selected narratives can be found in the Section 12.1.5.

Participants with ARIA events that were SAEs in studies 101, 104 and 004.

No SAEs of ARIA occurred in study 101, 104 and 004. Participant (b) (6) had an SAE of cerebral hemorrhage > 1 cm in the SAD portion of Study 101 (See Section 5.5.2 Cerebral Hemorrhage for details).

Participants with ARIA events that were SAEs in 201 Core

(b) (6)
This participant is a 56-year-old white female with mild dementia due to AD with an ε4/ε4 ApoE genotype randomized to receive LEC10-BW in 201 Core. Four days after the third dose of study drug (Study Day 32), the participant awoke from sleep with an acute, severe headache and vomited. She was noted to be confused and also complained of blurred vision. In the hospital she was found to be able to see palms but not fingers, have hyperreflexia, clonus and a left homonymous hemianopsia as well as moderately severe hypertension (160/91 mmHg). MRI showed findings consistent with ARIA-E, with vasogenic edema in the right frontal, right temporal-nonhippocampal, right parietal, right occipital and left frontal, parietal and occipital locations, leukoencephalopathy and nonparenchymal subdural hemorrhage with midline shift. The participant was diagnosed with radiographically severe ARIA-E and cerebral microhemorrhage (ARIA-H) and admitted to the hospital.

After treatment with lurasidone (a second-generation antipsychotic), dexamethasone, nifedipine, levetiracetam, and clonazepam, her symptoms improved and she was discharged after a week in the hospital. Follow up MRI on Study Day 41, showed severe vasogenic edema (ARIA-E) with new cerebral microhemorrhages (ARIA-H). Subdural hematoma had completely resolved. On Study Day 58, at the early termination visit, the symptoms resolved and the participant's MMSE score was 20 (baseline 23). On Study Day 69, MRI showed ARIA-E improved from severe to moderate in severity. There were > 10 microhemorrhages present in the area of past and present vasogenic edema. On Study Day 71, the events of ARIA-E and ARIA-H were improving. On Study Day 114, MRI results showed ARIA-E further improved to mild in radiographic severity and disappeared from most of the brain regions. No new cerebral microhemorrhages (ARIA-H) were present. On study day 209, the event of ARIA-E resolved on MRI. The events of cerebral hemorrhage (ARIA-H) and hypertension (no baseline history of hypertension) were ongoing at the time of study discontinuation.

Reviewer Comment: This participant with an ApoE ε4/ε4 genotype on LEC10-BW, experienced fulminant ARIA-E after the third dose of study drug at ~ Week 4 presenting with headache, vomiting, visual field deficit. Her presentation also includes subdural hemorrhage which is not commonly described as part of ARIA. While subdural hemorrhage is not traditionally associated

with ARIA-E, the co-occurrence with ARIA-E and ARIA-H, raises the possibility that the study drug may have played a role in this participant's subdural bleed. The risk of subdural hematoma increases with aging due to stretching of the subdural bridging veins with brain atrophy. In the case of participant (b) (6)*, who was a 56 year-old woman, this age-related etiology seems less likely. Furthermore, subdural hemorrhage has been described with amyloid angiopathy, which has similarities with ARIA.*[30]

(b) (6)

This 72-year-old white male with ApoE ε4/ε4 genotype on LEC10-BW developed increased confusion one day after the 6th dose of study drug on Study Day 73. An MRI 5 days later confirmed radiographically severe ARIA-E with ARIA-H (> 10 cerebral microhemorrhages). The ARIA-E occurred in the right and left frontal lobes, right and left temporal lobes, right parietal lobe, and right and left occipital lobe. He had a possible seizure, witnessed by wife en route to the hospital. During hospitalization, he was treated with dexamethasone, and risperidone as needed and study drug was permanently withdrawn. His hospital course was complicated by bradycardia, lethargy, increased confusion and delusion. The participant was switched from dexamethasone to methylprednisolone and started on levetiracetam, ceftriaxone, ampicillin, acyclovir, vibramycin, and 3% sodium chloride solution to induce hyperosmolarity. The participant became more confused and obtunded; and transferred to the intensive care unit in another hospital where he was intubated. On Study Day 83, lumbar puncture was performed but results are not available. On Study Day 84, the participant remained intubated with no improvement. On Study 105, MRI results showed new occurrence of >10 new cerebral microhemorrhages (ARIA-H). After 100 days in the hospital (Study Day 179) he was discharged home. It was reported that his mental state fluctuated from lucid to incoherent during conversation. He had delusions intermittently and his agitation was reduced. His usage of zolpidem and lorazepam was reduced to as needed frequency. His balance was unstable; and he required a walker for mobility assistance. On Study Day 200, MRI revealed complete resolution of ARIA-E with stable microhemorrhages. He was still having delusions and hallucinations with brief episodes of confusion. On Study Day 212, the participant's condition improved, and his hallucinations reduced, his walking was improving, and he was not experiencing agitation. This participant did not return for a follow up visit. The outcome in this case remains unknown.

Reviewer Comment: This is another example of a participant having severe symptomatic ARIA-E resulting in intensive care unit admission. This participant may have had a generalized seizure en route to the hospital at the onset of his symptoms

(b) (6)

[30] Viguer et al. Subarachnoid and Subdural Hemorrhages in Lobar Intracerebral Hemorrhage Associated With Cerebral Amyloid Angiopathy. Stroke:2019;50:1567-1569

This participant who carried the ApoE ε4/ε4 genotype on LEC10-BW experienced transient tingling in the fingers in the right hand, and difficulty finding words occurring 11 days after the 6th dose (Study Day 80). MRI showed enlargement of sulci in the bilateral posterior parietal lobe (prominent on the right side),consistent with mass effect and some white matter changes in bilateral posterior parietal lobes along with few subtle areas of temporal lobe and occipital lobe. The participant was hospitalized and diagnosed with aphasia, TIA and ARIA-E (radiographically severe); aphasia resolved the same day. The participant was treated with clopidogrel for presumed TIA given symptoms of transient right-hand numbness and aphasia. Study drug was permanently discontinued. Participant was discharged after 24 hours from the hospital. ARIA-E resolved on Study Day 150.

Reviewer Comment: Aphasia and right-hand tingling in this participant were likely secondary to the ARIA-E and not due to a separate event of transient ischemic attack (TIA). Transient neurological symptoms have been reported previously with ARIA-E.[15]

There was one more SAEs of ARIA-E in the LE10-M arm in 201 Core. Participant (b) (6) on LE10-M was classified as moderate in severity and serious (due to being medically significant but not based on clinical symptoms). The narrative of this participant can be found in Section 12.1.4.

Participants with Serious ARIA Events in 201 OLE

Of the 14 ARIA-E cases in 201 OLE, 1 was identified as serious (b) (6). The events of ARIA-E and superficial siderosis in this participant were designated as serious because they were medically important event, however, the participant remained asymptomatic, and the radiological severity was mild for both ARIA-E and superficial siderosis. There were no other factors to suggest this was otherwise a serious adverse event. Therefore, this case will not be described in detail.

Participant (b) (6) had a cerebral hemorrhage and will be described under Section 7.5.2 Cerebral Hemorrhage.

Discontinuations due to ARIA

During Study 201 Core, those with ARIA-E, superficial siderosis or cerebral hemorrhage were discontinued from study treatment as per protocol. I reviewed the 56 narratives of all the discontinuations in the LEC10-M and LEC10-BW arms. Most of these events simply represented treatment emergent asymptomatic ARIA-E or ARIA-H events that were discontinued as per protocol.

Additional ARIA Narratives:

Representative ARIA-E narratives are summarized below.

There were a total of 7 symptomatic ARIA-E cases across the lecanemab arms (See Table 59) Participants (b) (6) are described under SAEs of ARIA-E in this section. Narratives for participants (b) (6), can be found in the Section 12.1.5. The following two cases are provided as an example to demonstrate that at times the assessment of causality between ARIA and symptoms may not be clear cut. Participant (b) (6), was classified as having symptomatic ARIA-E, with bitemporal hemianopsia, and ARIA-E in the bi-occipital, right frontal and left parietal area. Since bitemporal hemianopsia is classically caused by a lesion in the chiasm it is difficult to conclude that ARIA-E in the occipital area is truly the cause of the symptoms. Participant (b) (6) was identified as having asymptomatic ARIA-E. This participant had an upper respiratory tract infection (URI), confusion and ARIA-E occurring on the same day. The applicant identified confusion to be secondary to the URI, but I cannot rule out that the confusion may have been caused by ARIA-E.

The following two narratives are briefly described to emphasize the importance of having a radiologists familiar with ARIA-E review scans of participants receiving treatment with monoclonal antibodies against amyloid. Both participants (b) (6) were thought to have cerebral infarction diagnosed within 2-3 weeks after the ARIA-E. In participant (b) (6), after re-review it was felt that the diagnosis of cerebral infarction was erroneous, and that the findings were consistent with ARIA-E. In the case of participant (b) (6) a new and unrelated infarct was confirmed with DWI sequences.

There were 5 participants (b) (6) who were dosed through ARIA-E in 201 Core, although per protocol they should have been discontinued. In a majority of the cases the participants remained asymptomatic, and no new ARIA events occurred. In one participant (b) (6), the size of the ARIA-E increased and radiographic severity evolved to severe from moderate, however the participant remained asymptomatic.

In Study 201 Core three participants had ARIA-E (b) (6) events occurring beyond 30 days after the last dose of study drug administration. These participants are discussed on page 118 of this review.

Study-Drug- Blinded Narratives for Participants with ARIA in Study 301 Core, 301 OLE and 303

As of the 120-Day Cut off of December 31, 2021, in 301 Core, there were 12 participants (b) (6) that had an SAE of ARIA or cerebral hemorrhage. The Agency was informed on December 14, 2022 that participant (b) (6), in whom cerebral hemorrhage led to death, was on placebo. Study drug remains blinded for other participants above. In 301 OLE there were 2 participants (b) (6) The majority of these participants were symptomatic with symptoms consistent with those that have previously been

associated with ARIA including sensory, changes, gait disturbance, falls, dysphagia, hemiparesis, decreased attention, headache, aphasia, forgetfulness, confusion. Participants (b) (6) had a seizure in the setting of a cerebral hemorrhage > 1 cm, and participants (b) (6) had a seizure due to ARIA. Participant (b) (6) had a seizure vs syncope in the setting of ARIA. Selected narratives can be found in Section 12.1.3.

At the time of the 120-Day Cut off period of December 31, 2021, 6 participants, (b) (6) (on placebo), (b) (6)) had one or more cerebral hemorrhage > 1 cm during their participation in the 301 Core study. In four (b) (6) the cerebral hemorrhage was not isolated and occurred in the context of ARIA-E and ARIA-H.. According to a response to an IR dated November 15, 2022 from the applicant there are a total of 4 participants in 301 OLE that had cerebral hemorrhage > 1 cm, including two deaths due to cerebral hemorrhage in the 301 OLE. See Section 7.5.2 for further discussion.

In study 301 OLE, participant (b) (6) had an SAE of cerebral hemorrhage as well as ARIA-E and ARIA-H superficial siderosis. The study drug was interrupted and outcome unknown. Participant (b) (6) had a radiographically moderately severe ARIA-E and remained asymptomatic. Study drug was temporarily interrupted.

In Study 303 Core, one participant (b) (6) had radiographically severe ARIA-E, as well as ARIA-H microhemorrhages and ARIA-H superficial siderosis. She was symptomatic with headaches and language difficulty. The study drug was permanently discontinued.

7.5.2. Cerebral Hemorrhage

In the 201 Core study the incidence of cerebral hemorrhage was 1/161 (0.6 %) in participants receiving lecanemab and 0 in placebo. In 201 OLE the incidence of cerebral hemorrhage, was 1/180 (0.6 %). Both participants received LEC10-BW prior to the cerebral hemorrhage and were on Aspirin (325 mg and 81 mg).

In 201 Core, participants were discontinued from the study after a cerebral hemorrhage > 1 cm. In 201 OLE study drug was suspended for symptomatic intracerebral hemorrhage, but continued dosing was allowed in asymptomatic cerebral hemorrhage. The one occurrence of cerebral hemorrhage (b) (6) in Study 201 OLE was symptomatic. The study drug was suspended until stabilization of the cerebral hemorrhage, and then resumed with the participant continuing with study drug without further cerebral hemorrhage events.

During the review, the Division became aware of two deaths in 301 OLE due to cerebral hemorrhage, occurring in (b) (6). The narratives of these two deaths (b) (6) are described under Study 301 OLE below. The Agency requested the additional information from the applicant related to risk of cerebral hemorrhage in general and cerebral hemorrhage in the context of antithrombotic use in 301 Core. In a response to the

information request dated November 15, 2022, the sponsor provided the following topline analyses: "Overall, there were 8 cases of macrohemorrhage in the Core Study, 2 on placebo (2/897, 0.2%, one fatal) and 6 on lecanemab (6/898, 0.7%, none fatal). There were no macrohemorrhages in placebo participants on anticoagulation (0/75, 0.0%). There were two macrohemorrhages in lecanemab participants on anticoagulation (2/84, 2.4%)." Based on data presented by the applicant at the 2022 Clinical Trials on Alzheimer's Disease Meeting, the presentation of which was submitted to the BLA on January 5, 2023, as of data cutoff of October 22, 2022, in 301 Core and OLE combined the incidence of cerebral hemorrhage > 1 cm in those receiving lecanemab was 10/1608 (0.6%). Among participants who were on anticoagulation the incidence was 5/140 (3.6%). The incidence of death with concurrent cerebral hemorrhage > 1 cm in those on anticoagulation was 2/140 (1.4 %). These data have not been formally verified by the Division.

Reviewer Comment: While the numbers are small, the incidence of cerebral hemorrhage in those on LEC10-BW in Study 201 and 301 appear to be slightly higher than placebo. The data from the OLE studies is of limited interpretability given the absence of a control group. There is insufficient data on patients who experienced cerebral hemorrhage while taking antithrombotic or thrombolytic medications with lecanemab to make any definitive conclusions. The interpretation of this data is additionally colored by the presence of underlying pathological CAA in patients with AD (moderate to severe CAA in up to 48%), which can increase the risk of hemorrhage but may not yet have manifested as microhemorrhages, superficial siderosis or cerebral hemorrhage.[26] Given that cerebral hemorrhages greater than 1 cm have been observed in patients taking lecanemab, and the high prevalence of CAA in the target population, I recommend that a statement is included in labeling that additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient taking lecanemab.

Narratives of participants with Cerebral Hemorrhage:

The narratives of participants with cerebral hemorrhage in studies 201 Core, 201 OLE, and 104 are provided below. The study drug blinded narratives for participants with cerebral hemorrhage in 301 Core and OLE, and the two unblinded cases of cerebral hemorrhage in 301 OLE are also summarized below. Full narratives can also be found under Appendix Section 12.1.3 Death and SAE Narratives for Study 301 Core and 301 OLE.

<u>201 Core</u>

Participant (b) (6) is a 77 year-old man with mild dementia due to AD who had an ApoE ε3/ε3 genotype and was randomized to receive LEC10-BW in the core study. His medical history is positive for thrombocytopenia as a potential risk factor for cerebral hemorrhage. He was on aspirin 325 mg daily. On Study Day 172, the day of his 12th dose of study drug, MRI showed 1 new cerebral microhemorrhage (right parietal occipital) and cerebral hemorrhage > 1 cm (left

occipital parenchyma). He had 3 microhemorrhages at baseline. No treatment was reported for this event, and he remained asymptomatic. The participant's MMSE score was 23 at screening and 24 at baseline and 13 at Study Day 182. A repeat MRI on Study Day 208 showed parenchymal cerebral hemorrhage in the left occipital lobe had resolved. His MMSE on Study Day 292 was 17. On Study Day 302, the participant's MRI showed a new right occipital microhemorrhage. On Study Day 337, the participant was discontinued from the study. Ongoing events at the time of discontinuation were agitation and delusion.

Reviewer Comment: This participant has thrombocytopenia listed in his medical history. Reviewing his laboratory data, it looks like his platelet counts ranged from 111-230 x 10^9 /L with 7/11 measurements lower than the lower limit of normal (<125 x 10^9 /L) during his participation in 201 Core. His platelet count about a month prior to the cerebral hemorrhage was 116 x 10^9 /L. This level of thrombocytopenia is usually not associated with spontaneous bleeding. This participant did not have any ARIA-E events during participation in 201 Core, but had both baseline and incident microhemorrhages. Unlike the ApoE ε2 or ε4 alleles, the ApoE ε3 has not been associated with an increases risk of cerebral hemorrhage. It is possible that the intermittent low platelet count, use of full dose ASA increased his risk for cerebral hemorrhage. Given the small number of incidents of cerebral hemorrhage, I cannot rule out that these risks were additive to the risk of cerebral hemorrhage due to being on LEC10-BW. I also cannot rule out the possibility of underlying CAA, although e3 homozygosity is not a known risk for CAA or for cerebral hemorrhage.

<u>201 OLE</u>

(b) (6)

This participant is a 68-year-old white female also with a ε3/ε3 genotype who was randomized to placebo in 201 Core. She then started receiving LEC10-BW as part of her participation in the 201 open label extension study. Her relevant past medical history included a history of daily use of aspirin 81 mg daily. On Extension Day 27, she received the third dose of study drug. On Extension Day 34 (~week 5), 7 days after the 3rd dose, she reported intermittent headache for several days, and awoke with tightness in her shoulders and experienced loss of vision in her right visual field, which did not resolve. She saw an ophthalmologist who diagnosed a right visual field defect, and MRI showed a 3.8x2.8 cm left occipital hematoma associated with edema and mass effect. She was diagnosed with cerebral hemorrhage and was hospitalized, for this event classified as moderate in severity and serious. The study drug was temporarily interrupted due to the event of cerebral hemorrhage with the last dose taken on Extension Day 27. She received treatment with levetiracetam as a seizure prophylaxis. On Extension Day 36 the participant was discharged from the hospital. Follow up MRIs showed decreased in size of the hemorrhage. On Extension Day 115, the study drug was restarted. On Extension Day 720, after 720 days of dosing the participant received the 46th dose of BAN2401 10 mg/kg. As of data cutoff of 31 Dec 2021, the participant was ongoing in the Extension Phase of the study.

The events of cerebral hemorrhage, visual field defect and rash were ongoing at the time of the Extension Phase data cutoff of 31 Dec 2021.

Reviewer Comment: In this case, the applicant and investigator posited that this cerebral hemorrhage was due to underlying amyloid angiopathy. This participant did not have any baseline or incident microhemorrhages or superficial siderosis that would support a diagnosis of CAA. She does not have an ApoE allele such as ε4 that would increase her risk for CAA or, ε2 that would increase her risk of cerebral hemorrhage. Given that this participant was also an e3 homozygote, which is not a known risk factor for either cerebral hemorrhage, or underlying CAA and the temporal relationship to study drug that was started in the OLE (as she received placebo during the 201 Core) I cannot rule out the possibility that the study drug, possibly combined with baby aspirin played a role in the cerebral hemorrhage. In this participant's case, study drug was resumed after stabilization of the cerebral hemorrhage, and she tolerated an additional 43 doses without further hemorrhagic events. Symptoms of visual field cut were not reported to have resolved.

Study 104

Participant (b) (6) is an 81 year-old man with AD dementia who was randomized to receive a single dose of study drug at 1 mg/kg. His past medical history was silent to risk factors for cerebral hemorrhage. The participant's MRI brain at baseline showed minimal to mild small vessel ischemic changes. 20 days after the last dose of study drug, the safety brain MRI showed a new left parietal hemorrhage that was 10.1 mm in the largest diameter. The severity of this was considered mild, and participant remained asymptomatic. A follow up MRI on day 50, showed reduction in the size of the cerebral hemorrhage > 1 cm, and 180 days after last dose administration the intracerebral hemorrhage was resolved.

Reviewer Comment: Whether this event was related to a single dose administration of study drug is unclear. The location of the bleed is not consistent with hypertensive bleed, and participant's vital signs were not consistent with ongoing hypertension. There was no trauma preceding the event. The location of the bleed is consistent with intracerebral hemorrhages that may be seen with CAA. However, at baseline, this participant's MRI scan did not show any findings that would support a diagnosis of amyloid angiopathy. While older age, and possibly male sex are potential risk factors for cerebral hemorrhage > 1 cm in this participant[31], I cannot entirely rule out a role of study drug in this case.

Study 301 Core
The narratives for those with cerebral hemorrhage in Study 301 Core and OLE and 303 were reviewed. The blinded nature of some of these narratives precludes any firm conclusions.

[31] *Lioutas et al. JAMA Neurol. 2020;77(10):1252-1260*

There were 6 participants (b) (6) who had one or more cerebral hemorrhage > 1 cm during their participation in the 301 Core study at the time of the 120-Day Cut off period of December 31, 2021). In participant (b) (6) who was on placebo (per IR dated December 14, 2022), cerebral hemorrhage > 1 cm led to death.

In four of the participants (b) (6), the cerebral hemorrhage was not isolated and occurred in the context of ARIA-E and ARIA-H. In two participants (b) (6) cerebral hemorrhage occurred after the 4th dose of study drug, in participant (b) (6) after the 8th dose, and in participant (b) (6) after the 18th dose. Two of the participants (b) (6) were on rivaroxaban at the time of the cerebral hemorrhage. Two participants (b) (6) had an ARIA-E or ARIA-H microhemorrhage event which was dosed through preceding the intracerebral hemorrhage. Participant (b) (6) also had a subarachnoid hemorrhage with the cerebral hemorrhage. She had a seizure in the emergency room, as well as symptoms of left arm weakness, homonymous hemianopsia and headache. Participant (b) (6), who also had a cerebellar infarct, had accompanying symptoms of drooling, dysphagia, gait disturbance and musculoskeletal stiffness. Participant (b) (6) had a cerebral hemorrhage, after the second occurrence of ARIA-E (dosing was interrupted after the first ARIA-E event), and accumulation of up to 50 ARIA- H microhemorrhages (from 4 at baseline) prior to the cerebral hemorrhage. Study drug was permanently discontinued due to ARIA-H microhemorrhage. Participant (b) (6) also had a subdural hemorrhage in addition to the ARIA-E and cerebral hemorrhage > 1 cm. She had been on ticagrelor for recent cardiac stent placement. She was discontinued from study. Participants (b) (6), both had isolated cerebral hemorrhage later during treatment (after the 25th and 26th dose), when compared to the other 4 participants, and did not have ARIA-E or ARIA-H at the time of the cerebral hemorrhage. Participant (b) (6) who was on placebo died due to intracranial hemorrhage. See Section 12.1.3 for selected narratives

Reviewer Comment: Given that the study drug is blinded for most of these cases, it is difficult to ascertain causality, however I cannot rule out a role of the study drug in the instances where cerebral hemorrhage, occurred in the setting of ARIA-E and ARIA-H and occurred earlier during lecanemab treatment. Two of the six participants in 301 Core were on anticoagulation (rivaroxaban) and (b) (6) on an antithrombotic (ticagrelor).

Study 301 OLE

According to a response to an IR dated November 15, 2022 from the applicant there are a total of 4 participants in 301 OLE that had cerebral hemorrhage > 1 cm. One is a participant with thalamic hemorrhage not included in this review as this information was not provided at the time of the 120-Day Update. The other three (b) (6) will be described below. Participant (b) (6) was also presented in a New England Journal of

Medicine correspondence.[32] Participants (b) (6) also occurred after the 120-day Update but will be described further as both resulted in death.

Participant (b) (6) is an 80 year-old woman, with unknown ApoE genotype, on apixaban, who one day after the 5th dose of study drug, had radiographically severe ARIA-E, ARIA-H superficial siderosis and a cerebral hemorrhage (measuring 1.3 × 1.6 × 0.9 cm) occurring in the same brain region as ARIA-E. Study drug was discontinued and she remained asymptomatic.

Participant (b) (6) was an 87 year-old man with early AD, who was not a carrier of the ApoE ε4 allele. He received placebo in the 301 Core Study. His relevant past medical history included, atrial fibrillation, aortic stenosis, aortic valve replacement, coronary artery disease and coronary artery bypass surgery, history of lacunar stroke, and cerebral microhemorrhage (3 at baseline), and hyperlipidemia. He was on donepezil, apixaban and atorvastatin, at the time of participation in the 301 OLE. After the 6th dose of study drug (Extension Day 77), the participant sustained a fall and was seen in the emergency room. On the same day he received the 7th dose of study drug, chest x-ray showed pneumonia, and CT head was negative. Two days after the 8th dose of study drug he was diagnosed with COVID. Eight days after the COVID diagnosis (Extension Day 106), he developed severe pain in his right arm and was diagnosed with a right ulnar pseudoaneurysm. He was admitted to the hospital and received an ultrasound guided thrombin injection of the right ulnar artery and subsequently discharged. Six days after discharge (on Extension Day 112), he fell out of his bed and bruised his left arm. On his scheduled infusion day study drug was held due to trauma sustained to both arms, and multiple medical concerns. A routine safety MRI on Extension Day 116 showed a left occipital intracerebral hemorrhage and participant's apixaban was stopped. Six days later participant was seen in the ER for chest pain shooting down his left arm. EKG changes and troponin elevation ruled in a myocardial infarction. He received heparin bolus and then a heparin drip which was discontinued due to the recent brain bleed. He was treated with aspirin and nitroglycerin and admitted to the telemetry unit. After a few days he was discharged wit prn nitroglycerin for chest pain. On Extension Day 126 he had 4 TIA like events of garbled speech and right sided weakness. He declined to go to the ER. The next day, participant enrolled in hospice, and continued with treatment with Plavix, as well as lorazepam for comfort and passed away on Extension Day 144.

A brain autopsy was performed on (b) (6), and the results were provided by the applicant to the Agency on November 18, 2022. The autopsy report confirmed neuropathological AD, small vessel ischemic disease and a left occipital subacute intracerebral hemorrhage. While the report stated that the most likely etiology for the intracerebral hemorrhage was thought to be CAA, it also mentioned that there was absolutely no amyloid present in the vicinity of the hemorrhage. Microscopic examination did note minimal to mild amyloid angiopathy on immunohistochemical staining in the left occipital cortex, but no

[32] Reish NJ, Jamshidi P, Stamm B, et al. NEJM, January 4, 2023, DOI: 10.1056/NEJMc2215148.

obvious plaque deposition. The neuropathologist hypothesized that the cause of the bleed may have been a potential side effect of lecanemab, CAA where the amyloid was removed by lecanemab, or a lingering effect of anticoagulation treatment. There also was evidence of subarachnoid hemorrhage, in the left occipital cortex, subacute to chronic which the neuropathologist felt was separate from the left occipital hemorrhage and may be explained by history of multiple falls. There was no evidence of inflammatory changes secondary to COVID-19. The pathologist also opined that there was no cause of death within the brain.

Reviewer Comment: This case of cerebral hemorrhage has a number of confounders, including a history of cardiovascular disease requiring the use of anticoagulants, two recent falls in the setting of anticoagulant use, and recent treatments with thrombin for an ulnar pseudoaneurysm and heparin for a myocardial infarction. The presence of these confounders preclude the ability to assess the relationship of the cerebral hemorrhage to the study drug. On autopsy both the intracerebral hemorrhage and the subarachnoid hemorrhage were in the left occipital area. Co-localization of the subarachnoid hemorrhage and cerebral hemorrhage >1 cm in the left occipital lobe, may point to a common etiology.

The second participant (b) (6), a 65 year old woman with MCI, homozygous for ApoE ε4, completed 301 Core on placebo and enrolled in 301 OLE. Four days after the third dose of study drug, the participant was noted to have garbled speech, and was taken to an ER. A CT of the head diagnosed an occlusive left-sided ischemic stroke due to an LM3 occlusion. Tissue plasminogen activator (tPA) was administered. Within 8 minutes after tPA she experienced a headache, and within 40 minutes she became agitated. Repeat imaging showed bilateral intracerebral hemorrhage with subarachnoid hemorrhage. The tPA was stopped and cryoprecipitate and tranexamic acid were given for reversal of tPA. She was treated with Haldol for agitation and lorazepam and Keppra for seizures. Her blood pressure was greater than 200 mmHg, for which she was started on nicardipine infusion. Her encephalopathy worsened and she was intubated. Per participant's wishes of not remaining on life support indefinitely she was extubated. MRI performed 3 days after the CT scan[33] showed extensive multicompartmental ICHs, innumerable hematomas, SAH and right intraventricular hemorrhage with 5 mm leftward midline shift and bilateral uncal herniation. Eight days after the 3rd dose of study drug the participant expired shortly after extubation.

Reviewer Comment: While treatment with intravenous (IV) thrombolysis within 4.5 hours of acute ischemic stroke onset is associated with an increased early risk of intracerebral hemorrhage of 5 to 7 percent, I cannot rule out a role of study drug in this participant's case due to the fact that this incident occurred 4 days after the third dose of study drug in a participant who was on placebo previously, and the resulting intracerebral bleeding was extensive. While there is no data on the use of thrombolytic drugs in participants who are also receiving anti-amyloid monoclonal antibodies, there is some evidence to suggest that participants with a

[33] Sabbagh M, van Dyck CH. NEJM, January 4, 2023. DOI: 10.1056/NEJMc2215907

diagnosis of CAA who receive thrombolytics have a higher risk of bleeding and a higher risk of more extensive bleeding with multilocular bleeds or bleeds outside the primary ischemic area.[34,35] Her MRI 4 months prior to this incident, did not show cerebral microhemorrhages or superficial siderosis to suggest underlying CAA. This participant's ischemia was in the left cerebral hemisphere, however the brain hemorrhages post-tPA were extensive, multilocular in bilateral hemispheres with intraventricular extension and associated cerebral edema leading to uncal herniation and death. Since she only had a CT in the emergency room, whether she had ARIA-E and ARIA-H prior to tPA administration is not known. The autopsy describes extensive, multi-focal intraparenchymal hemorrhage by gross pathology examination with microscopic examination demonstrating AD neuropathologic change and widespread necrotizing vasculitis involving blood vessels with cerebral amyloid angiopathy.[32] This is a single case of a patient with underlying CAA, with no prior findings on MRI consistent with CAA, who received a thrombolytic (tPA) while on lecanemab treatment who developed catastrophic cerebral bleeding leading to death. Given the high prevalence of CAA in the AD population, and that cerebral hemorrhage may be seen during treatment with lecanemab, a warning statement in the label, should be considered alerting prescribers to exercise caution when administering antithrombotics or thrombolytics in patients during lecanemab treatment.

7.5.3. Infusion Related Reactions

Infusion Related Reaction in 201 Core

There was a dose dependent higher incidence of infusion related reactions in those receiving lecanemab versus placebo (Table 67). At the proposed dose 32/161 (19.9%) participants experienced one or more infusion related reactions compared to placebo 8 (3.3 %) (Table 67), Four participants discontinued study treatment after the first infusion (b) (6) due to an infusion related reaction

Most infusion related reactions 28/32 (87.5 %) at the proposed dose occurred at the time of the first infusion. Of these, some were given preventive medications (corticosteroids, antihistamines, and nonsteroidal anti-inflammatory medications) prior to subsequent infusions. Overall, 20/27 (74.1 %) of participants who had subsequent infusions did not have subsequent infusion related reactions, and 7 /27 (25.9 %) experienced subsequent infusion related reaction, six of whom had a subsequent infusion reaction despite pre-medication. The maximum severity of the infusion related reaction was mild in 18 /32 (56 %) participants, and moderate in 14/32 (44%) participants. There was one participant who had a moderately severe infusion related reaction categorized as an SAE at the proposed dose arm. Infusion related reactions were

[34] Block et al. Cerebral Amyloid Angiopathy in Stroke Medicine. Dtsch Arztebl Int 2017; 114: 37–42. DOI: 10.3238/arztebl.2017.0037
[35] Felling et al. Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis. J Neurol Transl Neuroscie. 2014; ()1:1034

treated with nonsteroidal anti-inflammatory, analgesic/antipyretic, antiemetics, antihistamines or corticosteroids (Based on applicant ISS Appendix 2, Table 3.1.3.2).

Review of vital signs and laboratory measures identified two additional findings possibly related to infusion related reactions. After the first infusion at week 1, 7 (4 %) participants receiving lecanemab had an elevated temperature compared to 0 in the placebo arm (See Section 7.4.4).

Additionally, after the first dose of study drug in 201 Core, it has been observed that there is a reduction in lymphocyte count and increase in neutrophil count (See Section 7.4.3 Laboratory findings).

Grading of Infusion Reactions

The applicant used the NCI-CTCAE, Version 4.0, grading of allergic/hypersensitivity reactions/cytokine release, as follows (revised per Amendment 06):

•Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated
•Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), IV fluids); prophylactic medications indicated for <24 hours
•Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization required for clinical sequelae (e.g., renal impairment)
•Grade 4: life-threatening consequences; urgent treatment needed (e.g., vasopressor or ventilatory support)
•Grade 5: death

The incidence of infusion reactions was higher in the proposed dose arm compared to placebo with evidence of a dose response (Table 67). At the proposed dose of LEC10-BW, most infusion reactions were of Grade 2 severity.

The symptoms commonly described by participants who experienced an infusion related reaction were fever and flu-like symptoms (chills, generalized aches, feeling shaky and joint pain). Some participants experienced hypotension, hypertension, nausea, vomiting, or oxygen desaturation.

The majority of infusion related reactions occurred at the time of the first infusion. In 75 % of the participants the infusion reaction duration was 2 days, and in 97 % was 6 days (ranging from 1 to 71 days). At the proposed dose of LEC10-BW, the first infusion related reaction in those who had one or more infusion-related reaction occurred at the time of the first infusion in 28/32 (87%), at the time of the second infusion in 3/32 (0.1 %), and at the time of the 2nd and 33rd infusion, in one participant each.

At the proposed dose arm, 76 % of infusion reactions were classified as grade 1 or 2. (Table 67). compared to 8/8 (100 %) in the placebo arm. No participant experienced an anaphylactic reaction (Grade 4 infusion reaction) (Table 66). Of the 2 participants with a grade 3 infusion reaction in the LEC10-BW group, participants (b) (6) had a grade three infusion reaction which was classified as an SAE.

The symptoms reported by participants who experienced a grade 3 infusion related reaction were rash, nausea, vomiting, agitation/confusion, fever in one participant and fever, thrills, hypertension, asthenia, and desaturation in the other participant. One of these participants (b) (6) also had reduced lymphocyte count. See narratives for participant (b) (6) who had an SAE later in this section for more details.

Table 66 Incidence of infusion reactions in 201 Core

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Infusion related reaction	**3 (6)**	**4 (8)**	**11 (12)**	**59 (23)**	**32 (20)**	**8 (3)**
Grade 1	2/3 (67)	3 /4 (75)	2/11 (18)	15/59 (25)	10 /32 (31)	4 (1.6)
Grade 2	1/3 (33)	1/4 (25)	9/11(82)	40/59 (68)	19 /32 (59)	4 (1.6)
Grade 3	0	0	0	4/59 (7)	2 /32 (6)	0
Missing	0	0	0	0	1 (3)	0

Reviewer created using the ISS ADAE dataset, selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL =Y,: dictionary derived term= infusion related reactions. The highest grade of infusion reaction for each individual was selected. This dataset then was grouped by dictionary derived term, USUBJID, and actual treatment for period 01 and tabulated by actual treatment for period 01 and maximum standard toxicity grade. Toxicity grade was missing for participant (b) (6)

Investigator ratings of severity of infusion reactions were mostly mild or moderate for Grade 1 and 2 infusion-related reactions, and was moderate for all Grade 3 infusion reactions. Based on the maximum severity, the incidence for both mild and moderate infusion reactions separately was 9 % (55/609 for mild, and 52/609 for moderate) in the lecanemab arms. At the proposed dose of the 32 infusion related reactions the maximum severity was mild in in 56 % (18/32) and moderate in 44 %. (14/32).

There were two treatment emergent infusion related reactions identified as SAEs across all dose arms. One was a Grade 3 infusion reaction in the proposed dose (b) (6), and another was in the placebo arm.

Management of Repeated Infusion Reactions in Study 201 Core

See Appendix Section 12.1.6 for Management of Infusion Related Reactions as described in the Protocol BAN2401-G000-201 for Study 201.

In the proposed dose arm, 27/ 32 (83 %) participants had one or more subsequent infusions after their first infusion related reaction.

The following information is obtained from the applicant ISS Table 3.1.3.1:

Of the 27 participants who had one or more subsequent infusions 7 /27 (25.9 %) had additional infusion reactions with subsequent doses; 6/7 continued to have subsequent infusion-related reactions despite preventive treatment.

The medications that were used to treat and prevent infusion-related reactions included nonsteroidal anti-inflammatory, analgesic/antipyretic, antiemetics, antihistamines or corticosteroid agents.

Infusion interruptions due to infusion related reaction:

Based on my analysis, infusion interruption due to an infusion related reaction occurred in 3 participants: 1/92 (1.1 %) in the LEC5- BW group (b) (6), 2/ 253 (0.8 %) (b) (6) in the LEC10-M group. There were no participants who had infusion interrupted due to an infusion related reaction in the LEC10-BW group.

SAEs and Study Drug Discontinuation due to infusion related reaction

Of the participants who had an infusion related reaction, 2 were reported as SAEs; one in the LEC10-BW arm (b) (6) and one in the placebo arm. There was a higher rate of study drug discontinuations due to infusion related reactions in the proposed dose compared to placebo (2.5 % vs 0.8 %) (Table 67).

Table 67 SAEs and Study Drug Discontinuation due to infusion related reaction

	LEC2.5-BW N=52 N (%)	LEC5-M N=51 N (%)	LEC5-BW N=92 N (%)	LEC10-M N=253 N (%)	LEC10-BW N =161 N (%)	Placebo N= 245 N (%)
Infusion Related reaction	3 (6)	4 (8)	11 (12)	59 (23)	32 (20)	8 (3)
Serious	0	0	0	0	1 (1)	1 (<1)
Drug discontinuation	0	0	0	5 (2)	4 (2)	2 (1)

All of the infusion related reactions leading to discontinuation in the proposed arm were categorized as moderate in severity. One was serious leading to hospitalization. Most included fever, chills, body aches with or without hypotension, nausea, vomiting, or desaturation occurring within hours of study drug administration.

The narratives of SAEs and drug discontinuations in 201 Core due to infusion related reactions will be described under the Narratives in this section.

201 OLE

The total number of infusion related reactions in 201 OLE is 37 (21 %), which is comparable to the 20 % seen in the 201 Core study. This total includes 2 participants with 2 PTs that were not coded to the PT "infusion related reaction" but were categorized as infusion-related reaction in the AE case report form (CRF) by the investigator (PTs were pyrexia and injection site joint erythema).

In the OLE there was one SAE (b) (6) due to infusion related reaction, and this participant was the only discontinuation due to infusion related reaction.

Narratives of Infusion Related Reactions in 201 Core and 201 OLE

There were no deaths due to an infusion related reaction in Study 101, 104, 004, 201 Core and 201 OLE.

SAEs due to infusion related reactions:

Studies 101, 104 and 004
There were no participants in study who experienced an SAE infusion related reaction in studies 101, 104 and 004.

201 CORE and OLE

(b) (6)
This 78-year-old white male with mild dementia due to AD on LEC10-BW in 201 Core, complained of dizziness, and had vomiting, chills and fever (38.5°C) on Study Day 15, 3 hours after the second infusion of study drug. A grade 3 infusion related reaction was reported, classified as moderate in severity, and serious. Participant was hospitalized and treated with dexchlorpheniramine 5 mg IV TID, iv fluids, methylprednisolone, ondansetron, dexketoprofen, and pantoprazole. The next day symptoms of dizziness and vomiting improved but fever persisted. While neurological exam was non-focal, participant was noted to be confused. On Study Day 16, the participant was discharged from the hospital with analgesics. The study drug was permanently discontinued due to the event of infusion related reaction. The participant completed efficacy assessment Visit 42 and was discontinued from the study on Study Day 551.

OLE

(b) (6)

This 68-year-old white male with mild dementia due to AD was on placebo in Study 201 Core. Two hours after the 1st dose of LEC10-BW in 201 OLE, the participant experienced an infusion related reaction that was rated as severe, and serious. His symptoms included nausea, vomiting, agitation/confusion and fever (up to 38.8°C). The participant's laboratory results showed elevated C-reactive protein of 67.2 mg/dL (normal range [NR]: 0.0-5.0 mg/dL), low eosinophil percentage of 0.1% (NR: 1.00-4.00%), low lymphocyte count of 0.62 × 10^3/µL (NR: 1.00-4.00 × 10^3/µL), low monocyte of 0.09 × 10^3/µL (NR: 0.20-1.00 × 10^3/µL), and increased neutrophil percentage of 86.30% (NR: 42.00-74.00%). These hematological values, except an elevated eosinophil count, were normal at baseline. She did not have a baseline CRP measured. No treatment was reported for this event. The study drug was permanently discontinued due to the event of infusion related reaction.

<u>Discontinuations due to infusion related reactions:</u>

There were 11 discontinuations due to dictionary derived term infusion related reactions. There were 2/245 (0.8 %) in the placebo group (b) (6), 5/253 (2 %) in the LEC10-M group, and 4 /161 (2.5 %) in the LEC10-BW group. 9 were discontinued due to the TEAE of infusion related reaction and 3 per participant request.

Of the 11 that discontinued from study due to infusion related reaction, one was a serious event of moderate severity and is further described under the SAEs (b) (6). Of the remaining 10, 1 (grade 3) was determined to be mild (b) (6), and the rest (grade 2 or three) were identified as moderately severe (b) (6)

Infusion reactions in the placebo group
One of the placebo participants (b) (6) developed an urticarial rash, became hypotensive, and experienced a tightness in her chest; the infusion related reaction was rated as a grade 3 reaction. The other participant (b) (6) experienced recurring episodes of diarrhea, nausea, abdominal pain, and or vomiting during or after infusions and eventually discontinued after the 21st study dose

Infusion reactions occurring in the highest two dose arms (LEC10-M and LEC10-BW)
In some participants (b) (6) in 201 Core, study drug was discontinued after a single episode of infusion related reaction that occurred right after or within a few hours after the infusion. All were rated as moderate in severity, one was serious. All but one participant (b) (6) received treatment with one or more of the following medications, antihistamines, chlorphenamine, dexamethasone, paracetamol or ibuprofen.

As an illustrative narrative, participant (b) (6) experienced generalized weakness 2 hours after the infusion, followed by temperature of 40 C, itchy bumps in his abdomen and reported shortness of breath. He was treated with ibuprofen and diphenhydramine, and received fluids in the emergency department. Study drug was discontinued.

(b) (6) experienced sudden onset myoclonus and tremor, while she was speaking on the day of the 6th infusion (study day 71 and study drug was permanently discontinued on study day 71.

Reviewer Comment: Whether the myoclonus and tremor are truly due to an infusion reaction is unclear. There were no changes in blood pressure, no other symptoms of an infusion reaction documented in the narrative. Therefore, I believe this may not have been an infusion reaction

Two participants (b) (6) in 201 Core, had recurrent episodes of infusion related reactions. (b) (6) experienced recurrent episodes of flu like symptoms, headache, generalized aches, pains, and diaphoresis, starting on the third dose of study drug administration. She was discontinued after continued recurrent episodes after the 5th dose of study drug. Participant (b) (6) experienced chills, and a temperature of 38.8 C, 2 hours after the first infusion and treated with analgesics. He did not have a reaction after his second dose as he was pretreated with dexamethasone, diphenhydramine and paracetamol, however, he had recurrent symptoms of chills, rigors, headache and fever after the third infusion without premedication and was discontinued from study.

One participant (b) (6) was discontinued from study due to infusion related reactions in 201 OLE, described under the SAEs above.

7.5.4. Hypersensitivity Reactions

201 Core

Overall, I note an increase in the incidence of TEAEs belonging to Hypersensitivity SMQ (narrow)[36] in the lecanemab arms compared to placebo (Table 68). This was mainly driven by the increased frequency of infusion related reactions in the lecanemab arms compared to placebo. For example, of the 43 TEAES in the LEC10-BW arm that were captured under the Hypersensitivity SMQ narrow, 32 were infusion related reactions.

Table 68 Incidence of A Participant Reporting at Least One Hypersensitivity-Related TEAE in the Placebo-Controlled Period of Study 201 Core.

[36] *The Hypersensitivity SMQ Narrow included the following Preferred Terms: Infusion related reaction, Allergic sinusitis, Application site dermatitis, Contrast media reaction, Dermatitis, Dermatitis allergic, Dermatitis atopic, Dermatitis contact, Drug eruption, Drug hypersensitivity, Eczema, Eye allergy, Hand dermatitis, Hypersensitivity Infusion related reaction, Multiple allergies, Palatal swelling, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash pustular, Rhinitis allergic, Swelling of eyelid, Urticaria, Urticaria cholinergic*

	LEC2.5-BW N=52	LEC5-M N=51	LEC5-BW N=92	LE10-M N=253	LEC10-BW N=161	Placebo N=245
Hypersensitivity SMQ (Narrow)	7 (13)	11 (22)	22 (24)	74 (30)	43 (27)	28 (11)
Hypersensitivity SMQ (Narrow), excluding infusion reactions	4 (8)	8 (16)	14 (15)	23 (9)	12 (7)	23 (9)
Skin Reaction Terms*	3 (6)	4 (8)	4 (4)	10 (4)	3 (2)	6 (2)

Reviewer created table using the MedDRA Based Adverse Event (MAED) program to analyze the ISS ADAE dataset, selected for Study ID= BAN2401-G000-201, SAFFL=Y, TRTEMFL =Y. and Hypersensitivity SMQ Narrow.
** Preferred Terms included are drug eruption, rash macular, rash pustular, rash erythematous, rash maculopapular, dermatitis, rash*

Excluding infusion related reactions, only drug eruption showed a 2% higher incidence in the combined lecanemab arms (2 %) compared to placebo (0); dermatitis contact, dermatitis, and eczema were more frequent in the lecanemab arms, with a frequency of 1 % higher compared to placebo.

Excluding infusion related reactions, only the following preferred terms under Hypersensitivity Narrow SMQ had a higher frequency in the LEC10-BW arm compared to placebo, each occurred in 1 % (1/161) in the LEC10-BW arm vs 0 in placebo: drug eruption, eczema, rash macular, hypersensitivity, allergic sinusitis, and multiple allergies. When combining PTs related to skin reaction (rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash, dermatitis, drug eruption) the incidence of one or more skin reaction was similar between the proposed dose arm and placebo, however all lecanemab arms combined had a higher incidence of having one or more skin reaction compared to placebo (4 % vs 2 %). Of the 32 skin reactions in the 24 participants receiving lecanemab, 65.6 % were mild, and 34. 4 % were moderate, none was severe or serious. 90 % of the time dosing continued, in 6.2 % drug was interrupted, 3.1 % (one participant) drug was discontinued. Participant (b) (6) who was in the LEC10-BW arm, was discontinued due to a drug eruption. This was classified as nonserious and mild in severity. Narrative is provided below.

Reviewer Comment: It appears that drug related skin reactions occurred at a slightly higher incidence in participants receiving lecanemab compared to placebo, were mostly mild, and managed without interruption of dosing in most cases.

Eyelid edema (b) (6) was reported in one participant in the LE10-M group. This was mild in severity and nonserious. It occurred 6 days after the 27th dose of study drug and was reported to be resolved approximately 18 days later. The participant continued with dosing with the study drug and completed the study as planned without recurrence.

Reviewer Comment: It is unclear from the narrative, whether this incident of eyelid swelling represented a hypersensitivity reaction such as angioedema, or whether the eyelid swelling was

from another cause. However, the fact that it did not recur through continued dosing in the remainder of the study, makes this less likely,.

There were 5 participants with a preferred term of hypersensitivity in 201 Core, 3 in the placebo arm and one in the LEC10-BW arm, and one in the LEC5-M arm. Participant (b) (6) who was randomized to receive LEC10-BW experienced a skin eruption on the hand and foot (forearm, lip, lower leg, precordia area) prior to the study drug administration, which became worse 2 days after the first and second infusions. The rash disappeared at subsequent visits, and the participant received up to 30 doses without further skin reactions. This event was nonserious and mild in severity.

Reviewer Comment: Overall hypersensitivity reactions to the study drug, other than infusion related reactions, were usually mild and nonserious, and resolved without intervention.

The duration of TEAEs belonging to the hypersensitivity SMQ in the 201 Core study ranged between 1 and 512 days (25% quartile of 1 day, 50% quartile of 2 days, 75% quartile of 3 days). When excluding infusion related reactions, the 25th quartile was 3 days, 50th quartile was 10 days and 75th quartile was 28 days.

When excluding those with an infusion related reaction, in participants who experienced only one TEAE belonging to the SMQ hypersensitivity, approximately 25% had onset within 4 days of their most recent dose. Approximately 75% of participants had onset within 12 days of their most recent dose.

<u>201 OLE</u>

In 201 OLE 46 participants had TEAEs that fell under the Hypersensitivity SMQ Narrow in the 120-day updated ADAE dataset. Of these, 35 were infusion related reactions. The remaining TEAEs that fell under the Hypersensitivity Narrow SMQ in the OLE included the following in more than one participant: rash (n=4), dermatitis (n=3) dermatitis contact (n=3). The following only occurred in one participant: blepharitis allergic, catheter site dermatitis, dermatitis atopic, dermatitis bullous, drug eruption, eczema, urticaria. These were all categorized as mild in severity, and not serious. Participant (b) (6) had 19 occurrences of a TEAE of fever, or drug eruption/drug rash, and (b) (6) had 4 occurrences of a TEAE of fever or rash. The other TEAEs only occurred once.

<u>SAE, Discontinuations and Drug Interruptions Due to Hypersensitivity Reactions</u>

This section discusses TEAEs that fall under the hypersensitivity Narrow SMQ excluding infusion related reactions as these were separately discussed in Section 7.5.3.

None of the other TEAEs, outside of infusion related reactions, that fell under the hypersensitivity Narrow SMQ were identified as serious or severe.

Excluding infusion related reactions, study drug was interrupted for TEAEs under the Hypersensitivity SMQ Narrow in 4 participants for the following TEAES: Hypersensitivity (b) (6), drug eruption (b) (6), dermatitis contact (b) (6).

Excluding infusion related reactions study drug was discontinued for TEAEs under the Hypersensitivity SMQ Narrow for one participant (b) (6) for drug eruption.

Narratives 201 Core

Illustrative narratives for hypersensitivity related TEAEs are provided below.

Of the 10 participants with treatment emergent drug eruptions in the lecanemab arms, I identified a potential role of the study drug in 6 participants (b) (6) after review of narratives. The following narratives illustrate three different actions taken with study drug.

Participant (b) (6) is a 67-year-old white male on LEC5-BW, who reported an itchy rash in the groin ongoing for 4 days starting 15 days after the third dose of study drug on day 28. The investigator decided to hold the study drug, and referred participant to a dermatologist. The dermatologist initially diagnosed a fungal infection, but after development of a new rash on his shins, dorsal feet, lower anterior feet and arms 2 days later a skin biopsy diagnosed of purpura (representing a drug eruption). It was classified as mild and nonserious. The study drug was permanently discontinued.

Participant (b) (6) is a 64 year old man on LE10-M, who one day after the 3rd dose of study drug (on study day 30) experienced a macular rash on bilateral lower extremities (described as a drug eruption from knees to ankles). It was not itchy and classified as mild and nonserious. No treatment was given. Study drug was interrupted, and the AE resolved on Study Day 60, and treatment was restarted on Study Day 63. The participant did not have recurrent rash, and completed the study receiving the 38th (last) dose of study drug.

Participant (b) (6) is a 73 year-old man on LE10-M, who experienced a drug eruption consisting of hives on bilateral forearms and lower legs, after the third dose of study drug on study Day 30. This was classified as mild and nonserious. The participant was treated with cetirizine. On Study Day 44, he continued to have residual patches of redness in arms and ankles. On the same day he received the 4th dose of study drug, and complained of a sense of tingling in the right arm followed by hives on the right arm. He again was treated with cetirizine. On subsequent infusions he was premediated with diphenhydramine and

hydrocortisone as well as received study drug at a 50% iv rate reduction. No other action was taken due to this event, and he completed study with no further episodes of hives.

Of the participants with TEAEs of drug hypersensitivity, and dermatitis, I identified a potential role of study drug for only one participant (b) (6). This participant had recurrent episodes of rash, swelling in one leg 24-72 hours after infusions lasting for 2 days. She was treated with analgesics, and antihistamines and completed study despite recurrent rash after dosing throughout the study.

Of the participants with treatment emergent rash, three only experienced one occurrence of skin rash (b) (6), which resolved with topical steroid or oral antihistamine treatment, and all participants completed the study without recurrence of a rash with repeated doses. One participant, (b) (6), had two recurrent episodes of rash around the time of infusion, the first time occurring in the context of infusion site extravasation (mild severity rating, without skin damage but symptoms of mild pain), but the second time without an infusion site extravasation occurring about a week after the 25th infusion. I could not rule out a role of the study drug in occurrence of rash in these participants.

Narratives 201 OLE

The following illustrative narratives are provided for hypersensitivity related TEAES in 201 OLE.

4/180 (2 %) participants (b) (6) experienced a rash in the 201 OLE study. I reviewed the narratives of these participants and could not rule out a role of study drug in the occurrence of rash in these participants. Participants (b) (6) experienced a single occurrence of rash during the course of study participation without another identifiable cause. Participant (b) (6) also experienced pruritis and hematuria, during the course of the study.

In Study 201 OLE, there were 5/ 180 (2. 8%) participants (b) (6) who had treatment emergent events of dermatitis, dermatitis bullous or dermatitis atopic. I reviewed these narratives (except (b) (6) with no narrative). In all the cases I reviewed, the dermatitis occurred once, later during the course of the treatment, resolved and did not recur with repeated doses. I could not identify a clear role of study drug in these instances.

Participant (b) (6) is a 62 year-old male randomized to receive placebo in 201 Core. Starting with Extension Day 2, one day after the 1st dose of study drug, had recurrent episodes of pyrexia and drug eruption (alone or in combination). In total he experienced 7 occurrences of drug eruption and 12 occurrences of pyrexia. He received treatment with antipyretics, antihistamines, steroids and topical treatments, but was never treated pre-infusion. All of these events were categorized as mild in severity, and nonserious by the investigator. The participants withdrew from the study after the 18th dose.

(b) (6) is a 59 year-old male who received LEC10-BW in 201 Core. After his 10th dose in the Extension Phase (on extension day 128), the participant experienced a rash on the arm, which was classified as mild and nonserious. The rash resolved in 4 days. He then experienced pyrexia after his 48th dose, and then again after the 51st dose (Extension Day 714) both of which resolved the next day without intervention. All of these were rated as mild in severity and nonserious. No action was taken, and it resolved the next day. The participant experienced a rash on Study Day 891, which was mild in severity and non-serious, no action was taken. The participant received the 71st dose of study drug, and participation is still ongoing.

Study 301 Core

For the ongoing Study 301 Core and 301 OLE, clinical symptoms associated with treatment emergent infusion related reactions were headache, respiratory symptoms, pyrexia, rash rigors, chills, vomiting, lightheaded, nausea and low blood pressure, consistent with lecanemab associated infusion reactions reported in Study 201 Core and OLE. One reaction consistent with anaphylaxis (with respiratory and gastrointestinal symptoms) was also reported. Because these studies remain blinded, it is not possible to ascertain relatedness to lecanemab.

7.5.5.Suicide Risk

I did not identify a higher risk of suicidal ideation or suicidal behavior in those receiving lecanemab compared to placebo.

In Study 201 Core, the incidence of an affirmative response on the C-SSRS related suicidal ideation was 12/161 (7%) at the proposed dose arm, and 19/245 (8 %) in the placebo group. The incidence of suicidal behavior at baseline was 3/161 (2 %) at the proposed dose arm and 4/245 (2 %) in the placebo arm.

In Study 201 Core of the participants with a baseline visit, the incidence of affirmative response on the C-SSRS related to suicidal ideation at one or more postbaseline visit were 6/159 (4 %) at the proposed dose arm, and 9/244 (4%) in the placebo. There were no participants with an affirmative response to suicidal behavior postbaseline.

In Study 201 OLE, at baseline 11/191 (6 %) participants had an affirmative response on the C-SSRS related to suicidal ideation, and 9/191 (5 %) had an affirmative response to suicidal ideation related questions on the C-SSRS on one or more postbaseline visits. The incidence of an affirmative response to suicidal behavior was 2/191 (1 %) at baseline, and 0/191 at one or more postbaseline visit.

There was one participant (b) (6) in 201 Core who had an SAE of suicidal ideation and is described under the SAEs. This participant had a history of psychiatric disease, with past

medical history of suicidal ideation, and it did not appear that the study drug played a role in this participant's suicidal ideation.

In Study 104, per the clinical study report, a wish to die was expressed by 1 participant (20.0%) in the placebo group and 2 participants (10.5%) in the BAN2401 treatment group (1 participant in the 2.5 mg/kg group and 1 participant in the 10 mg/kg group). Nonspecific active suicidal ideation was expressed by 1 participant (5.3%) in the BAN2401 treatment group (2.5 mg/kg). y.

In Study 101, per the clinical study report, a wish to die was expressed by one placebo-treated participant and one participant who received a single dose of 0.3 mg/kg of study drug. No other suicide signals were detected during the administration of the C-SSRS in the SAD or MAD studies.

In 301 Core, which is ongoing, and only provides blinded study data, 3 participants were identified with an SAE of suicide attempt (in one participant with self-inflicted gun-shot wound) or suicidal ideation. In one of these participants suicidal ideation led to study discontinuation. Given that these participants are receiving blinded study drug, I cannot ascertain whether there is a role of study drug in these cases.

7.5.6. Other

Similar to observations with other monoclonal antibodies directed against amyloid, in the pharmacodynamic subset analysis in Study 201 Core, those receiving LEC10-BW compared to placebo had higher rate of brain atrophy, and ventricular enlargement through the course of the study. The underlying mechanisms leading to this finding, and its long term effects are unknown. Please see Dr. Kevin Krudys' Clinical Review of Efficacy for further details.

7.6. Safety Analyses by Demographic Subgroups

I evaluated the most common TEAES reported in the 201 Core study by the following demographic parameters: sex, age group, race, region, BMI and baseline clinical stage of AD.

Overall, the numbers for most TEAEs when divided by demographic subgroups was too small to make any clear conclusions. The frequency of ARIA-E, headache, and diarrhea were greater in women than in men, for both LEC10 BW and for placebo. (Table 69).

Table 69 Incidence of Common TEAEs by PT in 201 Core by Sex[37]

	LEC10-BW		Placebo	
Preferred Terms	F N=70	M N=91	F N=138	M N=107
Infusion related reaction	13 (19)	19 (21)	5 (4)	3 (3)
ARIA-E	9 (13)	7 (8)	2 (14)	0
Cough	6 (9)	8 (9)	6 (4)	6 (6)
Headache	11 (16)	11(12)	20 (14)	5 (5)
Diarrhea	7 (10)	6 (7)	9 (6)	3 (3)
Paresthesia	3 (4)	2 (2)	1 (1)	0
Dental Caries	3 (4)	2 (2)	1 (1)	0
Atrial Fibrillation	3 (4)	3 (3)	2(1)	1 (3)
Lymphopenia and Lymphocyte reduced	2(3)	4 (4)	1(1)	0

It appeared that in the proposed dose arm, cough occurred at a much higher incidence in those under the age of 65 (Table 70). I am unable to explain this finding with a clear underlying mechanism by which the study drug could cause a higher incidence of cough in younger participants. It is unclear, whether this finding is by chance or represents or represents a truly higher risk in this age group. I did not note any other clear age-related trends in the TEAEs.

[37] Tables in this section were reviewer created using the OCS Analysis Studio, Custom Table Tool. Columns-Dataset Demographics: Filter: SAFFL=Y, Study ID=BAN2401-G0000-201, Adverse Event Filter: SAFFL=Y, Study ID= BAN2401-G000-201, Treatment Emergent Flag=Y, percent threshold=2%.

Table 70 Incidence of Common TEAEs by PT in 201 Core by Age Groups (years)

	LEC10-BW (n=161) N(%)			Placebo (n=245 N(%)		
Preferred Terms	<65 (N=28)	≥ 65 to <80 (N=99)	≥ 80 (N=34)	<65 (N=56)	≥ 65 to <80 (N=150)	≥ 80 (N=39)
Infusion related reaction	6(21)	17 (17)	9(27)	6(11)	2(1)	0
ARIA-E	2 (7)	11 (11)	3 (9)	0	2 (1)	0
Cough	6 (21)	7 (7)	1 (3)	3 (5)	5 (3)	4 (10)
Headache	3(11)	15 (15)	4 (12)	9 (16)	14 (9)	2(5)
Diarrhea	1 (4)	10 (10)	2 (6)	3 (5)	9 (6)	0
Paresthesia	1(4)	4(4)	0	1(2)	0	0
Dental Caries	0	1(1)	4(12)	1(2)	0	0
Atrial Fibrillation	0	3 (3)	3 (9)	0	2 (1)	1(3)
Lymphopenia and Lymphocyte reduced	1(4)	2(2)	3(9)	0	0	1(3)

The number of races other than white was too small to make any meaningful comparisons of the incidence of TEAEs in the 201 Core study (Table 71).

Table 71 Incidence of Common TEAEs by PT in 201 Core by Race

	LEC10-BW(n=161) N(%)			Placebo (n=245) N(%)			
Preferred Terms	Asian (N=7)	Black or African American (N=4)	White (N=150)	Asian (N=17	Black or African American (N=5)	Other (n=1)	White (n=222)
Infusion related reaction	1(14)	0	31(21)	0	1(20)	1(100)	6(3)
ARIA-E	1(14.3)	0	15(10)	0	0	0	3 (1)
Cough	0	0	14(9)	1(6)	0	0	11(5)
Headache	0	0	22	3(18)	1(20)	0	21(10)
Diarrhea	1(14)	0	12(8)	0	1(20)	0	11 (5)
Paresthesia	0	0	5(3)	0	0	0	1 (<1)
Dental Carries	0	0	5 (3)	0	0	0	1 (<1)
Atrial Fibrillation	0	0	6(4)	0	0	0	3 (1)
Lymphopenia/Lymphocyte Count decreased	0	0	6(4)	1(6)	0	0	0

The numbers in regions other than North America were too small to reach any conclusions regarding the incidence of common TEAEs by region (Table 72).

Table 72 Incidence of Common TEAEs by PT in 201 Core by Region

	LEC10-BW (n=161) N(%)			Placebo (n=245) N(%)		
Preferred Terms	Asia (N=7)	North America (N=142)	Europe (N=12)	Asia N=0	North America N=201	Europe N=28
Infusion related reaction	1 (14)	29 (20)	2 (17)	0	5 (2)	3 (11)
ARIA-E	1(14)	14(10)	1(8)	0	2(1)	0
Cough	0	11(8)	3(25)	0	11(5)	1(4)
Headache	0	22 (15)	0	3 (19)	18 (9)	4 (14)
Diarrhea	1 (14.3)	11 (8)	1 (8)	0	12 (6.0)	0
Paresthesia	0	5(3)	0	0	1 (<1)	0
Dental Caries	0	5 (3)	0	0	1 (<1)	0
Atrial Fibrillation	0	6 (4)	0	0	3 (1)	0
Lymphopenia and Lymphocyte reduced	0	5 (3)	1 (8)	1 (6)	0	0

Those who were ApoE ε4 allele carriers had a higher incidence of ARIA-E both at the proposed dose arm, and in the placebo group. (Table 73)

Table 73 Incidence of Common TEAEs by PT in 201 Core by APO genotype

Preferred Terms	LEC10-BW (n=161) N(%)		Placebo (n=245) N(%)	
	Negative (N=113)	Positive (N=48)	Negative (N=72)	Positive (N=173)
Infusion related reaction	23 (20)	9 (19)	2 (3)	6 (4)
ARIA-E	8 (7.1)	8 (17)	0	2 (1)
Cough	14 (12.4)	0	1 (1)	11 (6)
Headache	17 (15)	5 (10)	4 (6)	21 (12)
Diarrhea	11 (10)	2 (4)	1 (1)	11 (6)
Paresthesia	4 (3)	1 (2)	0	1 (1)
Dental Caries	5 (4)	0	0	1 (1)
Atrial Fibrillation	6 (5)	0	0	3
Lymphopenia and Lymphocyte reduced	4 (3)	2 (4)	1 (1)	0

I did not identify a clear pattern of MCI or mild AD participants having higher risk of any one TEAE. (Table 74)

Table 74 Incidence of Common TEAEs in 201 Core by baseline diagnosis

	LEC10-BW (n=161) N(%)		Placebo (n=245) N(%)	
Preferred Terms	MCI (N=96)	Mild AD (N=65)	MCI (N=158)	Mild AD (N=87)
Infusion related reaction	19 (20)	13 (20)	5 (3)	3 (3)
ARIA-E	9 (9)	7 (11)	2 (1)	0
Cough	10 (10)	4 (6)	8 (5)	4 (5)
Headache	11 (11)	11 (6)	15 (9)	10 (11)
Diarrhea	9 (9)	4 (6)	8 (5)	4 (5)
Paresthesia	2 (2)	3 (5)	1 (1)	0
Dental Caries	0	5 (8)	1 (1)	0
Atrial Fibrillation	2 (2)	4 (6)	1	2 (2)
Lymphopenia and Lymphocyte reduced	4(4)	2(3)	0	1(1)

Table 75 Incidence of TEAEs by BMI category in 201 Core

	LEC10-BW (n=161) N(%)				Placebo (n=245) N(%)			
Preferred Terms	<22.5 N=30	>=22.5, <24/9 N=32	x>=24.9 but <27.9 n=32	>=27.9 98	<22.5 N=52	>=22.5, <24.9 N=60	x>=24.9 but <27.9 n=60	>=27.9 131
Infusion related reaction	5 (17)	5 (16)	0	22 (22)	2 (4)	2 (3)	0	4(3)
ARIA-E	4 (13)	3 (9)	0	9 ()	1 (2)	0	0	1 (1)
Cough	2 (7)	2 (6)	0	10 (10)	1 (1)	3 (5)	0	8 (6)
Headache	3 (10)	8 (25)	0	11 (11)	4 ((8)	9 (15)	0	12 (9)
Diarrhea	2 (7)	5 (16)	0	6 (6)	1 (2)	6 (10)	0	5 (4)
Paresthesia	4 (13)	0	0	1 (1)	1 (2)	0	0	0
Dental Caries	0	1 (3)	0	4 (4)	0	0	0	1 (1)
Atrial Fibrillation	2 (7)	1 (3)	0	3 (3)	0	1 (7)	0	2 (1)
Lymphopenia and Lymphocyte reduced	1 (3)	3 (9)	0	2 (2)	1 (2)	1 (7)	0	0

7.7. Specific Safety Studies/Clinical Trials

Not Applicable

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

I did not identify an imbalance in the incidence of AEs belonging to the SOC Neoplasm between LEC10-BW and placebo arms; however, a conclusion about the carcinogenic potential of lecanemab cannot be drawn due to the short duration of exposure. Mean exposure to the proposed dose of LEC10-BW in the 201 Core study was 52 weeks (30 (SD), median 78, range 2 - 80 weeks).

In the 201 OLE study the average duration of exposure for the 180 participants was 89 weeks (35 (SD), 2-131 (range)98 (median). Of these 45 were new exposures to study drug as they received placebo in 201 Core. The duration of exposure in this group was 88 weeks (39 (SD) 2 - 131 (range) 100 (median).

In an analysis of incidence of participants reporting an AE within the SOC Neoplasm in Study 201 Core, LEC10-BW assigned participants (7/161, 4 %) did not have a higher incidence compared to placebo (20/245, 8 %). I grouped AEs belonging to the SOC of Neoplasm by organ system. The proposed dose arm had a 1 % higher incidence of bladder cancer compared to

placebo. This was driven by one participant in the LEC10-BW group compared to none in placebo, and therefore this finding is of unclear significant. (Table 76)

Table 76 AEs Belonging to the SOC of Neoplasm in the Placebo-Controlled Period of Study 201

	LEC2.5-BW N=52	LEC5-M N=51	LEC5-BW N=92	LE10-M N=253	LEC10-BW N=161	Placebo N=245
Skin	**12 (23%)**	**4 (4 %)**	**13 (14%)**	**15 (6 %)**	**6 (4 %)**	**20 (8%)**
Acrochordon	0	0	0	0	0	1 (<1)
Basal cell carcinoma	4 (8)	2 (4)	6 (7)	4(2)	3 (3)	6 (2)
Bowen's disease	1 (2)	0	1 (1)	0	1 (1)	0
Dysplastic naevus	1 (2)	0	1 (1)	2 (1)	0	0
Hair follicle tumor benign	1 (2)	0	0	0	0	0
Keratoacanthoma	0	0	2 (2)	0	0	1 (<1)
Lip squamous cell carcinoma	0	0	0	1 (<1)	0	0
Malignant melanoma	1 (2)	0	0	1 (<1)	0	4 (2)
Seborrheic keratosis	1 (2)	1 (2)	1 (1)	1 (<1)	0	3 (1)
Skin cancer	0	0	0	1 (<1)	0	0
Squamous cell carcinoma of skin/ Squamous cell carcinoma	3 (6)	1 (2)	2 (2)	5 (2)	1 (1)	4 (2)
Skin papilloma	0	0	0	0	1 (1)	0
Urological	**0**	**0**	**2 (2 %)**	**1 (<1)**	**1 (1)**	**0**
Bladder cancer	0	0	0	1 (<1)	0	0
Bladder cancer recurrent	0	0	0	1 (<1)	0	0
Transitional cell carcinoma	0	0	0	0	1 (1)	0
Hematological	**0**	**0**	**2 (2)**	**1 (<1)**	**0**	**0**
Chronic lymphocytic leukemia stage 0	0	0	0	1 (<1)	0	0
Hypergammaglobulinemia benign monoclonal	0	0	1 (1)	0	0	0
Lymphoma	0	0	1 (1)	0	0	0
Gastroenterology	**0**	**0**	**1 (1)**	**1 (1)**	**0**	**0**
Ductal adenocarcinoma of pancreas	0	0	0	1 (<1)	0	0
Hepatocellular carcinoma	0	0	0	0	0	1 (<1)
Breast and Reproductive	**0**	**0**	**1 (1)**	**4 (1)**	**0**	**2 (1)**
Intraductal proliferative breast lesion	0	0	0	0	0	1 (<1)
Invasive ductal breast carcinoma	0	0	0	1 (<1)	0	1 (<1)
Prostate cancer	0	0	1 (1)	3 (1)	0	0
Vascular	**0**	**0**	**0**	**2 (1)**	**0**	**1**
Eye hemangioma	0	0	0	1 (<1)	0	0
Hemangioma	0	0	0	1 (<1)	0	1 (<1)
Connective Tissue	**1 (2)**	**0**	**0**	**2 (1)**	**0**	**1**
Lipoma	0	0	0	0	0	1 (<1)
Osteoma	0	0	0	1 (<1)	0	0
Sarcoma	0	0	0	1 (<1)	0	0
Nervous System	1	0	0	0	0	0
Brain neoplasm	**1 (2)**	**0**	**0**	**0**	**0**	**0**
Nasopharyngeal	**0**	**0**	**0**	**0**	**0**	**1 (<1)**
Pharyngeal neoplasm	0	0	0	0	0	1(<1)

Reviewer created using Analysis Studio v1.6.0, Safety Explorer, Treatment Emergent Flag, Safety Population Flag =yes, SOC+PT query.

The incidence of a participant experiencing an SAE within the SOC Neoplasm was lower in the LEC10-BW group (1/161 (1%) compared to placebo (4/245 (2 %) (Table 77). See Section 7.4.2 for the narratives of these treatment-emergent serious adverse events.

Table 77 Treatment Emergent Serious Adverse Events Belonging to the SOC of Neoplasm in the Placebo-Controlled Period of Study 201

	LEC2.5-BW N=52	LEC5-M N=51	LEC5-BW N=92	LE10-M N=253	LEC10-BW N=161	Placebo N=245
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (2)**	**0**	**1**	**3 (1)**	**1 (1)**	**4 (2)**
Brain neoplasm	1 (2)	0	0	0	0	0
Ductal adenocarcinoma of pancreas	0	0	0	1 (<1)	0	0
Hepatocellular carcinoma	0	0	0	0	0	1 (<1)
Intraductal proliferative breast lesion	0	0	0	0	0	1 (0<1)
Invasive ductal breast carcinoma	0	0	0	1 (<1)	0	1 (0<1)
Lymphoma	0	0	1 (1)	0	0	0
Malignant melanoma	0	0	0	0	0	1 (<1)
Prostate cancer	0	0	0	1 (<1)	0	0
Sarcoma	0	0	0	0	0	1 (<1)
Transitional cell carcinoma	0	0	0	0	1(1)	0

In Study 201 OLE the incidence of a participant experiencing a TEAE within the SOC Neoplasm was 12 % (21/180). This is higher than the incidence of 4 % observed in the LEC10-BW arm in the 201 Core study. This may be due to the longer duration of exposure in the OLE study (89 weeks) compared to 201 Core (52 weeks). Of these adenocarcinoma of the colon, metastatic breast cancer, lung adenocarcinoma and transitional cell carcinoma, metastases to the central nervous system, and neuroendocrine carcinoma were identified as serious TEAEs.

Table 78 Treatment Emergent Serious Adverse Events Belonging to the SOC of Neoplasm in the Open-Label Period of Study 201

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**21 (11.7)**
Adenocarcinoma of colon	1 (0.6)
Basal cell carcinoma	10 (5.6)
Blepharal papilloma	1 (0.6)
Bowen's disease	1 (0.6)
Breast cancer metastatic	1 (0.6)
Colon adenoma	1 (0.6)
Lung adenocarcinoma	1 (0.6)
Melanocytic naevus	1 (0.6)

Metastases to central nervous system	1 (0.6)
Neuroendocrine carcinoma	1 (0.6)
Seborrheic keratosis	2 (1.1)
Squamous cell carcinoma of skin	5 (2.8)
Transitional cell carcinoma	1 (0.6)

I noted that there were three participants who had brain neoplasms in the lecanemab program (b) (6) The narratives for these participants are described under Section 7.4.2 (b) (6) and Section 12.1.2 (b) (6) I reviewed these narratives and could not identify a clear role of study drug given the relatively short duration of treatment compared to the latency for the development of malignancies.

7.8.2. Human Reproduction and Pregnancy

There is no safety data on the use of lecanemab in pregnant women. The applicant notes that no pregnancies have been reported in any clinical study of lecanemab.

7.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overall, I did not identify a safety signal for abuse potential, withdrawal or rebound in a search of TEAEs related to abuse potential.

In 201 Core, there were no participants who had a TEAE of overdose or related PTs [38]. In 201 OLE, there was one participant (b) (6) who had a TEAE of an accidental overdose at the time of the 20th dose administration. The participant had no adverse events ongoing at the time of accidental overdose and no treatment was given. The participant continued dosing with no adverse events from the accidental overdose.

In accordance with the Guidance for Industry, "Assessment of Abuse Potential of Drugs", I searched for TEAEs related to abuse potential.[39] I did not identify a signal for abuse related

[38] Accidental overdose, or Higher Level Term of Overdose Not Elsewhere Classified
[39] The following preferred terms were used: abnormal behavior, abnormal dreams; apathy; affect lability, aggression, agitation, confusional state, delusion, delusional disorder, depersonalization/derealization disorder; dizziness, dysphoria; euphoric mood; feeling abnormal, feeling drunk; hallucination; hallucination visual; hallucination auditory; illusion; mental impairment, mental status change, mood swings, and somnolence

To assess for withdrawal and rebound, I evaluated the TEAEs occurring in participants occurring within 30 days after the last treatment. With this approach ARIA-E, cerebral microhemorrhages and atrial fibrillation were the most frequent TEAEs during the follow up period occurring at 2% or higher frequency at the proposed dose arm compared to placebo.

When I repeated this analysis this time limiting the adverse events to those that occurred after the full cycle of last treatment (> 14 days after last dose), without using the treatment emergent flag, cerebral microhemorrhage, dizziness, headache and URI had a frequency of 2% or higher than placebo (Table 79). While the higher incidence of cerebral microhemorrhages was driven by the participants who were discontinued due to ARIA-E and were being followed by safety MRI's the reason for the slightly higher frequency of dizziness, headache and URI is unclear. Given the very small numbers of participants with these TEAEs, there is no clear evidence that there is any withdrawal or rebound after discontinuing treatment with lecanemab.

Table 79 Incidence of AEs which occur after study drug discontinuation, occurring at an incidence of 2 % in LEC10-BW arm and at an incidence of 2 % or higher compared to placebo

	LEC2.5-BW N=52	**LEC5-M N=51**	**LEC5-BW N=92**	**LE10-M N=253**	**LEC10-BW N=161**	Placebo N=245
Cerebral microhemorrhage	1 (2)	0	3 (3)	13 (5)	6 (4)	2 (1)
Dizziness	0	0	0	1 (<)	4 (2)	1 (<1)
Headache	1 (2)	0	0	2 (1)	3 (2)	1 (<1)
Upper respiratory tract infection	1 (2)	0	0	0	3 (2)	1 (<1)

This table was created by the reviewer using ISS ADAE dataset, Study ID: BAN2401-G000-201, Safety Population = yes, Phase (C): Follow up, Days since last treatment > 14 Days
All the above flags etc, AND treatment emergent this was the only one with 2 % or more for LEC10-BW.

7.9. Safety in the Postmarketing Setting

7.9.1. Safety Concerns Identified Through Postmarketing Experience

Not applicable. Lecanemab is a new molecular entity. It is not approved in other regions of the world.

7.9.2. Expectations on Safety in the Postmarketing Setting

Not applicable.

7.9.3. Additional Safety Issues From Other Disciplines

The reader is referred to the OCP review of risks associated with immunogenicity.

7.10. Integrated Assessment of Safety

Safety findings from BLA 761178 are summarized below.

Deaths: There were 10 deaths occurring in participants who received lecanemab in 201 Core and OLE. There was not an excess of deaths in lecanemab-treated groups compared to placebo-treated groups. Most participants had underlying risk factors for events with fatal outcome. No deaths were attributed to treatment with lecanemab.

Serious Adverse Event: The incidence of SAEs in the LEC10-BW arm was lower than placebo. ARIA-E was the most frequent SAE reported in the 201 Core study, reported in 1.9 % of LEC10-BW group vs 0 in placebo. In the 201 OLE study, the most common SAEs reported (1.7 %) were, transient ischemic attack, seizure, and acute kidney injury.

AEs leading to drug or study discontinuations: There is a high incidence of discontinuation due to TEAEs at the proposed dose arm (14.9 %) vs in the placebo arm (5.7 %). The most frequent adverse events leading to study withdrawal in the placebo-controlled period Study 201 Core was ARIA-E (10 % at the proposed dose arm vs 0.4 % in the placebo arm). This discontinuation was required per protocol. The next highest frequency TEAE that led to study discontinuation at a higher incidence at the proposed dose arm (2.5 %) vs placebo (0.8 %) was infusion related reactions.

Significant AEs: Evaluation of severe AEs did not identify a new safety signal.

Most common AE: The most commonly reported TEAEs in the LEC10-BW were infusion related reactions (20% in LEC10-BW vs 3% in placebo), ARIA-E (10% in LEC10-BW vs 1% in placebo), and headache (14% in LEC10-BW vs 10% in placebo). The incidence of infusions related reactions and of ARIA-E in the 201 OLE were comparable to the incidence of those reactions in the 201 Core Study. ARIA has been observed with other monoclonal antibodies. Risk mitigation strategies for ARIA will be inclusion of a Warning in the label and instructions for monitoring and management of ARIA. The most common AEs occurring in participants without ARIA at the proposed dose in the 201 Core study were infusion related reactions (24 %), headache (16 %), cough (6 %), and diarrhea (6 %).

Laboratory evaluations: There was a dose dependent reduction in lymphocyte count and increase in neutrophil counts in those receiving lecanemab compared to placebo occurring a few hours after the first infusion. This is thought to be due to a subclinical infusion related

reaction, and majority of the participants did not have persistent changes in lymphocyte or neutrophil counts, and there was no clinically significant adverse events, such as infections associated with these changes. Labeling should include a description of these changes.

The proposed dose arm appeared to have a higher incidence of individuals having one or more post baseline low globulin and protein values. The clinical significance of these findings is not known. Those receiving lecanemab also had a higher incidence of individuals having one or more post baseline value with high glucose values compared to placebo. This was consistent with a medical query group search "diabetes glucose intolerance, hyperglycemia, HbgA1C, glycosuria, and ketones: showing an incidence of 5 % in the proposed dose arm versus 1 % in placebo. This may partially have been driven by the fact that a higher percentage of participants in the safety database with LEC10-BW arm compared to placebo had Type 2 diabetes (13 % % vs 8 %) and obesity (3 % vs 1 %) at baseline.

Hepatic Safety – There was no signal of hepatotoxicity identified.

Vital sign evaluations: After the first infusion at week 1, 7 (4 %) participants receiving the three highest doses of lecanemab had an elevated temperature compared to no participants in the placebo arm, which was likely consistent with an infusion related reaction. This should be included in the Label under the description of infusion related reactions. There appeared to be a clinically nonsignificant slight decline in heart rate of 2-3 beats/minute between pre-infusion and post infusion measurements in those receiving lecanemab.

ECG evaluations: There did not appear to be a trend towards higher incidence of abnormal clinically significant, or abnormal clinically nonsignificant ECGs in the proposed dose arm compared to placebo. There was a higher incidence of TEAE of atrial fibrillation at the proposed dose arm (4 %), versus placebo (1 %). There was not a higher incidence of participants with a TEAE of QT prolongation in the lecanemab arms compared to placebo.

Immunogenicity: The ADA assay used by the applicant was not reliable for accurate classification of ADA status, due to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. As a result, no comparisons can be conclusively made in the incidence of TEAEs in ADA negative vs positive participants. Postmarketing requirements will be imposed to improve the assay sensitivity and to use the improved and validated assay to assess the impact of antibody formation on pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in patients enrolled in the confirmatory study.

Adverse Events in Participants Without ARIA: The most common TEAEs in those without ARIA were infusion related reactions, headache and cough, all of which occurred at an incidence of 10 % or higher at the proposed dose arm.

Suicidality: There was no evidence of an increased risk of suicidality on lecanemab.

ARIA: In the placebo-controlled portion of Study 201 Core, any occurrence of ARIA) was observed in 12.4 % of participants who received LEC10-BW and in 5.3 % of participants who received placebo. ARIA-E (with or without co-occurrence of ARIA-H) was observed in 9.9 % of participants receiving LEC10-BW and 0.8 % in placebo. In the LEC10-BW group clinical symptoms occurred in 5/20 (25%) of participants with ARIA, and in 5/16 (31 %) of participants with ARIA-E, and in none of the placebo participants. SAEs of ARIA in the placebo-controlled portion of Study 201 occurred in 2% of participants in the LEC10-BW group, compared with 0 of participants on placebo; all of these SAEs were ARIA-E related. The most common symptoms reported in participants with ARIA-E at the proposed dose arm occurring in 2 or more participants were headache, confusion/altered mental status , visual disturbance , agitation , followed by the following, all occurring in one participant each,: paresthesia, labile affect, aphasia, hallucinations, vomiting. At the proposed dose 75 % of ARIA-E events occurred before the 7th dose, occurred on average 8 days (SD 7, range: 1-34) after a dose and on average lasted for 89 days (SD 58, range 37-258) before it resolved. ARIA-E occurred more frequently in ApoE ε4 carriers compared to noncarriers. The label should include Warnings about ARIA and instructions for ARIA monitoring and management. Because cerebral hemorrhage greater than 1 cm has been observed in patients taking lecanemab, a statement recommending that prescribers exercise caution when prescribing concomitant antithrombotics or thrombolytics should be included in the Warnings and Precautions section of the label.

Hypersensitivity Reactions: There was a higher incidence of TEAEs belonging to Hypersensitivity SMQ (narrow), in the lecanemab arms compared to placebo. This was mainly driven by the increased frequency of infusion related reactions in the lecanemab arms compared to placebo. The incidence of having a skin reaction (rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash, dermatitis, drug eruption) was 3.9 % in the combined lecanemab arms compared to 2.4 % in the placebo arm. Most of the skin reactions were mild, all were nonserious. One participant at the proposed dose arm had a drug eruption that was mild and nonserious but led to discontinuation.

Infusion Related Reactions: There was a dose dependent higher incidence of infusion related reactions in those receiving lecanemab versus placebo. At the proposed dose (19.9%) participants experienced one or more infusion related reactions compared to placebo (3.3 %). Most were mild or moderate in severity. The symptoms commonly described by participants who experienced an infusion related reaction were fever and flu-like symptoms (chills, generalized aches, feeling shaky and joint pain). The majority of infusion related reactions occurred at the time of the first infusion. No one experienced an anaphylactic reaction. One participant at the proposed dose arm had an SAE of infusion related reaction. Those who had an infusion related reaction were treated with preventive medications in subsequent infusions. Infusion related reactions were treated with nonsteroidal anti-inflammatory, analgesic/ antipyretic, antiemetics, antihistamines or corticosteroids (See Section 12.1.6).

8. Advisory Committee Meeting and Other External Consultations

Not Applicable

9. Labeling Recommendations

9.1. Prescription Drug Labeling

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. This will include a subsection to alert prescribers to exercise additional caution when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient taking lecanemab. Information regarding ARIA will also be addressed in the Medication Guide. Guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing will be provided in Sections 2.3 and 5.1 of the prescribing information.

Prescribers will be made aware of the risk of infusion related reactions in section 5.2 of Warnings and Precautions. This will also be addressed in the Medication Guide.

9.2. Nonprescription Drug Labeling

Not applicable

10. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for lecanemab. However, in addition to the Warning in section 5 of the prescribing information will inform prescribers about the risks of ARIA and infusion related reactions, and Medication Guide will inform patients and caregivers about those risks.

11. Postmarketing Requirements and Commitments

Post-marketing 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 participants with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding, or co-morbid cerebral amyloid angiopathy. This should also include evaluation of participant characteristics, including ApoE ε4 genotype if available. Information collected should be used to optimizing monitoring and minimizing risk. Additionally post-marketing enhanced pharmacovigilance should also include evaluation of safety in participants who are dosed through an ARIA, and of those who have multiple ARIA-E and ARIA-H events. Information collected should be used to optimize monitoring and minimize risk.

It should be noted that the data supporting the prescribing information 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.

12. Appendices

12.1.1. Schedule of Assessments for Study 201

201 Core

Table 8 Schedule of Procedures/Assessments, Core Study BAN2401-G000-201, Panel A, Visits 3 through 27, Weeks 1 through 49 – Core Study

Phase	Randomization																								
Period	Treatment																								
Visit[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Week	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49
Procedures/ Assessments																									
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[e]	X						X							X						X					
Routine physical exam					X				X					X						X					
12-lead ECG					X				X					X						X					
Urine pregnancy test[f]							X							X						X					
Blood for laboratory tests[g]	X	X		X			X			X				X						X					
Urinalysis (revised per Amendment 06)	X	X		X			X			X				X						X					
MMSE[h]							X							X						X					
CDR[h]							X							X						X					
ADAS-Cog[h]							X							X						X					
FAQ[h]							X							X						X					
C-SSRS			X		X		X							X						X					
Safety MRI[i]					X		X							X						X					
Volumetric MRI (for PD)[j]					X		X							X						X					
Abbreviated MRI[k]				X																					
Informed consent[l]																									
Amyloid PET[m]																									
Randomization	X																								
Study drug administration	X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X	X[n]	X[n]	X[n]	X[n]	X[n]
Blood for serum BAN2401 PK[o]	X						X							X						X					
Blood for exploratory PD biomarker analysis																									
Blood for serum anti-BAN2401[p]	X						X							X						X					
CSF sampling[q]																									
Prior / concomitant meds	X			X			X			X			X			X			X			X			X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 8 Schedule of Procedures/Assessments, BAN2401-G000-201, Panel B, Visits 28 through 43, Weeks 51 through 90 – Core Study

Phase	Randomization																	
Period	Treatment															Early Termination Visit[b]	Follow-up Visit	Unscheduled Visit[c]
Visit[a]	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42		43	-
Week	51	53	55	57	59	61	63	65	67	69	71	73	75	77	79		90	
Procedures/ Assessments																		
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[e]		X						X									X	
Routine physical exam		X						X							X	X	X	X
12-lead ECG		X						X							X	X	X	X
Urine pregnancy test[f]		X						X							X	X		X
Laboratory tests[g]		X						X							X	X	X	X
Urinalysis (revised per Amendment 06)		X						X							X	X	X	X
MMSE[h]		X						X							X	X	X	
CDR[h]		X						X							X	X	X	
ADAS-Cog[h]		X						X							X	X	X	
FAQ[h]		X						X							X	X	X	
C-SSRS		X						X							X	X	X	X
Safety MRI[i]		X						X							X	X[i]	X	X
Volumetric MRI (for PD)[j]		X						X							X	X	X	X
Abbreviated MRI[k]																		
Informed consent[l]													X					
Amyloid PET[m]		X													X			
Randomization																		
Study drug administration	X[n]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X				
Blood for serum BAN2401 PK[o]		X						X						X		X		X
Blood for exploratory PD biomarker analysis		X													X			
Blood for serum anti-BAN2401[p]		X						X							X	X	X	X
CSF sampling[q]		X												X				
Prior / concomitant meds			X			X			X			X		X		X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale, AE = adverse event, ARIA = amyloid-related imaging abnormalities, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EU = European Union, FAQ = Functional Assessment Questionnaire, LP = lumbar puncture, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamic, PET = positron emission tomography, PK = pharmacokinetic. (revised per Amendment 01)

a: Assessments should take place on the first day of the study visit in the designated study week except as noted below (footnotes h, i, and j pertaining to imaging assessments, and footnote o pertaining to CSF sample collection). A visit window of ± 8 days will be allowed for each visit, except for Visit 3. A visit window of ± 7 days will be allowed for the follow-up visit (Visit 43). (revised per Amendment 01)

b: Subjects who discontinue the study or study drug early must comply with the Early Termination Visit (within 7 days after discontinuation the last dose of study drug) and the Follow-Up Visit (3-months after the last dose of study drug). They may also have unscheduled visits for safety assessments. Subjects who discontinue due to APOE status are expected to return for their Early Termination Visit and 3-month Follow-Up Visit (ie, 3 months after the last dose of study drug). Subjects who discontinue due to AE (including ARIA) are not allowed to rescreen for Study BAN2401-G000-201 (revised per Amendment 06). In addition, subjects who discontinue from study drug are expected to return after the Early Termination Visit for each scheduled visit when the clinical assessments of efficacy are to be conducted (Visits 9, 16, 22, 29, 35, and 42). At these visits clinical efficacy assessments (MMSE, CDR, ADAS-Cog, and FAQ) will be conducted and information on concomitant medications, AEs, and SAEs will be collected. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) of the Early Termination Visit or the 3-month Follow-Up Visit. Subjects who discontinue from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. (revised per Amendment 01)

c: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that assessments indicated under Unscheduled Visits need not always be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

d: Vital signs will be measured both at predose and after infusion. During Visits 3, 4, 5, and 6, vital signs should be recorded at least 2 hours after study drug infusion, in addition to predose. If at those visits no untoward effects of infusion on vital signs are detected ≥2 hours after infusion, these assessments at subsequent study visits may be conducted at a shorter interval after infusion. (revised per Amendment 06) –At visits where no infusion takes place (Visits 42 and 43), vital signs will be measured once. Vital sign measurements will consist of systolic and diastolic blood pressure (mmHg) measured after at least 3 minutes in a semi supine position, pulse (beats per minute), respiratory rate (per minute), and body temperature (in centigrade).

e: Weight will be taken in the clinic at designated visits (Visits 3, 9, 16, 22, 29, 35, and 43). If a subject misses a clinic visit where weight is to be collected, subsequent visits should use the most recent, previous collected weight for infusion calculations until the next clinic visit. Under such circumstances, weight is to be taken at the next clinic visit and entered into the IVRS even if the visit is not designated for weight data collection.

f: Females of childbearing potential only

g: Blood for laboratory tests will be taken 4 hours after the end of infusion at Visit 3 and predose at all other visits as indicated.

h: Scales are to be completed in the morning (or, if not possible, consistently at the same time of day) in the following order on the days indicated: MMSE, CDR, ADAS-Cog, and FAQ. Caregivers/informants (defined as a person able to support the subject for the duration of the study) need only to be present at visits where clinical assessment of MMSE, CDR, and ADAS-Cog takes place. (revised per Amendment 01)

i: MRI imaging should be conducted at any time following the immediately preceding visit and prior to each of the following Visits according the Schedule of Procedures/Assessments: Visits 7, 9, 16, 22, 29, 35, and 42 and at the Follow-up Visit (Visit 43). The MRI may be conducted on the same day as the immediately preceding visit, after dosing at that visit. In all cases, the safety MRI must be reviewed by the imaging vendor and a local reader prior to a subject receiving the next dose of study drug. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an Early Termination Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. (revised per Amendments 04, 06, and 07)

j: A volumetric MRI sequence will be collected in ALL subjects immediately following all safety MRI assessments. Volumetric MRI data will be analyzed at the Screening Visit and at Visits 16, 29, and 42.

k: The Visit 6 abbreviated MRI will be conducted at EU sites only, and should be conducted at any time following the immediately preceding visit (Visit 5) and prior to dosing at Visit 6. The Visit 6 MRI may be conducted on the same day as Visit 5 after subjects have been dosed. This abbreviated MRI will be comprised of a safety MRI to detect ARIA, lasting approximately 8 to 10 minutes. Volumetric MRI sequences will not be conducted at this visit. The safety MRI must be reviewed by the imaging vendor and a local reader prior to a subject receiving the next dose of study drug. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an Early Termination Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. (revised per Amendment 07).

l: Subjects can reconsent to enter the Extension Phase at this visit or any subsequent visit at which they are eligible. Subjects must consent to the longitudinal PET substudy for the Extension Phase to participate in the substudy. (revised per Amendment 11)

m: In the imaging subgroup only, amyloid PET imaging will be conducted on or within 10 days after the scheduled Visits 29 and 42 (12 and 18 months). For those subjects who also consent to CSF assessment in addition to PET, CSF should be collected 2 to 4 days after study drug infusion at Visit 29, and the amyloid PET procedure should be scheduled to take place on a separate day within 10 days of Visit 29, but after CSF collection. (revised per protocol Amendment 06) For those subjects who did not consent to the imaging substudy in the Core Study, a baseline scan can be taken at Visit 42 (Week 79). Subjects who consented to the imaging subgroup in the Core Study may continue into the OLE if they reconsent. (revised per Amendments 08 and 11).

n: Subjects may be given the option to receive home infusions (per DSMB charter, if allowed and conducted according to country and local guidelines; home infusions will not be allowed in Germany) for study drug administration during Visits 13, 14, and 15, and Visits 17 through 21, Visits 23 through 28, Visits 30 through 34, and Visits 36 through 40, inclusive, provided they express no clinical features related to drug infusion during the first 4 months of the study. Upon implementation of Amendment 07 newly enrolled subjects will not be offered the option for home infusions. Subjects opting for home infusions before the implementation of Amendment 07 will be allowed to continue with home infusions for the duration of their participation in the study. (revised per Amendments 01, 03, and 07)

o: At Visit 3, blood will be taken for the BAN2401 assay approximately 4 hours after the end of infusion (before subjects leave the clinic for home). Subjects must stay in clinic for the full 4 hours following infusion during this first infusion visit. Subjects must stay in clinic for at least 2 hours following infusion up through Week 13 (Visit 9). After the Week 13 (Visit 9) Visit, if no untoward effects of infusion are noted, or infusion reactions can be prevented with prophylaxis, then subjects may be discharged from clinic 30 min after the end of infusion if judged medically stable by the investigator. At Visits 9, 16, 22, 29, 35, and 41, blood will be taken for the BAN2401 assay both predose and at least 2 hours after the end of infusion (before subjects leave the clinic for home). Subjects are required to remain in clinic for at least 2 hours following infusion at visits where PK samples are taken (except Visit 3, the first infusion visit). PK samples should be taken at least 2 hours after the end of infusion. These samples can be taken any time after those 2 hours and should generally be taken just prior to the subject leaving the site. (revised per Amendment 01) For subjects who participate in the CSF sub-study, serum PK sample should also be taken immediately following the CSF collection that is to take place 2 to 4 days after study drug infusion at Visit 29. For the same CSF sub-study subjects, the CSF sample should be taken predose at Visit 41 and the predose serum PK sample at Visit 41 should be taken immediately after the CSF sampling. (revised per Amendments 06 and 07)

p: Blood for the BAN2401 anti-drug antibody assay will be taken as follows: predose at Visits 3, 9, 16, 22, 29, 35, and 42, and the Follow-up Visit (Visit 43). Blood for the BAN2401 anti-drug antibody assay will also be taken at the Early Termination Visit when applicable.

q: Those subjects who consent to CSF assessments should have CSF drawn via LP 2 to 4 days after the scheduled study Visit 29 (12 months) infusion, and serum PK samples should be taken immediately following the CSF collection. CSF samples should be collected predose on the day of the Visit 41 infusion. (revised per Amendment 06)

201 OLE

Table 12 Schedule of Procedures/Assessments for Study BAN2401-G000-201: Extension Phase (revised per Amendment 12)

Phase		Extension (Visit 44 through Visit 75, Extension Phase Week 1 through Extension Phase Week Phase 63)																						
Period	Screen	Treatment																						
Visit(s)[a]	Scrn	44	45	46	47	48	49	50	51,52	53	54, 55, 56	57	58, 59	60	61, 62	63	64, 65	66	67, 68, 69	70	71, 72	73	74, 75
Extension Phase Week(s)	0	1	3	5	7	9	11	13	15,17	19	21, 23, 25	27	29, 31	33	35, 37	39	41, 43	45	47, 49, 51	53	55, 57	59	61, 63
Procedures/ Assessments																								
Informed consent	X																							
Medical history	X																							
Inclusion/Exclusion	X																							
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[c]		X						X				X				X				X				
Routine physical exam	X											X								X				
12-lead ECG	X											X								X				
Serum pregnancy test[d]	X																							
Urine pregnancy test[d]		X						X				X				X				X				
Blood for laboratory tests[e]	X[t]		X		X			X		X		X								X				
Urinalysis	X		X		X			X		X		X								X				
Urine Drug Screen	X																							
MMSE[f]	X											X								X				
CDR[f]	X											X								X				
ADAS-Cog[f]	X											X								X				
C-SSRS	X											X								X				
Safety MRI[g]	X					X		X				X								X				
Volumetric MRI[h]	X					X		X				X								X				
Amyloid PET[i]	X							X[m]				X[m]								X				
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for serum BAN2401 PK[j]		X	X			X		X				X				X				X				
Blood for exploratory PD biomarker analysis	X							X				X								X				
Blood for serum anti-BAN2401[k]		X	X			X		X				X				X				X				
Prior / concomitant meds	X				X			X		X		X		X		X		X		X		X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Phase	Extension (Visit 76 through Visit 97, Extension Phase Week 65 through Extension Phase Week 117)																
Period	Treatment															Follow-up	
Visit(s)[a]	76	77, 78	79	80, 81, 82	83	84, 85	86	87, 88	89	90, 91	92	93, 94	95	96	Early Termination Visit[a]	97	Unscheduled Visit[a]
Extension Phase Week(s)	65	67, 69	71	73, 75, 77	79	81, 83	85	87, 89	91	93, 95	97	99, 101	103	105		117	
Procedures /Assessments																	
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[c]	X				X				X							X	
Routine physical exam					X									X	X	X	X
12-lead ECG					X									X	X	X	X
Urine pregnancy test[d]	X				X				X					X	X		X
Blood for laboratory tests[e]					X									X	X	X	X
Urinalysis					X									X	X	X	X
MMSE[f]					X									X	X	X	
CDR[f]					X									X	X	X	
ADAS-Cog[f]					X									X	X	X	
C-SSRS					X									X	X	X	X
Safety MRI[g]					X									X	X[g]	X	X
Volumetric MRI[h]					X									X	X	X	X
Amyloid PET[i]														X	X		
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X				
Blood for serum BAN2401 PK[j]					X								X	X	X	X	X
Blood for exploratory PD biomarker analysis														X	X		
Blood for serum anti-BAN2401[k]					X									X	X	X	X
Prior / concomitant meds	X		X		X		X		X		X		X		X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale, CDR = Clinical Dementia Rating, CDR-SB = Clinical Dementia Rating – Sum of Boxes, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire, IVRS = Interactive Voice Response System, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamic, PET = positron emission tomography, PK = pharmacokinetic.

a Visit 3 should be conducted no more than 10 days after completion of the Screening Visit and confirmation of eligibility to continue in the study. Assessments should take place on the first day of the study visit in the designated study week except as noted below (footnotes g, h, and i pertaining to imaging assessments). A visit window of ±8 days will be allowed for each visit. A visit window of ± 7 days will be allowed for the follow-up visit (Visit 97).

b Vital signs will be measured both at predose and after infusion. During Visits 44, 45, 46, and 47, vital signs should be recorded at least 2 hours after study drug infusion, in addition to predose. If at those visits no untoward effects of infusion on vital signs are detected ≥2 hours after infusion, these assessments at subsequent study visits may be conducted at a shorter interval after infusion. Vital sign measurements will consist of systolic and diastolic blood pressure (mmHg) measured after at least 3 minutes in a semi supine position, pulse (beats per minute), respiratory rate (per minute), and body temperature (in centigrade).

c Weight will be taken in the clinic at designated visits. If a subject misses a clinic visit where weight is to be collected, subsequent visits should use the most recent, previous collected weight for infusion calculations until the next clinic visit. Under such circumstances, weight is to be taken at the next clinic visit and entered into the IVRS even if the visit is not designated for weight data collection.

d Females of childbearing potential only. For all females of childbearing potential, an additional urine pregnancy test must be done on the day of Amyloid PET scanning.

e Blood for laboratory tests will be taken predose at all visits as indicated.

f Scales are to be completed in the morning (or, if not possible, consistently at the same time of day) in the following order on the days indicated: MMSE, CDR (including CDR-Global and CDR-SB), and ADAS-cog. Caregivers/informants (defined as a person able to support the subject for the duration of the study) need only to be present at visits where clinical assessments take place.

g MRI imaging must be completed within the Screening Period and before the first dose of study drug in the Extension Phase. During the Treatment Period, MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted at any time following the immediately preceding visit and prior to each of the following Visits for **ALL** subjects according to the Schedule of Procedures/Assessments. In all cases, the safety MRI must be reviewed by the imaging vendor and a local reader prior to a subject receiving the next dose of study drug. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an Early Termination Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. (revised per Amendment 12)

h A volumetric MRI sequence will be collected in ALL subjects immediately following all safety MRI assessments.

i Before dosing in the Extension Phase, all subjects who underwent amyloid PET for inclusion in the Core Study should receive a baseline amyloid PET scan. In Japan, those who consented to the longitudinal imaging substudy will only undergo amyloid PET at Extension Phase Visit 70 [Extension Week 53], and Visit 96 [Extension Week 105]. The baseline amyloid PET scan must be conducted with the same imaging tracer that was used for inclusion at the baseline visit for the Core Study. During Screening, Amyloid PET imaging will be conducted within 10 days **before** the first dose of study drug in the Extension Phase for qualified subjects. During the Treatment Period, Amyloid PET imaging will be conducted on or within 10 days after the scheduled 3 month (Cohort 1 only), 6 month (Cohort 2 only), and 12 month (all subjects in the PET substudy), and 24 month Visits (all subjects in the PET substudy) in the Extension Phase (Visit 50 [Week 13; Cohort 1 only]; Visit 57 [Week 27; Cohort 2 only], Visit 70 [Week 53; all subjects in the PET substudy], Visit 96 [Week 105; all subjects in the PET substudy], and at the Early Termination Visit [all subjects in the PET substudy]). (revised per Amendment 12)

j At Visit 44, blood will be taken for the BAN2401 assay approximately 4 hours after the end of infusion (before subjects leave the clinic for home). Subjects must stay in clinic for the full 4 hours following infusion during this first infusion visit. Subjects must stay in clinic for at least 2 hours following infusion up through Visit 50. After Visit 50, if no untoward effects of infusion are noted, or infusion reactions can be prevented with prophylaxis, then subjects may be discharged from clinic 30 minutes after the end of infusion if judged medically stable by the investigator. Blood will be taken for the BAN2401 assay both predose and at least 2 hours after the end of infusion (before subjects leave the clinic for home). Subjects are required to remain in clinic for at least 2 hours following infusion at visits where PK samples are taken (except Visit 44, the first infusion visit). PK samples should be taken at least 2 hours after the end of infusion. These samples can be taken any time after those 2 hours and should generally be taken just prior to the subject leaving the site.

k Blood for the BAN2401 anti-drug antibody assay will be taken predose at the specified Visits. Blood for the BAN2401 anti-drug antibody assay will also be taken at the Early Termination Visit when applicable.

l Clotting screen (prothrombin time [PT, INR], activated partial thromboplastin time [APTT]) will be performed at the Screening Visit.

m Subjects will have PET amyloid testing at Visit 50 (Extension Week 13) or Visit 57 (Extension Week 27) based on stratification. Cohort 1 will have amyloid PET assessments performed at Visit 50 (Extension Week 13); Cohort 2 will have amyloid PET assessments performed at Visit 57 (Extension Week 27).

n Subjects who discontinue the study or study drug early must comply with the Early Termination Visit (within 7 days after discontinuation the last dose of study drug) and the Follow-Up Visit (3-months after the last dose of study drug). They may also have unscheduled visits for safety assessments.

o Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that assessments indicated under Unscheduled Visits need not always be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

12.1.2. Death and SAE Narratives for 201 Core and 201 OLE

Death Narratives

201 Core

Brain neoplasm with surrounding vasogenic edema
Participant (b) (6) is an 81 year-old woman with who received LEC2.5-BW in the core study. After receiving the 32nd dose of study drug, the safety MRI showed an area of vasogenic edema in the anterior left temporal lobe. On serial safety MRIs over time, an enhancing ring lesion suspicious for an underlying neoplasm became evident. The participant ultimately died, and the autopsy showed a high-grade infiltrating astrocytic neoplasm.

Reviewer Comment: This participant had exposure to study drug for 1 year and 2 months prior to the diagnosis of primary brain tumor. I could not identify a clear role of study drug given the relatively short duration of treatment compared to the latency for the development of malignancies..

Cardiac Arrest
Participant (b) (6) is a 75 year-old white female with AD receiving LEC2.5-BW in the 201 Core study. Seventeen days after the 28th dose of study drug participant experienced sudden onset shortness of breath, became pulseless while at home, and eventually died in the Emergency Department. Her past medical history was significant for risk factors for cardiopulmonary arrest including hyperlipidemia, hypertension, hypomagnesemia, chronic obstructive pulmonary disease, a history of cardiac catheterization.

Reviewer's Comment: While the cause of death is not clearly identified in this participant, she had cardiac and pulmonary risks that may have increased her risk for a cardiopulmonary arrest.

Multiple Organ Dysfunction Syndrome
Participant (b) (6) is a 79 year-old white female who was randomized to receive LEC5-BW. On study day 420 she was treated for moderately severe dehydration with iv fluids. Her family reported that she had reduced po intake over the course of several days prior to this. She received the 31st dose of study drug on Study Day 421. On the same day she was found to have hepatitis with confusion, jaundice, secondary to shock liver from dehydration and hypotension, leading to hospitalization. She was also diagnosed with acute kidney injury. On Study Day 423, while in the hospital, she was diagnosed with lymphoma, although the details of how this diagnosis was made is not clearly stated in the narrative. On Study Day 425 she was diagnosed with coagulopathy (low platelet count), gram negative bacteremia, leukopenia, metabolic encephalopathy, and multiple organ dysfunction syndrome. She was ultimately placed on

hospice and died. In the CRF the applicant stated that she had elevated markers for pancreatic cancer as well.

Reviewer Comment: This participant had a relatively short exposure to study drug for 1 year and 2 months, and age over 60 is a known risk factor for lymphoma., I cannot identify a clear role of study drug in the occurrence of lymphoma and related death in this participant.

Spinal Cord Injury

Participant (b) (6) is a 78 year-old white male with AD randomized to receive LEC10-M. Eleven days after his 15th dose of study drug, participant sustained a fall leading to a spinal cord injury. The applicant provided narrative states that he "had an accidental fall while he was eating in a restaurant, probably due to a syncope of unknown origin/cause". The participant eventually died due to resulting neurogenic shock, and complicated hospital course due to severe spinal cord compression at C5-C6.

Reviewer Comment: The etiology of the fall, presumed to be a syncopal event by the applicant is not clear. It is unclear if the fall occurred, while seated eating (and caused by post prandial syncope or choking), versus occurred after participant stood up and had orthostatic syncope) or just simply due to gait problems. I could not identify a clear role of the study drug in this participant's death.

Respiratory Failure

Participant (b) (6) is an 82 year-old white male with AD randomized to receive LEC10-M. Thirteen days after the participant received the 32nd dose of study drug he was hospitalized for elective cardiac stent replacement, developed congestive cardiac failure and subsequent anterolateral myocardial infarction. He had an early termination visit and discontinued study treatment. This participant, continued to have multiple admissions and interventions related to underlying cardiac disease and ultimately was placed on hospice for congestive cardiac failure and died 189 days after his last study drug dose from acute respiratory failure.

Reviewer Comment: While this participant was listed under the SOC of Respiratory, Thoracic and Mediastinal disorders, the underlying cause of respiratory insufficiency was cardiac failure, which was unrelated to study drug and was related to underlying cardiac disease.

201 OLE

Cervical Vertebral Fracture

Participant (b) (6) is an 80 year-old white female with mild AD, who received LEC5-BW in the Core study. The 36th dose of study drug was administered on Extension Day 488. On study day 495 she had a car accident resulting in cervical vertebral fracture at which point she was discontinued from study. Participant died 10 days after the cervical fracture due to failure to recover from complications of cervical fracture.

COVID Pneumonia

Participant (b) (6) *is a* 76-year-old white female with MCI due to AD randomized to LEC10-BW during the placebo controlled period, and then participated in the OLE period. On Day 241 during her participation in the OLE phase she developed symptoms of COVID 19 and on Extension Day 267 (last day of study drug was 204) ultimately died from COVID pneumonia.

AD progression

Participant (b) (6) is an 82 year-old white female with MCI due to AD, who was randomized to receive LEC10-BW in the core study. On Extension Day 194, 47 days after the last dose of study drug, the participant was discontinued from the study due to progression of AD and transitioned to hospice. She died on Extension Day 196.

Metastatic Neuroendocrine Cancer

Participant (b) (6) is a 76 year old white male who was randomized to receive LE10-M in 201 Core. He received the 70th dose (last dose)in the 201 extension study on Extension Day 966. On Extension Day 974 he experienced dyspnea, and was diagnosed with pneumonia. He had ascites, and after a biopsy of the liver was diagnosed with metastatic neuroendocrine cancer. Study drug was permanently discontinued. On Study Day 2106 he died due to the cancer while on hospice care. He had a past medical history of diabetes mellitus, which is a risk factor for pancreatic neuroendocrine tumors, although the original source of his metastasis was not provided as the participant did not undergo an autopsy.

Metastatic Brain Tumor, and seizures

(b) (6) is a 79 year old white male who was randomized to receive placebo in 201 Core. He received the last dose (40th) of study drug on Extension Day 837. On this day he was noted to have reduced attention, decreased speech fluency and disorganized thought, motor slowing, repetitive events, including staring spells, and noted to be fatigued. On Extension Day 838, he was hospitalized and testing revealed metastatic brain disease and extensive metastasis including to the spine and abdomen. MRI of the brain revealed 3 discrete intracranial enhancing lesions and 2 discrete upper cervical cord enhancing lesions. On Extension Day 840, the participant experienced a seizure. He was started on an antiepileptic. A CT of the chest revealed multiple lung masses and nodules, multiple right pleural-based metastases, widespread hepatic metastases widespread splenic metastasis and scattered metastasis within the subcutaneous soft tissue of the chest and abdomen and bone visualized within the left iliac crest. On Extension Day 879 he died due to metastatic brain disease.

Reviewer Comment: I could not identify a clear role of the study drug in any of the deaths that occurred during the 201 OLE.

SAEs Narrative

ARIA
Briefly, there were a total of 4 ARIA-E events reported as SAEs during the 201 Core Study. Three [redacted] were ApoE e4 homozygotes in the LEC10-BW group and one [redacted] was heterozygote in the LEC10-M group. Two [redacted] also had cerebral microhemorrhages, and participant [redacted] also had a subdural hemorrhage. In 201 OLE there was one ARIA-E event that was reported as an SAE [redacted]. These narratives are provided under Section 7.5.1.

Infusion and Hypersensitivity Reactions
There was one SAE of infusion related reaction identified as severe in study 201 Core [redacted] and one SAE of infusion related reaction reported in the OLE [redacted] These will be further described under Section 7.5.2 under Infusion Related Reactions.

SAEs occurring in 2 or more participants in the Study drug arm compared to placebo in 201 Core

Seizures

201 Core
In the placebo-controlled period of study 201 Core there were a total of 3 treatment emergent seizure events, two of these were reported as SAE [redacted] in which the seizure was triggered by hyponatremia, and hypokalemia; and [redacted] after a ventriculoperitoneal shunt placement and hypernatremia, both of which can increase risk of seizures.) and one occurred in the setting of an SAE of severe ARIA-E [redacted] and was not identified as a separate TEAE and severity was not graded. One additional seizure was identified when using the 90-day flag for TEAE; occurred beyond 90 days after the last dose of study drug in participant [redacted] who had a hypoglycemic seizure, which occurred beyond 90 days after last study drug dose. There was no SAE of seizure in the placebo arm. In the OLE there were 4 seizure events that were SAEs in Participants [redacted] (an 87 year old participant, subsequently treated with levetiracetam and continued in the study), [redacted] (focal seizures possibly due to an ischemic event of left basal ganglia lacunar infarct that is not a common cause of seizures or possibly due to reported left occipital microhemorrhage, treated with brivaracetam and completed the study), and [redacted] (58 year old with tonic-clonic seizure, continued in the study), and in Participant [redacted] (60 year old with seizure in the setting of aspiration pneumonia) that was not reported as an SAE. None of these participants had a past medical history of seizures. Given that age, AD, and cerebrovascular ischemia are risk factors for seizures, it is less likely that these SAE's of seizures are related to study drug. Selected narratives are provided below.

Participant [redacted], a 73 year-old white male with AD, randomized to receive LEC5-BW in the 201 core study and experienced an SAE of confusion and later an SAE of focal seizures. On

Study Day 547, fourteen days after his 37th dose of study drug, during a scheduled study visit, participant was noted to have automatism, described as scratching his left elbow with his right hand, moving his leg up and down while seated and turning the head to the right. He had bilateral ptosis, visual hallucinations and was confused and disoriented. After an hour, his symptoms briefly resolved, but returned a few hours later. He was admitted to the hospital for focal dyscognitive seizures (partial complex seizures). This was classified as a severe serious adverse event. A brain CT did not reveal any acute findings. An MRI showed moderate to severe chronic deep periventricular white matter small vessel disease without restricted diffusion, which suggested an acute ischemia or infarction. His labs were significant for hyponatremia (sodium level of 126, rated as moderate in severity) and hypokalemia (potassium of 2.3, severe in severity). On Study Day 550, an EEG was performed which was found to be abnormal with slowing of background rhythm and multiform epileptiform activity. He was started on levetiracetam, and received treatment for several days in the hospital. He completed the study (last dose was 37th dose) as planned. The SAE of partial complex seizures were ongoing at the time of study completion. The participant's narrative did not note a past medical history of seizures prior to this event.

Participant (b) (6) is a 76 year-old white male with mild AD dementia for 2 years, who was hospitalized for a diagnosis of normal pressure hydrocephalus, 8 days after his 5th dose of study drug (LEC10-M). He underwent a ventriculoperitoneal shunt placement. He was discharged from the hospital and continued with study participation in the 201 Core. 13 days after receiving his 6th dose of study drug, the participant was hospitalized for seizures, hypernatremia, and acute respiratory arrest due to the seizure. He was treated with lorazepam and levetiracetam for seizures, and with Combivent for respiratory failure. He also experienced hematuria. He was discontinued from the study due to the SAE of seizures. Ongoing events at the time of study discontinuation included diabetes insipidus, agitation, and hypertension.

Participant (b) (6) reportedly had a seizure which occurred in the setting of severe symptomatic ARIA-E in a participant taking LEC10-BW. This seizure event was not separately reported as an SAE. This event was described by the applicant in the ISS under Section 3.7.2.1.1.1 ARIA-E and Concurrent Seizure. This event is described under Section 7.5.1

Participant (b) (6) a 77 year-old white male with mild dementia due to AD , who was randomized to receive LEC10-BW. The participant received the 39th dose (last dose) of study drug on Study Day 534. On Study Day 602, the participant experienced seizure and was unconscious. His blood sugar was noted to be in the 30s and he was diagnosed with hypoglycemia. An ampule of D50 (50% dextrose) was given and the participant became alert. The event of hypoglycemic seizure resolved on the same day (note this was a TEAE identified using the TEAE flag for 90 days after last dose, not 30 days)

Reviewer Comment: In both participants (b) (6) and (b) (6) seizures were not related to ARIA and, the seizures seem to be provoked by events unrelated to study drug. In participant

[redacted], *seizures occurred after a ventriculoperitoneal shunt placement and hypernatremia, both of which can increase risk of seizures. In participant* [redacted], *the seizure was triggered by hyponatremia, and hypokalemia. The cause of the hypokalemia and hyponatremia are unclear. In both of these cases, it is less likely that the seizures are related to study drug. In one of the three participants in the Core period with seizures* [redacted], *the seizure occurred in the setting of radiographically severe ARIA-E that occurred in a participant taking lecanemab. In participant* [redacted] *the seizure likely resulted from the radiographically severe ARIA-E.*

OLE

There were 4 seizure events in the OLE study that were SAEs in Participants [redacted] (an 87 year old participant, subsequently treated with levetiracetam and continued in the study), [redacted] (focal seizures possibly due to an ischemic event of left basal ganglia lacunar infarct that is not a common cause of seizures or possibly due to reported left occipital microhemorrhage, treated with brivaracetam and completed the study), and [redacted] (58 year old with tonic-clonic seizure, continued in the study), and in Participant [redacted](60 year old with seizure in the setting of aspiration pneumonia) that was not reported as an SAE [one of the 4 was submitted at the 120-Day Update [redacted]]. The dictionary derived terms for these events were as follows: [redacted] (seizure), [redacted](epilepsy), [redacted] (generalized tonic clonic seizure) and [redacted](focal dyscognitive seizure). Three of these were considered serious [redacted] While the seizure occurring in participant [redacted]was not identified as an SAE, it will be described here as it is an event of interest. None of these participants had a past medical history of seizures. Given that age, AD, and cerebrovascular ischemia are risk factors for seizures, it is less likely that these SAEs of seizures are related to study drug.

Participant [redacted] is an 87 year- old white female with MCI due to AD randomized to receive LEC10-BW arm in 201 Core. Seven days after the 34th dose in the OLE period she had was diagnosed with a seizure after experiencing uncontrolled bilateral arm movement while sitting in a chair, resulting in an ER visit and hospitalization. She was started on levetiracetam with no recurrent seizures and had a negative work up. Her seizure event was not associated with ARIA. Her study participation in the OLE is ongoing and so far she has completed the 53rd dose of study drug administration without any further seizures.

Participant [redacted] completed the CORE study randomized to LEC10-BW. Eight days after her 6th dose during the OLE phase, the participant experienced language disturbance with slight block in spontaneous language. She was treated with fibrinolytic (thrombolytics) for a presumed stroke. EEG showed abnormal wakefulness activity and an MRI showed left occipital microhemorrhage. A CT scan (per applicant on an unknown date in December), showed progressed appearance of lacunar infract on left basal ganglia, and an unspecified extra axial calcification that measures 6 mm was observed on left parieto-occipital (sulcus). A poorly

defined hypo density was observed on the corona radiata/centrum semiovale, which was corresponding corresponded to asymmetrical leukoariosis from a previous test. The following day after her symptom onset, she had worsening in her aphasia with motor agitation. Later that same day she was noted to have aphasia with fallen lip commissure, altered speech expression, and recurrent anomalous movement on the right hand, thought to be focal seizures (acquired epileptic aphasia). Repeat MRI showed chronic lacunar infarcts in the left basal ganglia, anterior arm of the left internal capsule and microbleed on the left occipital area. Participant was discharged from the hospital on brivaracetam 50 mg PO BID and simvastatin 40 mg PO daily. No action was taken with the study drug. The participant continued on treatment in the OLE period, received her 53rd dose in the Extension period, and participation is ongoing as of the cutoff date of December 31, 2021.

Participant (b) (6) is a 58 year- old white female with mild dementia due to AD who was randomized to receive LEC10-M in 201 Core. She had a generalized tonic-clonic seizure (severe, treatment-emergent SAE) on Extension Day 804 that was classified as severe and serious. No action was taken with study drug. The participant received the 52nd dose of study drug on study day 855. As of data cut off the participant was ongoing at the time of the data cut off of December 31, 2021.

Participant (b) (6) is a 60 year- old man with mild dementia due to AD who received LEC10-M during 201 Core. The participant received the 36th dose of study drug on Extension Day 505. On extension day 508, the participant was hospitalized for seizure (focal dyscognitive seizures), vomiting and a fever. Work up revealed elevated white blood cell count of 19900, and. The participant was diagnosed with aspiration pneumonia and treated with antibiotics, and started on levetiracetam for seizures. The event of aspiration pneumonia resolved on Extension Day 514. The participant discontinued from the study on Extension Day 605 due to withdrawal by participant as it was too difficult to return for follow up appointments.

Reviewer Comment: Given that age, AD, as well as and cerebrovascular ischemia are risk factors for seizures, it is less likely that these SAEs of seizures are related to study drug. However, in Participant (b) (6) it is possible that the participant had a seizure secondary to either an ischemic event or the left occipital microhemorrhage. However, a left basal ganglia ischemic event could present with language difficulties, but are not common cause of seizures.

Subdural Hemorrhage/Subdural Hematoma

201 Core

There were a total of 4 participants in Study 201 Core that had a subdural hemorrhage or subdural hematoma. Three participants were in the placebo arm (subdural hematoma: (b) (6), subdural hemorrhage (b) (6)), and one participant was on LEC10-BW

(b) (6). Please see Section 7.5.1 for participant (b) (6) narrative. who had a subdural hemorrhage with ARIA-E and ARIA-H

201 OLE

There were three participants in the OLE who had subdural hemorrhage or subdural hematoma. These included participant (b) (6), subsequent to a bike accident, (b) (6) subsequent to falls resulting from orthostatic hypotension, and (b) (6) that occurred 30 days after the last dose of study drug also due to falls. I could not identify a clear role of the study drug as a cause of the subdural hemorrhage or hematoma in these instances.

(b) (6) is a 74 year -old white male randomized to receive LEC2.5 BW in study 201 Core. The participant received the last dose of study drug on day 281 (b) (6) The participant withdrew his consent shortly after, due to frequent falls, diagnosis of PD, and inability of the caregiver to provide transportation. On (b) (6), the participant had a fall and imaging showed a chronic subdural hematoma.. This was not considered treatment emergent as it occurred beyond 30 days since last dose of study drug, but was identified when using the treatment emergent flag for 90 days after last dose.

Cerebrovascular Event

201 Core

There were 6 participants who were identified as having an SAE of TIA or stroke in 201 Core. After review of the narratives, I don't believe that participants (b) (6) and (b) (6) had cerebrovascular disease (see narratives below). (b) (6), who had cerebrovascular risk factors, had a cerebrovascular accident occurring 22 days after an ARIA-E. Participants (b) (6) had a cerebrovascular event and all had one or more risk factors for cerebrovascular disease. Narratives are provided below

Participant (b) (6), is a 71 year-old white female, ApoE4 e3/e4 genotype, with mild AD, as well as cerebrovascular risk factors including hypertension, diabetes, and past history of CVA, receiving LEC10-M, had worsening hallucinations 4 days prior to the third dose of study drug. .. She then again had worsening hallucinations on the day she received the third dose of study drug, was confused and had difficulty answering questions and was hospitalized. She was diagnosed with a TIA, and during the MRI obtained a superficial siderosis that was missed on an earlier screening MRI was identified. She was discontinued from study due to superficial siderosis.

Reviewer Comment: Although this participant has cerebrovascular risk factors, the events described in the narrative sound more consistent with fluctuations in mental status, and

hallucinations that can be seen with dementia due to AD, rather than a TIA. The superficial siderosis preceded the study drug administration.

Participant (b) (6) had a serious ARIA-E event with symptoms of transient difficulty finding words and tingling in the right hand, diagnosed as transient ischemic attack (TIA). Further described under Section 12.1.5. Symptoms in this participant were likely related to ARIA and not a separate cerebrovascular event.

Participant (b) (6), is a 72 year-old white male with mild dementia due to AD, APOE e3/e4 genotype randomized to receive LEC5-BW. His narrative was silent to stroke risk factors. Twelve days after the 13th dose of study drug, on Study Day 181, he was diagnosed with ARIA-E in the left posterior parietal lobe. The event was rated as mild in nature and nonserious. On the same day he experienced a respiratory tract infection and confusion, which the investigator felt were not related to the ARIA-E. He received the 14th dose (last dose) of study drug 3 days after the ARIA-E diagnosis on Study Day 184, and subsequently was discontinued from the treatment on study day 197. On Study Day 203, 22 days after the ARIA-E was identified, the participant was diagnosed with a cerebrovascular accident in the left frontal lobe just anterior to motor strip, based on the MRI results. This MRI also showed superficial siderosis. This was classified as moderate in severity and a serious SAE.

Reviewer this participant had an ARIA-E event, and within a month of the ARIA-E, he had an infarct. Since there are no stroke risk factors listed for this participant, I cannot rule out that lecanemab may have played a role in this participant's infarct.

Participant (b) (6) is an 84 year-old white male, with AD randomized to LEC5-M in Study 201 Core. His stroke risk factors included a previous history of TIA, hyperlipidemia, type 2 DM, coronary artery disease. 13 days after the 7th dose of study drug the participant experienced sudden onset left-sided numbness and difficulty speaking lasting approximately 15 minutes. MRI completed in the emergency room was unremarkable. He was admitted with a diagnosis of TIA. The event was classified as mild in severity and serious (hospitalization). No treatment was reported for this event. No action was taken with the study drug in response to the event and the treatment with the study drug was continued. Participant's study safety MRI on week 39 was read as showing a left frontal cortical infarct. Participant's study treatment was continued.

7 days after the participant received the 26th dose of study drug on Study Day 358 (4 months after MRI finding of left cortical infarct), the participant experienced dizziness, which lasted for 15 minutes, and he was hospitalized for possible TIA (2nd occurrence). His Week 53 MRI results showed superficial siderosis of left frontal area and a cortical infarct >10 mm with partial resolution of cortical infarct which was seen on MRI on Week 39. According to the applicant, his superficial siderosis was felt to be due to evolution of the cortical infarct (hemorrhagic transformation stroke) and not due to amyloid related imaging abnormalities—hemorrhage (ARIA-H). On Study Day 359, brain MRI showed mild involutional changes. The event of TIA (2nd

occurrence) was classified as mild in severity and serious (hospitalization) and the event of hemorrhagic transformation stroke was classified as mild in severity and nonserious.

No treatment was reported for these events. No action was taken in response to the event of TIA (2nd occurrence) and the treatment with the study drug continued. The event of TIA (2nd occurrence) resolved on Study Day 360 and participant was discharged with no neurological deficits from the hospital. Based upon the finding of superficial siderosis left frontal, the applicant medical monitor, requested that the site suspend IP treatment and early terminate the participant from the trial. The participant received the 31st dose (last dose) of study drug on Study Day 450 and on study Day 470 came in for his early termination visit and discontinued study treatment in response to hemorrhagic transformation stroke.

Reviewer Comment: This participant has multiple risk factors for cerebrovascular disease, and it is more likely as not that the cerebrovascular events described above are related to underlying disease. What is less clear is whether the superficial siderosis reported on the safety MRI is indeed due to evolution of ischemic stroke and a result of hemorrhagic transformation, or unrelated to the infarct and represents ARIA-H. As per core protocol criteria, the participant was discontinued due to presence of superficial siderosis. Of note is that the superficial siderosis was identified after the 26th dose of study drug, but dosing continued until the 31st dose of study drug at which time the participant was discontinued.

(b) (6) is a 68 year- old white female who was randomized to receive LEC5-M. The participant received the 25th dose of study drug on day 335. On Day 344 she was found unconscious in bed with asymmetric labial sulcus (deviated to the left side). She was hospitalized and regained consciousness but was found to have a 7th cranial nerve deficit that persisted for an hour. The participant was diagnosed with TIA. She withdrew her consent from the study. She had stroke risk factor of hypercholesterolemia.

Participant (b) (6) is an 81 year-old white male with mild dementia due to AD who was randomized in Study BAN2401-G000-201 to LEC2.5-BW. Stroke risk factors included medical history of hypercholesterolemia, myocardial infarction, coronary artery bypass, atrial flutter, and lack of anticoagulation in the setting of atrial flutter. The participant underwent a safety MRI at week 13 as part of study participation. The MRI showed a lacunar infarct, and the participant was diagnosed with cerebellar infarction, which was classified as mild in severity and nonserious and no action was taken with the study drug. Eleven days after the 10th study drug administration (Study Day 162) the participant presented to an emergency room (ER) with complaints of weakness of left hand, difficulty in walking, and slurring of speech. An MRI of brain showed an and acute stroke in the right temporal lobe and right frontal lobe with hemorrhagic transformation. This was determined to be an SAE. Stroke work up also revealed akinetic septal wall. The participant was discontinued from the study drug as he was started on Coumadin® (warfarin) and due to the event of hemorrhagic transformation of stroke.

Reviewer Comment: Given the multiple risk factors for cerebrovascular disease in this participant, it is less likely that the study drug played a role in this participant's cerebrovascular infarction.

201 OLE

In the OLE, stroke or TIA occurred in Participants (b) (6), all with underlying risk factors. (b) (6) had a TIA in the absence of clear cut risk factors and is described further below.

Participant (b) (6) is a 70 year-old white male with MCI due to AD was randomized to receive placebo in the 201 Core study. Relevant medical history included first degree atrioventricular block and bradycardia, hyperlipidemia, and mitral valve prolapse. On Extension Day 390, 8 days after study drug administration, the participant experienced left sided numbness and was hospitalized and found to have a right thalamic and occipital lobe acute stroke. Study drug was held and restarted on Extension Day 436. The participant received the 29th dose (last dose) of BAN2401 10 mg/kg in the Extension Phase on Extension Day 436. The participant was discontinued from study drug and from the study Extension Day 527 due to withdrawal by participant (withdrawal of consent). At the time of study discontinuation, the participant had ongoing symptoms of upper airway cough syndrome, visual field defect, and hemianesthesia.

Reviewer Comment: This participant's stroke was likely related to his cerebrovascular risk-factors, I could not identify a clear role of study drug. drug.

Participant (b) (6) is a 71 year-old white male with MCI due to AD randomized in the Core Study to LEC10-M. Participant received the 21st dose of LEC10-BW in the OLE on Extension Day 285, and 9 days later the participant experienced a sudden lapse in memory and felt nauseated while shopping. He had an episode of vomiting and right sided weakness. Emergency medical service was called, and the participant was ultimately hospitalized. CT and EEG were completed. The participant was diagnosed with TIA. The event was classified as moderate in severity and serious (hospitalization). The event of TIA resolved on Extension Day 297 and the participant continued with study participation and received the 54th dose of LEC10-BW on Extension Day 810. However, the participant was hospitalized again after experiencing dizziness and double/blurry vision for approximately 3 months and fatigue for one year. The Hospital work -up only revealed a diagnosis of dehydration. The event of dehydration and headache resolved on Extension Day 822. On Extension Day 863, the participant again was hospitalized for symptoms of diplopia, dizziness, nausea, and vomiting and vertigo. No action was taken with the study drug due to this event. On Extension Day 865, the participant was discharged from the hospital and the event of vertigo resolved on Extension Day 867. The participant had

the 57th dose of BAN2401 10 mg/kg in the Extension Phase and as of data cutoff of 30 Jun 2021, the participant was ongoing in the Extension Phase of the study.

Reviewer's Comment: The participant's narrative suggests he had multiple admissions for possible posterior circulation TIAs. While these are less likely related to study drug, the patent's narrative is silent for clear cut cerebrovascular risk factors. These events are not associated with findings of ARIA.

(b) (6) is a 70 year- old Asian male with MCI due to AD, randomized to receive LEC10-M in the 201 Core study. The participant received the 8th dose of study drug on Extension Day 98. On Extension Day 106, the participant experienced a TIA and aggravated atrial fibrillation. He was started on apixaban and bisoprolol. He continued with participation in the extension phase of the study. He was re-hospitalized for symptomatic persistent atrial fibrillation and underwent ablation. He received the 68th dose of study drug on Extension Day 987 and is still ongoing in the study.

Reviewer Comment: The TIA in this case is likely related to underlying atrial fibrillation. Atrial fibrillation is unlikely to be related to study drug, as cardiovascular disease is highly frequent in this age group.

(b) (6) is an 80 year- old male with history of mild dementia due to AD who received LEC10-BW in the core study. His relevant medical history included carotid artery arteriosclerosis, sinus bradycardia, hyperlipidemia. He had transient episode of lymphopenia on study day 1, which resolved on Day 16. After he received the 57th dose of study drug on Extension Day 817, the participant reported feeling dizzy, lightheaded and described as "unresponsive without any loss of consciousness." He was unable to move his left leg or left arm. Exam in the ED showed left sided weakness and he was diagnosed with TIA.

Reviewer Comment: The TIA in this participant was likely related to his underlying cerebrovascular risk factors and less likely related to study drug.

Cerebral Hemorrhage (> 1 cm)

201 Core

(b) (6) is a 77 year- old man with mild dementia due to AD who was negative for the e4 allele for ApoE gene, receiving LEC10-BW in the core study. This participant experienced a new cerebral microhemorrhage and left occipital intracerebral hemorrhage (> 1 cm) on Study Day 172 on the day of his 12th dose of study drug. He had 3 microhemorrhages at baseline.

201 OLE

Participant (b) (6), who is a 68-year old woman with AD who was assigned to receive placebo in the 201 Core study, and 7 days after her 3rd dose in the Extension study (on extension day 34) she experienced intermittent headaches, tightness in her shoulder and loss of vision in her right visual field, and on MRI found to have a cerebral hemorrhage (> 1 cm) in the right occipital lobe. Study drug was restarted on Extension Day 115.

Study 101

Participant (b) (6) is an 81 year old white male that received a single dose of study drug at 1 mg/kg, and on study day 21 had a 10.1 mm left parietal hemorrhage, that remained asymptomatic.

Cardiac Disease

201 Core

There were 2 treatment emergent serious adverse events of atrial fibrillation (b) (6) and one of AV block (b) (6) in 201 Core. Narratives of these participants suggest that all these participants had risk factors for these cardiac events making it difficult to ascertain whether the study drug may have played a role in these events.

201 OLE

In the OLE study the following participants had treatment emergent serious cardiac events: (b) (6) had atrial fibrillation and chest discomfort, (b) (6) had angina pectoris, (b) (6) had coronary artery disease, (b) (6) had aortic valve stenosis, (b) (6) had myocardial infarction, and (b) (6) had atrial fibrillation and transient ischemic attack. I reviewed, these narratives, and all of the participants, with the exception of (b) (6), had pre-existing cardiovascular disease as risk factors, for these treatment emergent serious cardiac events, making it difficult to ascertain whether the study drug may have played a role. In the case of (b) (6), the participant was diagnosed with new- onset atrial fibrillation 5 months prior to the SAEs of aggravated atrial fibrillation and transient ischemic attack, but otherwise the narrative was silent to other cardiovascular risk factors, and I cannot rule out a role of the study drug in this event.

Arthralgia/Arthritis/Joint injury

In Study 201 Core, arthralgia was reported in three participants (b) (6) and arthritis was reported in one participant (b) (6) receiving lecanemab, and in none of the participants receiving placebo. In study 201 OLE, there was one participant who had a treatment emergent serious adverse event of joint injury (b) (6) I reviewed these

narratives, and could not identify a clear role of the study drug in these events, and none appeared to be a result of a hypersensitivity reaction.

In two of these cases of arthritis (b) (6) and one case of arthralgia in study 201, (b) (6) it appeared that the participants' underlying joint pain worsened during the course of the study requiring an intervention and seemed unrelated to study drug. In one participant in 201 Core, the hip arthralgia resulted from a fall (b) (6) leading to hospitalization. Similarly in one participant in 201 OLE (b) (6), treatment emergent SAE of joint injury, resulted from a fall during hiking, and required hospitalization and surgery for the right wrist fracture, and appeared unrelated to study drug.

Chronic Obstructive Pulmonary Disease

Two participants (b) (6) experienced treatment emergent SAEs of chronic obstructive pulmonary disease in 201 Core. I reviewed these cases and could not identify a role of the study drug. Both of these appeared to be related to underlying lung disease.

Chest discomfort/chest pain

201 Core

Participant (b) (6) is a 57 year-old white male, who is ApoE4 genotype e3/e4 positive, with mild dementia due to AD, who was randomized in Study 201 Core to LEC10-BW. On study Day 3 (2 days after first dose), the participant experienced shortness of breath and chest pain in the substernal region. The participant had moderate non-radiating, squeezing type of pain with heaviness of the chest. On the same day the participant was taken to the emergency room and was hospitalized. His work up was negative for coronary event, or pulmonary event (i.e., pulmonary emboli). The event of chest pain was classified as moderate in severity and serious (hospitalization). No action was taken with the study drug in response to this event and the treatment with the study drug continued. A cardiac stress test performed was normal. The event of chest pain resolved on the same day (Study Day 4) and the participant was discharged from the hospital. The investigator classified the event of chest pain to be not related to study drug. The participant received up to the 12th dose of study drug, without further mention of chest pain in the narrative, but was discontinued from study on Study Day 176 due to being ApoE4 positive and being on LEC10-BW.

Participant (b) (6) is an 86 year-old white female with mild dementia due to AD who was randomized in Study 201 Core to LEC10-BW. This participant is also described under SAEs subheading arthralgia, fall and fractures. The participant received the 15th dose of study drug on Study Day 199. On Study Day 211, the participant experienced shortness of breath and chest pain with sharp left-sided chest discomfort; the pain was non-radiating. On the same day the participant was hospitalized for observation. A chest x-ray was normal, and her troponin values

were negative for cardiac ischemia; ECG showed normal sinus rhythm and non-specific T-wave changes. The event of non-cardiac chest pain was classified as mild in severity and serious (hospitalization). The study drug was temporarily interrupted due to the event of non-cardiac chest pain. The participant was treated with acetylsalicylic acid 81 mg PO once and proton pump inhibitors. The event of non-cardiac chest pain resolved on Study Day 212, and the participant was discharged from the hospital. The investigator classified the event of non-cardiac chest pain to be not related to study drug. No change in study participation, the participant continued with study treatments.

Participant (b) (6) is a 77 year-old white male with AD who was randomized in Study 201 Core to LEC10-M. The participant received the 3rd dose of study drug Study Day 29. On Study Day 35, the participant was noted with transaminases increased and was hospitalized for non-cardiac chest pain along with diaphoresis. The event of transaminases increased was classified as mild in severity and nonserious and the event of non-cardiac chest pain was classified as severe in severity and serious (hospitalization). A magnetic resonance cholangiopancreatography and abdominal ultrasound performed were negative. No treatment was reported for the events. No action was taken with the study drug in response to these events and the treatment with the study drug continued. The event of non-cardiac chest pain resolved on the same day (Study Day 35). The event of transaminases increased resolved on Study Day 37 and the participant was discharged from the hospital. No change to study drug was made. The participant continued with study treatment and had AEs of mild pruritis twice (on Day 82, 11 days after 6th dose of study drug and again on Day 435, 28 days after 30th dose of study drug. The participant completed the 38th dose (last dose) of study drug.

Participant (b) (6) is a 58 year-old white male with AD who was randomized in Study 201 Core to LEC10. The participant received the 21st dose of study drug on Study Day 296. On Study Day 309, the participant had non-cardiac chest pain. It was not associated with diaphoresis or generalized discomfort, and non-radiating. On Study Day 310, the participant was taken to an emergency room for further evaluation to exclude ischemic heart disease; and he was hospitalized. The event was classified as mild in severity and serious (hospitalization). The cardiac enzymes were within normal range. The electrocardiogram revealed normal sinus rhythm and normal QT interval with no significant findings. A diagnostic ergometer revealed that the participant was negative for angina and ischemia. No action was taken with the study drug and treatment with the study drug continued. No treatment was reported for the event. On the same day, the event of non-cardiac chest pain completely resolved, and the participant was discharged from the hospital after 11 hours. The participant continued with study drug and received the 38th dose (last dose) of study drug on Study Day 527 and completed the study as planned on Study Day 625.

Reviewer Comment: I note that these events occurred within 1-13 days after the infusion for the participants, but were not accompanied by other symptoms that could support a hypersensitivity reaction. Noncardiac chest pain is not uncommon in this age group. Therefore,

while I cannot entirely rule out a role of the study drug in these events, I am also unable to directly link these events to study drug.

201 OLE
Participant (b) (6) is a 78 year-old white male with MCI due to AD who was randomized in the study 201 Core to LEC10-M. After completing the Core study the participant enrolled in the 201 OLE phase. The participant received the 20th dose of LEC10-BW on Extension Day 269. On Extension Day 272, the participant experienced chest discomfort and presented to the emergency room. The event of chest discomfort was classified as moderate in severity and serious (hospitalization). The participant was hospitalized and underwent cardiac catheterization. On the same day the participant was diagnosed with thrombocytopenia. The event of thrombocytopenia was classified as mild in severity and nonserious. No action was taken with the study drug due to these events and no treatment was reported for these events. The event of chest discomfort resolved on Extension Day 274 and was discharged from the hospital. The event of thrombocytopenia resolved on Extension Day 388. As of the data cutoff of 31 Dec 2021, the participant was continuing treatment in the Extension Phase of the study, with the 44th dose of study drug administered on Extension Day 823.

Participant (b) (6) is a 78 year-old white female with AD, ApoE e4 allele negative, randomized in Study 201 Core to placebo. On Extension Day 16 the participant experienced chest discomfort (intermittent chest pressure), which lasted for 30 minutes. The event was classified as moderate in severity and serious (hospitalization). The participant was treated with acetylsalicylic acid 182 mg PO. On Extension Day 17, the participant was hospitalized with a similar type of chest pressure and chest discomfort. On the same day Extension Day 17, a nonserious adverse event of tricuspid valve incompetence was discovered. The event was classified as mild in severity and nonserious. On Extension Day 18, the cardiology workup was negative, the event of chest discomfort resolved, and the participant was discharged from the hospital on the same day. The participant received the 72nd dose of study drug on extension day 1036, and participation is ongoing at the time of the cutoff date of 31 December 2021.

Participant (b) (6) is an 83 year--old white male with mild dementia due to AD randomized to LEC10-BW in Study 201 Core. Relevant history includes angina pectoris, coronary artery disease, coronary artery bypass, myocardial infarction. During the core study on Study Day 606, the participant was taken to an emergency department due to chest pain, cough, and runny nose. His chest pain was confined to the mid substernal region (bilateral and pressure-like), which was relieved with the administration of sublingual nitroglycerin. The event (chest pain) was classified as moderate in severity and serious (hospitalization). He was treated with aspirin in the emergency room and was admitted to the hospital for atypical chest pain (non-cardiac). His cardiac enzymes were normal, no acute ischemic electrocardiogram changes were reported, and CT of the chest showed no evidence of pulmonary embolism. On Study Day 608, the event of non-cardiac chest pain resolved, and the participant was discharged from the hospital with medication hydrocodone 1.5 mg PO PRN (b) (6) for the event of non-cardiac chest

pain. On Study Day 623, the laboratory test results showed increased levels of BUN at 7.85 mmol/L, creatinine of 88 µmol/L, urate of 0.375 mmol/L, low level of protein at 59 g/L, and albumin of 41 g/L. The event of acute kidney injury was ongoing at the time of study completion. The participant completed the study as planned on Study Day 623 and started in the Extension Phase. The participant received 10th dose of BAN2401 10 mg/kg in the Extension Phase on Extension Day 144. After 30 minutes of infusion, the participant reported complaints of double vision and chest pain (unspecified), which lasted for 10-15 minutes. The participant presented to the emergency room for further evaluation and was hospitalized for 24 hours observation. The participant's troponin value was <0.010 and brain natriuretic peptide value was 61 pg/mL (NR not provided). No additional treatment was reported for this event. No action was taken with the study drug in response to this event. On the same day, on Extension Day 144, the event of chest pain resolved. On Extension Day 145, the participant was discharged from the hospital in stable condition. The participant continued with study medication. The participant received the 71st dose of study drug in the Extension Phase on Extension Day 1047, after 1047 days of dosing. As of data cutoff of 31 Dec 2021, the participant was ongoing in the Extension Phase of the study.

Reviewer Comment: None of the events of noncardiac chest pain can be directly linked to study drug and are not uncommon in this age group.

Acute Kidney injury:
SAEs of acute kidney injury in study 201 Core and OLE were reviewed. There was one participant (b) (6) in the Core study and 6 participants (b) (6) in the OLE that had treatment emergent acute kidney injury. In all of these cases there were likely explanations for these events including dehydration, obstructive uropathy, UTI and sepsis, and I could not identify a clear role of the study drug. With the exception of participant (b) (6) who died from underlying lymphoma, all of the other cases of acute kidney injury resolved with hydration and treatment of underlying condition. There were two participants who had nontreatment emergent serious acute kidney injury, one due to obstructive neuropathy (b) (6). The other participant (b) (6) had non-serious elevation in BUN/creatinine during their participation in the study, and after the 37th dose of study drug administration on Study Day 533 was withdrawn from the study due to nursing home admission. On Study Day 596, this participant was admitted to the hospital for acute kidney injury and hypertensive crisis. Acute kidney injury was ongoing at the time of discontinuation from the study. Hypertension and diabetes were risk factors for kidney injury in this participant.

Mental Status Changes:
There were 3 participants (b) (6) in the 201 Core, and one participant in 201 OLE (b) (6) who had treatment emergent serious mental status changes. I reviewed the narratives of these participants and did not identify a clear role of the study drug in any of these cases. In all of these cases there were likely explanations for these events

including dehydration, acute bronchitis, metabolic encephalopathy with underlying lymphoma, fall and possible concussion. Mental status changes due to other medical events is not uncommon in AD. All of these mental status changes, (except in participant (b) (6) who died of complications of lymphoma) ultimately resolved.

Aggression/Agitation

One participant (b) (6) had a treatment emergent serious event of agitation, in the setting of increasing behavioral changes and paranoia towards his wife leading to hospitalization on Study Day 209, 9 days after his 15th dose of study drug. This ultimately resolved. The participant continued with study participation until Study Day 518, when he received the 37th (last dose) of study drug, and had early termination due to alcohol use.

Reviewer Comment: This participant's agitation was more likely related to underlying AD, and alcohol use and not related to study drug.

Hallucinations

I reviewed the narratives of the two participants (b) (6) in 201 Core who had treatment emergent serious hallucinations. Participant (b) (6) had worsening in pre-existing hallucinations 7 days after the 4th dose of study drug, and was discontinued from study drug. Participant (b) (6) started experiencing hallucinations starting on Study Day 66, but remained in the study until Study Day 316 with intermittent episodes of hallucinations. On Study Day 296, after the 21st dose of study drug, her hallucinations worsened requiring admission to a geriatric psychiatry unit on Study Day 304. In both of these cases, study drug was ultimately discontinued due to worsening hallucinations.

Reviewer Comment: As hallucinations are not uncommon in participants with AD during the course of their disease, it difficult to ascertain whether the study drug played a role in these two participants' hallucination.

Falls/ Injury /Fractures/Musculoskeletal Injury

There were 7 participants (b) (6) in 201 Core and 11 participants in OLE study (b) (6) (b) (6) who had a treatment emergent, serious fall, fracture, or musculoskeletal injury. I reviewed these narratives and could not identify a clear role of study drug. The falls were either mechanical in nature (tripping, slipping), due to underlying risk factor (such as spinal stenosis, osteoarthritis, poor vision, pre-existing gait problem or history of falls, pre-existing musculoskeletal injury) or accidents (bike or MVA accident). I also could not identify drug induced hypotension, dizziness or vertigo as a clear cause of the fall or injury in these participants. In one participant (b) (6) I identified AEs of dizziness (on Study Day 241) and vertigo (on Study Day 456). This study participant sustained a fall after slipping in the bathroom on Study Day 443. This participant had a pre-existing medical history of dizziness and vestibular neuronitis. Participant

(b) (6) tripped and sustained a mechanical fall on Study Day 634 and was hospitalized for hip fracture. She had hypotension listed as an AE on Study Day 897 but there is no narrative related to this to provide context to the AE of hypotension.

Retinal Detachment/Mono-ocular blindness:

Participant (b) (6) is a 64 year old man with AD randomized to receive LEC10-M in study 201 Core. The participant received the 38th dose of study drug on Study Day 519. The participant was admitted with loss of right monocular vision on Day 532 for retinal detachment. He had a medical history of hypertension which may be a potential risk factor for retinal detachment. The participant received the 39th dose (last dose) of study drug on Study Day 536 and completed the study as planned on Study Day 617. The event of retinal detachment was ongoing at the time of study completion.

Reviewer Comment: I could not identify a clear role of study drug in this participant's retinal detachment

Hepatic Failure/Hepatitis Acute/Cholangitis acute/ Cholecystitis Chronic

201 Core

Participant (b) (6) is further described under Death Narratives in this section. failure. This participant had dehydration ultimately leading to multiorgan failure, and found to have underlying lymphoma in the hospital.

Participant (b) (6) is an 87 year-old white male with AD randomized to receive LEC10-BW in study 201 Core. The participant received the 18th dose of study drug on Study Day 266. On Study Day 277 he presented to the ED with acute abdominal pain, fever, chills, and hypertensive state. Gallbladder ultrasound showed contracted gallbladder with sludge and stones, thickened gallbladder wall, dilated common bile duct by 1.1 cm and suspected with stone in the common bile duct. Mild intrahepatic biliary dilatation was also noted. On the same day (Study Day 277), the participant's laboratory results showed alkaline phosphatase of 218 U/L, alanine transaminase of 193 U/L, and aspartate transaminase of 224 IU/L (NR not provided). The participant was hospitalized for acute cholangitis, sepsis, and chronic cholecystitis with cholelithiasis. The study drug was temporarily interrupted due to the events of sepsis and acute cholangitis. In addition to medical treatment the participant had endoscopic retrograde cholangiopancreatography with endoscopic biliary sphincterotomy and stone extraction. He received antibiotics. On Study Day 286 the events of sepsis, acute cholangitis, and chronic cholecystitis were resolved, and the participant was discharged from the hospital on the same day. On Study Day 293, the study drug was restarted. The participant had the 36th dose (last dose) of study drug on Study Day 531 and completed the study as planned on (b) (6) (Study Day 621).

Reviewer Comment: I could not identify a role for study drug, in neither the hepatic failure, nor acute cholecystitis cases described above.

Pulmonary Embolism

201 Core

Participant (b) (6) is a 72 year old male with mild dementia due to AD, randomized to LEC10-M in study 201 Core. The participant received the 28th dose of study drug on Study Day 392. On Study Day 398, the participant had shoulder and neck pain, and was feeling abnormal. A CT of the chest revealed non-obstructive pulmonary embolism, and the participant was hospitalized for further evaluation. The event was classified as severe in severity and serious (hospitalization and life-threatening). The participant was seen by a cardiologist who confirmed the participant would need anticoagulant therapy indefinitely. The participant came in for his early termination visit on Study Day 421 and was discontinued from the study treatment due to initiation of anticoagulant therapy, which was a prohibited medication per protocol. The participant completed the continued efficacy assessment (CEA) Visit 42 and was discontinued from the study on Study Day 548.

Review: The etiology for pulmonary embolism in this participant is not clear. I cannot rule out a role of the study drug in this case, as there is no other etiology (post-surgery, prolonged travel or other immobility, or underlying hypercoagulable state)

Suicidal Ideation

201 Core

Participant (b) (6) is a 67 year old white female with mild dementia due to AD, who was randomized to LEC5-BW in study 201 Core. Relevant medical history includes a history of depression and suicide attempt. The participant received the 19th dose of study drug on Study Day 248. On Study Day 261, the participant experienced suicidal ideation. On Study Day 267, her CSSR grade was noted to be 4.3. On Study Day 268, the participant came to the clinic and reported that she had dark thoughts and suicidal ideation. On Study Day 269, she was taken to the emergency room and underwent psychiatric counselling for the event. Subsequently, she was hospitalized on Study Day 270. The event of suicidal ideation was classified as moderate in severity and serious (hospitalization). The study drug was temporarily interrupted due to the event. As per a geriatrician, the dosage regimen of her concomitant medications was adjusted and she was treated with risperidone 0.25 mg PO qd, bupropion 150 mg PO QD, and paroxetine 10 mg PO QD for the event. On Study Day 297, the event of suicidal ideation resolved and she was discharged from the hospital. On Study Day 331, the study drug was restarted. The event of suicidal ideation was suspected to be related to participant's history of anxiety, depression, and

suicidal attempts. The participant received the 34th dose (last dose) of study drug on Study Day 533 and completed the study as planned on Study Day 620.

Reviewer Comment: This participant had underlying risk factors for suicidal ideation, and it is less likely to be related to study drug.

Potentially Medically Significant SAEs

I did not identify the following SAEs using MedDRA Preferred Terms that fall under the designated medical events in study 201 Core and OLE: acute pancreatitis, amyotrophic lateral sclerosis (ALS), anaphylaxis and anaphylactoid reactions, ischemic colitis, congenital anomalies, deaf, disseminated intravascular coagulation endotoxic shock, confirmed or suspected, hemolysis, hemolytic anemia, liver necrosis, liver transplant, neuroleptic malignant syndrome, progressive multifocal leukoencephalopathy, product infectious disease transmission, pulmonary fibrosis, pulmonary hypertension, rhabdomyolysis, serotonin syndrome, Stevens-Johnson syndrome, suicide, Torsade de Pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

The following designated medical events were identified among the SAEs:

Acute respiratory failure occurred in participant (b) (6) in the context of a seizure. Hepatic injury and acute kidney injury occurred in participant (b) (6) due to underlying lymphoma. There were two additional cases of acute kidney injury in the OLE period (b) (6), described under heading Acute Kidney Injury, and in both cases I could not identify a role for the study drug in the acute kidney injury. A sudden death due to a cardiac arrest in participant (b) (6) as described earlier as well.

Pancytopenia

There was one participant with pancytopenia (b) (6). After completing the 201 Core study in the placebo arm, this participant enrolled in the OLE period. The study participant received the 57th dose of study drug on Extension Day 855, at which time she was noted to have pancytopenia. She had a bone marrow biopsy, but no results were available at the time of discontinuation. Study drug was permanently discontinued in response to pancytopenia with last dose on Extension Day 855. Participant was discontinued from study drug on Extension Day 866 due to pancytopenia, and progression of her symptoms.

In response to an IR from the Agency on 09/12/2022, the applicant was able to obtain additional medical history. This participant's bone marrow biopsy revealed 50 % myeloid blasts in 60 % cellular marrow with atypical small megakaryocytes and some megakaryoblasts consistent with post-myeloproliferative neoplasm Acute Myeloid Leukemia. The medical documents also mention that she carried a diagnosis of Jak2 + Essential Thrombocytopenia from (b) (6) and was on hydroxyurea 1-2 years.

Reviewer Comment: Based on the literature Essential Thrombocytopenia can develop into AML at a rate of 1-4 % in a median follow up of 7-10 years. Therefore, it is possible that her AML is related to her previous diagnosis of ET and less likely related to study drug.

12.1.3. Death, SAE, Discontinuation Narratives for Study 301 Core and 301 OLE

Study drug blinded selected Death and SAE Narratives for Study 301 Core and 301 OLE are provided below. It is difficult to ascertain causality in these study drug blinded narratives.

Death Narratives:

(b) (6)

This participant is an 82-year-old white female participant with mild AD who was randomized in the 301 Core Study to blinded treatment. On day 4 (three days after first dose of study drug), she was found by her husband unresponsive. She was taken to the hospital by paramedics, and diagnosed with acute hypoxic and hyper carbic respiratory failure, and acute renal failure. Given the severity of her symptoms she was placed on comfort measures, and died the same day. The cause of the acute respiratory failure was not identified. She did have a medical history of bronchospasm, and cardiovascular risk factors of hypertension, hyperlipidemia.

Reviewer Comment: Due to the blinded nature of this death, the relationship to study drug cannot be determined. The death occurred 3 days after the first study dose, and the cause of the sudden cardiorespiratory arrest leading to death is not known. This said, the participant had a history of cardiovascular risk factors (hyperlipidemia and hypertension), and risk for respiratory failure (bronchospasm). The narrative mentioned that she had an implantable cardiac monitor insertion on (b) (6) *suggesting that she may have had underlying cardiac rhythm abnormality. This said a delayed hypersensitivity reaction cannot be ruled out without knowledge of whether she received study drug or placebo.*

(b) (6)

This participant was an 81 year-old Asian male who completed blinded study treatment and entered the Extension Phase of the study and received the 1st dose of study drug on Extension Day 1. On the same day an ECG result was normal. The participant received the 11th dose (last dose) of BAN2401 10 mg/kg in the Extension Phase on Extension Day 134. On Extension Day 153, the participant was found lying in the bathtub of an open-air bath and was transported to another hospital where he was declared dead. The participant's past medical history is silent to any cardiovascular risk factors and only lists right and left cataract operations.

Reviewer Comment: The cause of the death in this case is unknown, and the relationship to study drug is difficult to ascertain due to the fact that the participant was receiving blinded study drug.

(b) (6)

This participant is a 72 year-old white male with mild cognitive impairment. He was randomized to receive placebo in 301 Core. His MRI scan on study day -38 showed a left frontal microhemorrhage. He received the 26th dose of study drug on study day 355. On Day 361, he was noted to be disoriented, and drove to a wrong city. He ran out of gas and was found by law officers, admitted to a local hospital for confusion, and discharged on study day 362. He remained confused. An MRI was obtained on an unknown date in (b) (6) which showed temporal lobe hemorrhage. On study day 402 the participant died due to intracranial hemorrhage. His relevant medications included acetylsalicylic acid 81 mg po daily.

(b) (6)

This participant is a 79-year-old white male randomized in Core Study to blinded treatment. No previous treatment for AD was reported. Medical/surgical history included: chronic kidney disease, eczema, mild Alzheimer's dementia, intervertebral disc degeneration, anemia, impaired fasting glucose, deafness, benign prostatic hyperplasia, depression, hyperbilirubinemia, oedema peripheral, osteoarthritis, coronary arterial stent insertion, essential tremor, rhinitis, asbestosis, chronic obstructive pulmonary disease, coronary artery bypass, coronary artery disease, diaphragmatic paralysis, hyperlipidemia, hypertension and diplopia.

On Study Day -71, an electrocardiogram (ECG) results showed mean heart rate of 57 beats/min, QRS duration of 133 msec, QT interval of 433 msec, QTcB of 423 msec, QTcF of 426 msec and RR interval of 1050 msec and findings confirmed atrial flutter. On Study Day 56, the participant experienced atrial fibrillation. The event was classified as mild in severity and nonserious. The participant was treated with apixaban 5 mg PO BID (b) (6) On (b) (6), on Study Day 263, participant presented to the ED with left sided paralysis and found to have large MCA distribution stroke. Participant had G-tube placed, and after this had sepsis and placed on ventilator. His condition declined and on study day 282 he was removed from the respirator and died.

(b) (6)

This participant is a 70-year-old white male who was receiving blinded study drug in 301 Core at the time of death, had a past medical history of back pain, cataract surgery, open angle glaucoma, mild AD, hyperlipidemia, benign prostatic hyperplasia, diabetic neuropathy, type 2 diabetes, depression, insomnia, angioplasty, GERD, coronary artery disease, myocardial infarction and hypertension.

On Study Day 230 the participant experienced shortness of breath, and refused to go to the hospital. Later that afternoon, the participant again began short of breath and suffered a sudden death. The event was reported as a suspected myocardial infarction. An autopsy was not performed, and the cause of death was reported as unknown.

(b) (6)

This participant is a 79-year-old white male who was randomized to blinded study drug in 301 Core. His past medical history included mild cognitive impairment due to AD, coronary artery stenosis, stent placement, vertigo, penile prosthesis insertion, dyspnea, hyperlipidemia, gallbladder operation, erectile dysfunction, blindness unilateral, hypertension, retinopexy, stent placement and diabetes mellitus.

On Study Day 28, the participant had ambulatory valvular procedure related to his coronary artery disease (coronary artery disease). On the same day (Study Day 28), the event of coronary artery disease was considered resolved. On Study Day 30, the participant experienced nasopharyngitis. The event of nasopharyngitis was classified as mild in severity and nonserious. On Study Day 36, the participant experienced an event of myocardial infarction (heart attack). The event was classified as severe in severity and serious (hospitalization and death), and died on (b) (6)

(b) (6)

This participant is an 86-year-old white female who was randomized in 301 Core to blinded study drug. On Study Day 404, the participant tested positive for COVID-19 and this was reported as an adverse event. The event was classified as severe in severity and serious (death, hospitalization). On Study Day 414, the participant's condition rapidly deteriorated due to COVID-19 and was hospitalized. The participant was sent directly for palliative care. On Study Day 416, the participant died, and the cause of death was reported as COVID-19

(b) (6)

This participant is an 85-year-old white male who was randomized to blinded study drug in 301 Core. On Study Day 73, the investigator noticed an increase in the jaundice. Furthermore, the participant also experienced fatigue and loss of appetite. On Study Day 74, the participant was diagnosed with pancreatic carcinoma with an onset date of Study Day 71. The study drug was permanently discontinued. The participant died while waiting for an appointment with an oncologist.

(b) (6)

This participant is a 79-year-old white male who was randomized to blinded study drug in 301 Core. Medical/surgical history included: mild Alzheimer's dementia, basal cell carcinoma, rhinitis allergic, drug hypersensitivity, hepatitis C, and drug hypersensitivity.

On Study Day 280, the participant requested for cancellation of Visit 23, as his wife tested positive for COVID-19 and the participant was under isolation. On Study Day 294, the participant had flu like symptoms (fever, sinusitis, and cough) and was under medication of Tylenol. The participant still did not test for COVID-19 and no hospitalization was reported. On study Day 296, the participant developed urinary tract infection and was treated with ofloxacin (unknown dose) for the event. On Study Day 300, the participant's wife reported that participant had cough and developed dizziness while driving. On Study Day 301, the participant developed cardio-respiratory arrest. The event was classified as severe in severity and serious (resulted in death). No treatment was reported for the event. On the same day (Study Day 301), the participant died due to cardio-pulmonary arrest. Per death certificate, immediate cause of death was reported as cardiopulmonary arrest with underlying condition leading to death documented as hyperlipidemia. An autopsy was not performed.

Selected SAEs in 301 CORE due to ARIA or cerebral hemorrhage > 1 cm

As of the 120 day update cutoff date of December 31, 2021, there were 11 SAEs of ARIA-H reported in Study 301 Core.

(b) (6)

This participant is a 78-year-old white female who was ApoE ε4 genotype positive. Her medical history in the narrative is silent to the use of antithrombotic medications. On Study Day 170, she received the 13th dose of study drug. On Study Day 180, she had a 15 mm right temporal superficial siderosis. On the same day, radiographically mild right temporal ARIA-E was reported. The participant was asymptomatic. On the same day, the diffusion weighted MRI imaging also revealed a 2 mm left cerebellar infarct on diffusion weighted imaging that was not presented radiographically on subsequent MRI on Study Day 213. On Study Day 213, the superficial siderosis resolved. On Study Day 239 the ARIA-E event progressed to a moderate radiographic severity from a mild radiographic severity and included the right temporal, parietal and occipital regions. The participant remained asymptomatic. On the same day a new ARIA-H superficial siderosis was reported in the right occipital regions, which was asymptomatic. The study drug was interrupted with the last dose (18th dose) received on Study Day 239.
On Study Day 267 two additional superficial siderosis were reported in the right frontal, and right temporal regions. No treatment was reported for these events. The study drug was interrupted with the 18th dose taken on Study Day 239. On Study Day 300, participant was taken to the emergency room for tingling burning, numbness on both arms and unable to sleep and seemed restless. CT head showed an acute parenchymal hemorrhage extending to the cortex in the right temporal occipital region measuring 3.2x2.8x2.6 cm . There was also a 3.1 cm intraparenchymal hemorrhage in the right parietal lobe, and areas of subarachnoid hemorrhage in the right parietooccipital lobes and right temporal lobes along with a 0.4 cm midline shift to the left. There was no history of recent fall. The participant had drooling, musculoskeletal stiffness, dysphagia and gait disturbance. The events ongoing at the time of the event of cerebral hemorrhage included: ARIA-E and superficial siderosis. On Study Day 367 MRI showed

the 25 mm intracerebral hemorrhage in the right temporal (non-hippocampal) and superficial siderosis in the right frontal and new right temporal (non-hippocampal) regions, and resolution of ARIA-E. The study drug continued to be interrupted due to the event of cerebral hemorrhage. The participant received 5 doses of study drug through ARIA-E and did not receive study drug through the superficial siderosis on. As of the interim data cutoff of Study Day 471, the participant was ongoing in the Core Study with no events ongoing.

Reviewer Comment: While this participant is receiving blinded study drug, the fact that the cerebral hemorrhage > 1 cm occurred in the setting of worsening ARIA-E and ARIA-H superficial siderosis, the cerebral hemorrhage is likely related to the same mechanisms of amyloid removal and is related to study drug.

(b) (6)

This participant is an 80-year-old white female who did not carry an ApoE ε4 allele.
On Study Day 32, the participant had the third dose of study drug. On Study Day 36 her daughter reported that she was acting different from her usual self, fell in the house, and had left upper extremity weakness, headache and high blood pressure. On Study Day 39, she was hospitalized, and her exam showed a left pronator drift, and weakness in the left arm and leg. A brain MRI on the same day, showed right frontal lobe vasogenic edema consistent with left frontal ARIA-E radiographically classified as moderate in severity, and ARIA-H with 10 right frontal cerebral microhemorrhages. The ARIA H event was moderate in severity and asymptomatic. The ARIA E in the left frontal regions, was thought to be symptomatic. Her symptoms included headache, fall and muscle weakness in the left arm and leg. On Study Day 40 the participant had decreased attention and mild left hemiparesis (left pronator drift left finger curling, and left arm fixing with rapid satellite movements). The participant was treated with dexamethasone 2 mg PO BID. On Study Day 41 the participant's MMSE score was 27/30; with the exception of a mild left upper extremity drift, her strength exam on the left was 5/5. She was fully oriented with intact attention, clinically stable and discharged from the hospital on the same day. The study drug was permanently discontinued due to the events of ARIA-H and ARIA-E. The participant did not receive the study drug through the ARIA-E and ARIA-H.
On Study Day 81, an MRI showed complete resolution of ARIA-E and the microhemorrhages reduced from 10 to 1 (less than 10 mm) in right frontal lobe. The participant was discontinued from the Core Study due to withdrawal by participant.

Reviewer Comment: These events of ARIA -E and ARIA-H are temporally related to study drug administration. However, the ARIA E in the left frontal area while causing gait impairment or headaches, would not cause left sided weakness (but should cause right sided weakness and possibly language deficits). Therefore, it is possible that the ARIA-H in the right frontal area was also symptomatic and the cause of the left sided weakness.

(b) (6)

This participant is an 80-year-old white female, who is a carrier of the ApoE ε4 allele.

On Study Day 50 she received the 5th dose of study drug. On Study Day 72 the participant developed aphasia, difficulty following instructions and shaking. She was not on any aspirin, other antiplatelets or anticoagulants. She was taken to the ED and hospitalized. She underwent a workup including an LP which was reported to be normal.

On Study Day 73, an MRI showed radiographically severe ARIA-E that was deemed symptomatic in the right occipital region. She also had associated ARIA-H, in the right frontal right temporal area. The study drug was permanently discontinued due to these events. The participant did not receive the study drug through ARIA-H and ARIA-E. On Study Day 74, the participant developed urinary retention.

On Study Day 82, the symptomatic ARIA-E event in the right cerebral hemisphere was considered resolved, and on Study Day 86 the participant was discharged from the hospital. On Study Day 82, a subdural hematoma was identified as well. On Study Day 95, the asymptomatic right cerebral ARIA E was resolved. On Study Day 109, a mild radiographic ARIA-E in the right occipital lobe was diagnosed as well as ARIA H (11 total) in the right temporal, non-hippocampal microhemorrhage. On Study Day 156, the ARIA-E resolved, and the total number of microhemorrhages of 11 remained unchanged. The participant had the last dose of study drug on Study Day 50, after 50 days of dosing. On Study Day 166, participant was discontinued from study due to symptomatic ARIA-E.

Reviewer Comments: Similar to several other ARIA events this participant also had a subdural hemorrhage at the time of the second occurrence of ARIA-E and ARIA-H. Subdural hemorrhage is not part of the ARIA-H definition, but has been observed in the lecanemab program as part of ARIA symptoms in a few other participants. Additionally, the second incidence of ARIA occurred more than 50 days after the study drug had been discontinued suggesting that the study drug's pharmacodynamic effects related to removal of amyloid may last longer than 5-half-lives of the drug.

(b) (6)

This participant is a 78-year-old white male negative for the ε4 allele of the ApoE gene. Relevant past medical history is that this participant was on apixaban for atrial fibrillation since (b) (6) (and on warfarin previous to that). On Study Day 8 (7 days after the 1st dose of study drug), participant had onset of confusion. On Study Day 18, the participant had more pronounced cognitive dysfunction and forgetfulness, difficulty with language, comprehension and additional issues, and challenges with playing cards, making himself toast and coffee, and incorrectly taking his medications. On Study Day 29, his MMSE score dropped to 15 (previously 22). Cognitive decline/confusion was rated as moderate in clinical severity. On Study Day 32, radiographically moderately severe ARIA-E located in the left parietal, right occipital, and left hippocampus regions were identified. It was symptomatic and the participant had increased confusion. On Study Day 44, the participant was discontinued from the Core Study due to ARIA-E.

Reviewer Comment: It is noted that although this participant was on apixaban (and warfarin prior to that) he experienced an ARIA-E event with no concurrent ARIA-H.

(b) (6)

This participant is a 68-year-old woman who is a carrier of the ApoE ε4 allele. She had not been on aspirin, other antiplatelets, anticoagulants or antithrombotic. On Study Day 148, the participant had the 11th dose of study drug. On Study Day 156, the participant had difficulty walking and on arrival at the emergency room, the participant had a convulsive seizure (generalized tonic clonic) followed by postictal neurologic defects of lateralized hemianopsia, aphasia, and confusion. Secondary generalized tonic-clonic seizures occurred shortly after, before the participant could recover from the first. An MRI performed in between the episodes showed asymmetric left parieto-occipital-temporal and right occipital-temporal vasogenic edema, without enhancing lesions, few microbleeds and hypersignal in the pulvinar. On the same day (Study Day 156), the participant was hospitalized for secondary generalized tonic-clonic seizures and an event of severe symptomatic ARIA-E was reported. She was treated with lacosamide and clonazepam. An EEG was consistent with metabolic encephalopathy. The study drug was permanently discontinued due to the event of severe ARIA-E symptoms with the last study drug dose administered Study Day 148. The participant had a prolonged and complicated hospital stay, including serious events of pulmonary edema, left ventricular dysfunction, respiratory decompensation requiring invasive ventilation, and had additional seizures. She received antibiotics for an infection and amiodarone for atrial fibrillation. The event of acute pulmonary edema resolved on Study Day 162. Her confusion fluctuated, and she sustained a fall. Ultimately was transferred to a rehabilitation center on Study Day 186. On Study Day 213, an early termination visit MRI revealed resolution of ARIA-E and no signs of ARIA-H and the event of severe symptomatic ARIA-E was considered resolved. On Study Day 225, the participant was neurologically stable except for some degree of cognitive decline following 2 months of in-hospital care, and gait instability secondary to T12 fracture. No further seizures were observed. Additional complications were T12, fracture, and T11-T12 laminectomy. The participant's generalized tonic-clonic seizures and thoracic vertebral fracture T12 were considered as the ARIA-E associated clinical symptoms. The participant did not receive the study drug through the ARIA-E.

Reviewer Comment: This participant's clinical course is an example of morbidity and long term sequela in participants with a neurodegenerative disease who may need prolonged hospitalization resulting from symptomatic severe ARIA-E.

(b) (6)

This participant is a 70-year-old female who was a carrier of the ApoE ε4 allele and who had 3 microhemorrhages noted at baseline on MRI scan on study day -42. This participant was on rivaroxaban at baseline. After the 4th dose of study drug, on Study Day 50 an ARIA-H event was reported (with three new microhemorrhages and ARIA-E involving the right frontal, right temporal (non-hippocampal), left temporal (non-hippocampal), right parietal, right and left

occipital, and right hippocampus regions. ARIA-E was described as moderate in radiographic severity. These events were asymptomatic. Study drug was interrupted due to ARIA-E. On Study Day 80, her MRI showed two new microhemorrhages for a total of 8 microhemorrhages. ARIA-E remained moderate in radiographic severity but increased in size to involve right frontal, right temporal (non-hippocampal), left temporal (non-hippocampal), right parietal, right and left occipital, and right hippocampus regions. On Study Day 85, at around 8:30 am the participant experienced sudden frontal and posterior headaches of moderate intensity associated with negative and positive visual symptoms for one minute (considered as a probable focal seizure). At 9:00 am, she experienced a brief episode of simple focal visual and motor seizure with intact awareness and secondary tonic-clonic generalization. She also showed mild transitory monoparesis of left arm (a post-ictal deficit). A CT brain scan performed on the same day (Study Day 85) revealed right occipital subarachnoid hemorrhage superimposed to a pre-existing active vasogenic edema (ARIA-E) in the right and left occipital and right parietal. A repeat brain CT scan showed an intracerebral lobar hemorrhage (32 mm), not associated with any vascular malformation, and no thrombophlebitis was observed on brain angiogram. The rivaroxaban was stopped. On Study Day 85, a right occipital cerebral hemorrhage (> 1 cm) was reported and classified as clinically severe and serious (hospitalization, medically significant and involving persistent or significant disability or incapacity). The participant was treated with Factor II (prothrombin)/Factor IX/Factor VII (proconvertin)/Factor X (Stuart-Prower factor)/protein c (coagulation inhibitor)/protein S 500 IU IV (unknown frequency) (b) (6) The participant's hematology results revealed a platelet count of 298000 × 109/L (normal range [NR]: 150-400 × 109/L), prothrombin time of 43 s (NR: 70-120 s), activated partial thromboplastin time of 33 s and anti-Xa activity of 300 ng/mL. She was admitted to the neurovascular department with left lateral homonymous hemianopsia and mild to moderate headaches. On Study Day 246, MRI scans revealed a 34 mm cerebral hemorrhage and ARIA-E that remained moderate in radiographic severity and one new microhemorrhage. On Study Day 299 ARIA-E resolved, microhemorrhage was stable and intracerebral hemorrhage decreased to 28 mm As of interim data cutoff of 31 Dec 2021, the participant's study participation is ongoing in the Core, but the study drug is interrupted.

Reviewer Comment: This narrative is of a participant who may have underlying amyloid angiopathy (as she had microhemorrhages on her baseline MRI). She was also on anticoagulation with rivaroxaban. She had an intracerebral hemorrhage in addition to ARIA-E and cerebral microhemorrhages. Her intracerebral hemorrhage occurred in the area of the ARIA-E highlighting that the processes and underlying mechanisms were likely related. It is possible that being on an antithrombotic further increases risk of bleeding in the setting of treatment with lecanemab, especially for those who have underlying microhemorrhages at entry to the study. suggesting underlying CAA pathology.

(b) (6)

This participant is a 79-year-old Asian female who is not a carrier of the ApoE ε4 allele received the 26th dose of study drug on Day 435. She had not been on any anticoagulation through the

study. On Study Day 439, the participant's relative informed the study staff that she had been exhibiting abnormal behavior and utterance and was eventually admitted to the hospital. Based on subsequent test results the participant was reported to have experienced an event of intracerebral hemorrhage on the same day (Study Day 439). She was then transferred to the neurosurgery department and admitted for observation. The study drug was permanently discontinued. On Study Day 536 the participant was discharged with a diagnosis of left parietal subcortical cerebral hemorrhage with edema measuring 3.4 cm x2.4 cm in the surrounding area. The participant discontinued from Core Study early due to withdrawal by participant.

(b) (6)

This participant is a 75 year old woman with an ApoE ε4 allele who on the day of the 4th dose of study drug, had cerebral hemorrhage of 30 mm in the right occipital area and ARIA-E in the left frontal, right temporal, and right and left occipital area. She also had acute subdural hemorrhages overlying the right cerebral convexity, as well as in the right parafalcine, right supratentorial, the left parietal-occipital regions. She had a 2 mm midline shift towards the left side. She had been on ticagrelor for stent placement which was discontinued after these events. She was hospitalized and started on levetiracetam prophylactically. Study drug was temporarily interrupted due to cerebral hemorrhage and ARIA-E, and she received treatment with methylprednisolone. She remained asymptomatic. Participant withdrew from the study before further dosing.

(b) (6)

This participant is a 68 year old man who was positive for the ApoE ε4 allele, and after the 3rd dose of study drug, he began to have progressive visual loss. Radiographically severe ARIA-E was discovered on MRI (on day 47) in the right and left frontal, right and left temporal (nonhippocampal), right and left parietal, right and left occipital regions. Associated ARIA-H with 25 new microhemorrhages were seen. The participant had a seizure 5 days after the ARIA-E was discovered and admitted to the hospital and treated with levetiracetam. Follow up MRIs Subsequent MRI on Study Day 68 showed 2 new microhemorrhages. Maximum number of microhemorrhages was reported on Study Day 104 with a total of 96 microhemorrhages. As of the interim data cutoff of 30 Jun 2021 (b) (6) the participant was ongoing in the Core Study. This patient had 4 microhemorrhages at screening

(b) (6)

This 71 year old women who was positive for the ApoE ε4 allele, experienced ARIA-H microhemorrhage (4 microhemorrhages) and ARIA-E after the 4th dose of study drug. Study drug was temporarily stopped, for ARIA-E . Follow up MRI revealed 26 additional microhemorrhages. Study drug was resumed after ARIA-E resolution. After the 8th dose of study drug, she had a new episode of ARIA-H (total 50 microhemorrhages), and a cerebral hemorrhage in the right temporal areas (12mm). and ARIA-E. Study drug was permanently discontinued due to ARIA-H. This patient has been on rivaroxaban for a pre-existing condition.

Reviewer Comment: Both of the participants above, who were ApoE ε4 allele carriers, sustained a high number of ARIA-H microhemorrhages during treatment with blinded study drug. The long term impact of sustaining this high number of ARIA-H microhemorrhages is not known and carries a risk of negatively effecting long term cognitive functioning based on clinical pathological studies[40].

(b) (6)

This 71 year old women who was negative for the ApoE ε4 allele experienced a fall caused by syncope vs seizure 6 days after the 13th dose of study drug. She was hospitalized where a CT scan diagnosed subarachnoid hemorrhage. MRI obtained subsequently identified ARIA-E and ARIA-H superficial siderosis. She experienced a second event of syncope a month after the original event. She was started on Keppra which was later switched to valproate. The narrative states that the event of seizure was ongoing at the time of the study discontinuation.

(b) (6)

This participant is an 80-year-old white female who 2 days after receiving the 42nd study dose experienced an asymptomatic intracerebral hemorrhage in the right temporal lobe which was 1.3x1.6.0.9 cm in size, and was asymptomatic. She also experienced an ARIA E event and superficial siderosis in the right parietal lobe on the same date. At the time of the study report the drug was interrupted and the outcome was not resolved, and not recovered.

(b) (6)

This participant is a 68-year-old white female who was a carrier of the ApoE ε4 allele. She completed 301 Core study on study day 529. On Extension Day 57 she received the 5th dose of the study drug. On the same date an event of ARIA-E which was moderate in radiographic severity and located in the right occipital and left cerebellum was reported. This was mild in clinical severity, asymptomatic. The study drug was temporarily interrupted. On Extension Date 57, MRI showed resolution of the ARIA-E. Study drug was restarted on Study Day 104. The participant received the 10th dose of 10mg/kg on Extension Day 174. As of data cutoff of 31 Dec 2021, the participant was ongoing in the Extension phase of the study.

<u>303 Core SAE ARIA narrative</u>

(b) (6)

This participant was a 69-year-old white female randomized in Study A45-Core to blinded study treatment. On Study Day 50 the participant experienced mild intermittent headache lasting minutes and worsening when sitting or standing. On Study Day 57 an event of ARIA-E was reported, which was severe in severity, symptomatic. 14 areas showed involvement of ARIA. An Event of ARIA-H with microhemorrhages and superficial siderosis was reported on Study Day

[40] Akoudad S, Wolters FJ, Viswanathan A, et al. Association of Cerebral Microbleeds With Cognitive Decline and Dementia. JAMA Neurol. 2016;73(8):934–943. doi:10.1001/jamaneurol.2016.1017

57. This was moderate in severity. There were 34 definite and 5 possible microhemorrhages and 29 definite and 4 possible areas of superficial siderosis reported.
On Study Day 57, the participant was experiencing mild word finding problems. The study drug was permanently discontinued due to the event of ARIA-E with the last dose taken on Study Day 57.

Discontinuation Narratives for 301 Core

Based on Table 16.2.7.3 Adverse Events Leading to Discontinuation from Study due to ARIA, infusion related reactions or hypersensitivity reactions, in 301 Core, there were a total of 25 such discontinuations. Of these, 6 discontinuations were due to ARIA-E (b) (6) 4 of which were symptomatic. There were 6 discontinuations due to ARIA-microhemorrhage (b) (6) There was one discontinuation due to arthralgia (b) (6) This participant also experienced dizziness and lethargy all of which occurred after the first infusion and felt to be due to an infusion related reaction. 11 discontinuations due to Infusion Related Reactions (b) (6) Of these Infusion Related Reactions, in one participant (b) (6) the Investigator Term was listed as Acute Respiratory Failure/Hypoxia. The narrative of this participant will be provided under Section 7.5.3

In a separately provided Table 16.2.7.3 Adverse Event Leading to Discontinuation from Study Drug due to reasons other than ARIA, infusion related reactions and hypersensitivity reactions, study drug discontinuation occurred in 2 or more participants with TEAEs falling under the following System Organ Class: Nervous System Disorders (n=7), Cardiac Disorders (n=7), Neoplasm Benign, Malignant and Unspecified (n=5) Psychiatric disorders (n=3), Infection and Infestations (n=3), Vascular Disorder (n=2), and Injury, poisoning and procedural complications (2). Because Study 301 remains blinded, it is not possible to ascertain the role of study drug.

Dizziness
Participant (b) (6) is a 66 year old white male who on study day 16 received the second dose of the study drug. His vital signs prior and post infusion were normal. After the infusion the participant experienced dizziness, arthralgia and lethargy. The arthralgia was considered an infusion reaction. He was permanently discontinued due to dizziness, lethargy and arthralgia with the last dose of study drug taken on day 16. His symptoms resolved on study day 41.

Acute Respiratory Failure
Participant (b) (6) is described under Death Narratives in this section.

Atrial Fibrillation

(b) (6) is a participant who was discontinued for atrial fibrillation. No narrative was provided for this participant, as this discontinuation is not a death or an SAE and not related to ARIA or infusion related reaction.

Psoriasis
Participant (b) (6) is an 83 year old women who on study day 190 experienced psoriasis in the right ear and eczema under breast bilaterally treated with tropical medications. These lesions were classified as moderate in severity and nonserious. Study drug was permanently discontinued due to the event of psoriasis.

Reviewer Comment: It is difficult to ascertain based on the limited information whether the psoriatic rash and the eczema under the breasts are related to study drug.

Thrombocytopenia
Participant (b) (6) is an 81 year old male who had mild transient thrombocytopenia but who also had an infusion related reactions.

Myocardial Infarction:
Participants (b) (6) and (b) (6) were participants who died due to cardiac disease and their narratives are described under Death Narratives in this section.

Worsening Liver Enzymes
Participant (b) (6) is a 56 year old woman who at screening and baseline had mildly elevated ALT of 40 and 45 (normal range ≤ 33 U/L) and normal AST at baseline. Her gamma-glutamyl transferase (GGT) at baseline was also elevated at 109 (*normal 5-36 U/l).

The participant received the 7th dose of study drug on day 86. On study day 86 her ALT was increased to 66 U/L, AST was mildly increased to 27 U/L (normal < 31), ALP was 106 (normal <104), and GGT was 178 UI/L. The values of ALT, AST, ALP and GGT remained elevated throughout the study.

On study day 199 the participant was diagnosed with nonalcoholic steatohepatitis. On Study Day 368 the laboratory results showed increased ALT of 199 U/L, AST of 215 U/L, ALP of 147 U/L, and GGT of 513 U/L, normal levels of direct bilirubin of <3 µmol/L, and total bilirubin of 4 µmol/L. The participant was discontinued from the study on (b) (6) (Study Day 537) due to the event of hepatic enzyme increased. At the time of study discontinuation, the participant had the following events ongoing: non-alcoholic steatohepatitis, diabetes mellitus inadequate control and hepatic enzyme increased (b) (6)

Reviewer Comment: Given that the LFTs were elevated at baseline, it is possible that the elevated LFTs in this participant's case are related to underlying non-alcoholic steatohepatitis

rather than study drug. However, I cannot rule out that the study drug played a role in worsening of baseline elevated LFTs.

Suicidal ideation/thoughts of suicide

Participant (b) (6) is a 79 year old white female with relevant past medical history of anxiety, and insomnia, who on study day 176 experienced suicidal ideation. It was classified as mild and nonserious. The study drug had been discontinued previous to this on Study Day 170 per participant withdrawal. On study day 184 the participant had no suicidal behavior but severe suicidal ideation on CSSRS. On study day 217 the participant was discontinued from the Core Study, and the event of suicidal ideation was ongoing at the time of the discontinuation.

Reviewer Comment: I cannot rule out a role of the study drug in this participant's suicidal ideation as this participant did not have a significant medical history of mental health disorders, and study drug is blinded in this narrative.

Subdural bleeds

Participant (b) (6) is a 73 year old male who was discontinued from 301 Core Study due to bilateral subdural bleeds which were related to a skiing accident and not related to study drug.

Plasmacytoma

Participant (b) (6) is a 67 year old white female, who on an unknown date in (b) (6), had increased lymphocyte count and sedimentation rate; and proteinuria was positive. On Study Day 183 the participant had elevated lymphocyte count. On Study Day 193 the participant was suspected to have plasmacytoma and was discontinued from the study on Study Day 221.

Reviewer Comment: The narrative provides scarce information how the diagnosis of plasmacytosis is made, and therefore it is difficult to ascertain whether there is any relationship between study drug and elevated lymphocyte counts in this participant.

Cardiac arrythmia/bradycardia

Participant (b) (6) is a 68 year old male with relevant medical history of ventricular extrasystole. On Study Day 85 the participant experienced arrhythmia and bradycardia. His EKG showed abnormal first degree AV block which was not present on his initial ECG. He was treated with flecainide. The study drug was permanently discontinued with last dose taken on Study Day 71. The participant was discontinued from study on Study Day 240.

Reviewer Comment: While this participant does have a history of cardiac rhythm problems, given the scarcity of his risk factors, and the fact that he is receiving blinded study drug, I cannot ascertain whether the study drug may have contributed to this AE that led to discontinuation.

Discomfort/General discomfort

Participant (b) (6) is a 68 year old white female who was on study day 20, 12 hours after the second infusion experienced dizziness and vomiting. The study drug was permanently discontinued on Study Day 20.

Common Bile Duct Stone/ Cholangitis

Participant (b) (6) is an 83 year old Asian female who had an infusion related reaction that consisted of low blood pressure post infusion. The following day she had a fever and a rash and diagnosed with a Grade 1 infusion reaction. Also on Study Day 1, this participant had elevated liver enzymes. On Study Day 4, she lost consciousness briefly and was hospitalized overnight. The following day she was re-hospitalized again, and eventually found to have cholangitis and treated with iv antibiotics. She was permanently discontinued due to cholangitis and bile duct stone.

Reviewer Comment: This participant's narrative and sequence of events are confusing. It is not clear if she truly had an infusion related reaction, or whether all of the findings starting on study day 1 were all related to cholangitis. I am unable to ascertain the role the blinded study drug may have played in this AE.

Syncope/Fall/Seizure

Participant (b) (6) is a 71 -year-old ApoEe4 allele negative woman who received the 13th dose of study drug on study day 169. On study day 175 she experienced a seizure, and syncope and was found on the floor. Her narrative is described earlier in this section

Discontinuations for Study 301 OLE

There were 5 discontinuations in study 301 OLE, three (b) (6) were not related to ARIA or Infusion Related Reactions/Hypersensitivity. These narratives were reviewed, and two narratives where I could not rule out a role of the blinded study drug for the event are provided below. Participant (b) (6) had COVID 19 infection which led to study discontinuation and ultimately death. This participant's narrative is not provided. ARIA and infusion related reaction narratives will be provided in sections 7.5.1 and 7.5.2.

Myocardial Infarction:

Participant (b) (6) is a 78 year old white female with relevant medical history of cardiac murmur, carotid artery stenosis, hyperlipidemia and hypertension. On extension day 1, after the infusion the participant's ECG showed ST Segment, T wave, and U wave changes felt to be not clinically significant, but were new compared to her previous EKGs. On Study Day 11 the participant had a myocardial infarction and died and discontinued from study.

Reviewer Comment: While the participant did have EKG changes on the day after the infusion, given her existing cardiovascular risk factors, the MI is more likely related to her underlying cardiovascular risk factors rather than blinded study drug.

Acute cardiac failure

Participant (b) (6) is an 81 year old Asian male who received the 11th dose of study drug on Extension Day 134. On Extension Day 153, the participant experienced acute cardiac failure and death. He was found lying in the bathtub of an open air bath and transported to a hospital where he death was declared. Medical history was silent for relevant cardiovascular risk factors.

Reviewer Comment: It is difficult to ascertain whether the participant's death is related to study drug or not, as there were no clear cut known cardiovascular risk factors for sudden death.

12.1.4. ODE-1 and FDA Query Groups (MQG) and Preferred Terms

Table 80 Serious Adverse Reactions by MQG and number of participants with one or more occurrence of the Preferred Term under that MQG.

Medical Query Group	Preferred Terms (n)
Infection All ODE-1 MQG	Urinary tract infection 2 Appendicitis 1 Bacteremia 1 Cellulitis 1 Cholangitis acute 1 Cholecystitis chronic 1 Clostridium difficile colitis 1 Clostridium difficile infection 1 Diverticulitis 1 Influenza 1 Pneumonia 1 Sepsis 1 Streptococcal sepsis 1 Upper respiratory tract infection 1 Urosepsis 1
Arthralgia, FDA MQG, N	Arthralgia 3
Hemorrhage FDA MQG, N	Cerebral microhemorrhage 2 Gastrointestinal hemorrhage 1 Hemorrhagic transformation stroke 1 Post procedural hemorrhage 1 Subdural hematomas 1

Chest Pain (noncardiac or unknown) ODE-1 MQG	Non-cardiac chest pain 3 Chest pain 1

Table 81 Treatment Emergent Adverse Events by MQG and number of participants with one or more occurrence of the Preferred Term under the MQG

Local administration reactions FDA N	Infusion related reaction 117 Infusion site extravasation 10 Infusion site pain 5 Infusion site bruising 4 Application site dermatitis 1 Incision site pain 1 Infusion site discomfort 1 Infusion site erythema 1 Infusion site hematomas 1 Infusion site irritation 1 Infusion site reaction 1 Infusion site swelling 1 Injection site bruising 1 Injection site discoloration 1 Injection site extravasation 1 Injection site induration 1
Cough FDA N	Cough 44 Upper-airway cough syndrome 4 hemoptysis 1 Productive cough 1
Hemorrhage FDA N	Cerebral microhemorrhage 57 Contusion 38 Hematuria 20 Ecchymosis 7 Epistaxis 6 Hematoma 6 Infusion site bruising 4 Hematochezia 3 Cerebellar microhemorrhage 2 Conjunctival hemorrhage 2 Eye hemorrhage 2 Hemorrhagic transformation stroke 2 Hemorrhoidal hemorrhage 2 Purpura 2 Rectal hemorrhage 2

	Subdural hematoma 2 Traumatic hematoma 2 Blood loss anemia 1 Blood urine present 1 Bone contusion 1 Brain stem microhemorrhage 1 Catheter site bruise 1 Catheter site hematoma 1 Catheter site hemorrhage 1 Cerebral hemorrhage 1 Cystitis hemorrhagic 1 Diverticulum intestinal hemorrhagic 1 Gastric ulcer hemorrhage 1 Gastrointestinal hemorrhage 1 Hemoptysis 1 Hemorrhage urinary tract 1 Hyphemia 1 Infusion site hematoma 1 Injection site bruising 1 Internal hemorrhage 1 Intra-abdominal hematoma 1 Lower gastrointestinal hemorrhage 1 Melaena 1 Periorbital hematoma 1 Periorbital hemorrhage 1 Petechiae 1 Post procedural hematoma 1 Post procedural hemorrhage 1 Retinal hemorrhage 1 Subcutaneous hematoma 1 Vessel puncture site bruise 1 Vessel puncture site hematoma 1
Lymphopenia ODE-1 MQG	Lymphopenia 10 Lymphocyte count decreased 3
Paresthesia FDA N	Paresthesia 9 Hypoesthesia 4 Hyperesthesia 2 Dysesthesia 1
Diarrhea FDA N	Diarrhea 65 Dysentery 1
Irritability FDA N	Agitation 25 Irritability 11

Headache FDA B	Headache 117 Head discomfort 5 Migraine 3 Occipital neuralgia 3 Tension headache 2 Sinus headache 1
Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones MQG	Glycosuria 6 Hyperglycemia 3 Diabetes mellitus 2 Diabetes mellitus inadequate control 2 Blood glucose increased 1 Glucose urine present 1
MQG: infection, viral	Influenza 17 Herpes zoster 11 Gastroenteritis viral 9 Viral infection 7 Viral upper respiratory tract infection 5 Gastrointestinal viral infection 3 Oral herpes 2 Respiratory tract infection viral 1 Viral pharyngitis 1

12.1.5. ARIA Narratives in Study 201 Core and 201 OLE

201 Core ARIA-E narratives

(b) (6)

Participant is a 72-year-old white female with AD with e3/e4 genotype randomized to receive LEC10-M in Study 201 Core. On Study Day 43, she received the 4th dose of study drug. On the same day the participant was diagnosed with ARIA-E and 4 new cerebral microhemorrhages on MRI, both of which were classified as radiographically moderate in severity. ARIA-E occurred in the right frontal, parietal, and occipital lobes, and in the left frontal lobe. No treatment was reported for the events. On Study Day 50, it was reported that the participant was asymptomatic, and had early termination On Study Day 73, a repeat MRI showed presence of mild right parietal ARIA-E decreased in size. The participant developed another 4 new cerebral microhemorrhages (ARIA-H) (now 8 in total), again rated as moderate in radiographic severity and nonserious. During the course of the study, this participant experienced dizziness and nausea that were attributed by the investigator to the reduction of the dose of escitalopram and not to any events of ARIA.

Reviewer Comment: It is not entirely clear if the intermittent dizziness that the participant experienced are related to study drug or not. This participant is another example of new ARIA-H occurring (cerebral microhemorrhages) >30 days after the last dose of study drug, 40 days after last study dose in this case, and 23 days after first occurrence of ARIA. The ARA-E was still radiographically present, and it is possible that the two separate events of ARIA-H microhemorrhages she experienced are due to the mechanisms underlying amyloid removal that led to ARIA-E and are both related to the same ARIA-E incident.

(b) (6)

Participant (b) (6), who has is an ApoE ε4 homozygote genotype was randomized to receive LE10-M had the first occurrence of ARIA-E and ARIA-H microhemorrhage 7 days after the 6th study dose on Study Day 77. On Study Day 133 (60 days after last study drug administration), the participant had new ARIA-H microhemorrhage and ARIA-H superficial siderosis. On this day ARIA-E was considered to be resolved.

Reviewer Comment: In this participant's case, given that the second incidence of ARIA-H microhemorrhage and superficial siderosis occurred on Study Day 133, 60 days after the last dose of study drug, and after ARIA-E was resolved, I cannot rule out that this event of ARIA-H was unrelated to study drug, and possibly related to underlying amyloid angiopathy for which being an ApoE4 homozygote is a risk factor

(b) (6)

This participant is a 70-year-old white male with ApoE e4/e4 genotype randomized to receive LEC10-M. On Study Day 351, he received the 26th dose of study drug. On the same day the participant was diagnosed with superficial siderosis of the central nervous system (ARIA-H) and vasogenic edema (ARIA-E) on MRI. The events were classified as mild in severity and nonserious. He was asymptomatic. No treatment was reported for the events. On Study Day 358, the participant came in for his early termination visit and discontinued study treatment due to the events of superficial siderosis of central nervous system (ARIA-H) and vasogenic edema (ARIA-E), with the last dose on Study Day 351. On Study Day 421, the event of superficial siderosis worsened to moderate in severity and remained nonserious. On Study Day 483 the participant discontinued from the study due to withdrawal of consent. On Study Day 519 the event of vasogenic edema (ARIA-E) worsened to moderate in severity and was nonserious; and the participant remained asymptomatic. On Study Day 589, the event of vasogenic edema (ARIA-E) resolved. The event of superficial siderosis of central nervous system (ARIA-H) was ongoing at the time of study discontinuation.

Reviewer Comment: The trajectory of ARIA in this participant is notable, because the study drug was discontinued on Day 351. However, participant's ARIA events continued to worsen. Both ARIA E and superficial siderosis worsened from mild to moderate more than 60 days after the initial onset of ARIA-E, and 168 days after the last dose of the study drug, without further dosing. The reason for continued worsening in ARIA so far out after the study drug

administration is not known. It may be related to underlying amyloid angiopathy for which being an e4 homozygote, as this participant is, is a risk factor.

(b) (6)

This is an 82-year-old white female with ApoE e2/e3 genotype, randomized to receive LEC10-BW. On Study Day 169, the participant received the 11th dose of study drug. On Study Day 178 (~week 25), 9 days after the 11th dose of study drug, participant's brain MRI showed bilateral occipital ARIA E and 4 new cerebral microhemorrhages [ARIA H]. The events were classified as mild in severity and nonserious. No treatment was reported for these events. On Study Day 184, the participant came in for her early termination visit and the study drug was discontinued due to the event of bi-lateral occipital ARIA-E. During the early termination visit it was reported that she could not read as well at night with reading glasses, which might be related to ARIA or a change in vision, but visual acuity assessed in the clinic was within normal limits. The participant was also found to have new onset atrial fibrillation, which was considered mild and not related to study drug. On Study Day 212, 43 days after the last dose of study drug, the participant's brain MRI scan showed 3 new cerebral microhemorrhages (ARIA-H). The event was classified as mild in severity and nonserious. On Study Day 254, the participant had increased forgetfulness and disorientation, was unable to follow a routine, and had dysphonia. Her heart rhythm was found to be irregular. Neurological examination revealed worse coordination and word finding problems. On Study Day 261 she exhibited a significant drop in MMSE score by 8 points over an 11-month period. On Study Day 268, MRI showed bi-occipital ARIA-E of moderate severity and >10 microhemorrhages (no new ARIA-H lesions). On Study Day 302 (133 days after the last study dose), the participant's brain MRI showed 5 new microhemorrhages (3 left occipital lobe and 2 right occipital lobe). No new symptoms related to the ARIA-E and ARIA-H were reported. The event was classified as mild in severity and nonserious. No treatment was reported for this event. On Study Day 331 (162 says after the last dose) the participant's brain MRI scan showed 1 new cerebral microhemorrhage (right occipital lobe) (totaling 13). The event was classified as mild in severity and nonserious. On study day 435 the event of bi-lateral occipital ARIA-E resolved. The events of cerebral hemorrhages (ARIA-H; all occurrences) were ongoing at the time of study discontinuation.

Reviewer Comment: This participant had one event of bi-occipital ARIA-E and ARIA-H microhemorrhage 9 days after the 11th dose, but continued to have new cerebral microhemorrhages, up to day 331 (162 days after last dose of study drug), 13 ARIA-microhemorrhage events over the course of the study). She was also noted to have a significant drop in her cognitive function over a course of 11 months of study drug treatment. The participant also had visual complaints, and while her acuity was reported to be normal, no visual field exam was reported. It is possible that the worsening of cognitive function, and visual complaints were related to the ARIA-E and multiple ARIA-H events.

Whether the study drug plays a role in these ARIA events that occur on average 84 days after last dose of study drug is unclear. These nontreatment emergent ARIA events occur at higher

incidence in participants who have received the study drug compared to placebo, and at higher incidence in ApoEe4 carriers, however participant (b) (6) *described above is an example of a noncarrier (e3/e2) who continued to have multiple ARIA-H microhemorrhage despite no further dosing. In clinical practice, it will be important to continue clinical monitoring for symptoms of ARIA up to 6 months after study drug discontinuation.*

(b) (6)

This participant is a 79 year old male with ApoE ε3/ε4 genotype was randomized to receive LEC10-BW. The participant received the 6th dose of study drug on Study Day 78. On Study day 81, the participant experienced bilateral burning sensation over the parietal occipital lobes. MRI showed increased subtle flair signal changes in the left parietal lobe that were noted on the day 50 MRI, but not on the day 46 MRI. The ARIA-E radiographic severity was mild, and clinical symptoms were classified as moderate in severity and serious (due to being medically significant). On Study Day 86, the participant experienced a headache that lasted for 2 hours in addition to the burning sensation. On Study Day 92, he came in for early termination visit with the last dose taken on Study Day 78. On Study Day 170, repeat MRI showed resolution of ARIA-E and event of amyloid related imaging abnormalities was considered resolved.

Reviewer: This participant's case unlike the other three serious ARIA-E events described earlier was only designated as serious as it was a medically significant event, not due to the severity of symptoms.

(b) (6)

This is a 65-year-old white male with ApoE ε4/ε4 genotype, randomized to receive LEC10-BW in Study 201 Core. On Study Day 71, the participant received the 6th dose of study drug. On Study Day 78 (week 11), 7 days after the 6th dose, the participant was diagnosed with ARIA-E in the right occipital region, on MRI, with new confluent edema in the right occipital lobe. The event was classified as moderate in radiologic severity and mild in clinical severity (by the investigator). On the same day the participant had his early termination visit and the study drug was permanently discontinued due to the event of ARIA-E, with the last dose taken on Study Day 71. On Study Days 79 and 81, the participant experienced a headache, both of which resolved on the same day with intake of fluids. Therefore, the event of ARIA-E was considered symptomatic. On Study Day 108, subsequent MRI showed decrease in the size of vasogenic edema and mild improvement in the T2 signal hyperintensity within the right posterior occipital and adjacent mass effect; however, the participant was diagnosed with a new cerebral microhemorrhage located in the area of vasogenic edema. The event of cerebral microhemorrhage (ARIA-H) was classified as mild in severity and nonserious. No treatment was reported for these events. On Study Day 162, an MRI showed previous findings including the 1 cerebral microhemorrhage that were previously detected (ARIA-H) with no other significant changes from the previous MRI results. On Study Day 444, the participant was discontinued from the study due to participant moving out of state and not wanting to travel back for

remaining visits. Other ongoing events at the time of study discontinuation included headache and cyst.

Reviewer Comment: This is a participant with moderate radiographic severity ARIA-E, and mild clinical symptoms which did not require hospitalization and resolved within a day.

(b) (6)

Participant is a 69-year-old white male with ApoE ε3/ε3 genotype randomized to receive LEC10-BW. On Study Day 57, the participant received the 5th dose of study drug. On Study Day 62 (~ week 8), 5 days after the 5th dose, the participant was diagnosed with ARIA-E on brain MRI, of moderate severity in the left temporal (non-hippocampal) and left parietal lobe; there was no microhemorrhage and no superficial siderosis. On Study Day 63, the participant came in for his early termination visit and was discontinued from the study treatment due to the event of ARIA-E, with the last dose taken on Study Day 57. On Study Day 74, the participant experienced mild pressure on left side of his head and blurred vision. On Study Day 96, these symptoms resolved with intake of fluids. On Study Day 121, the MRI result showed complete resolution of ARIA-E radiologically.

Reviewer Comment: This is another participant with radiographically moderately severe ARIA-E, and mild clinical symptoms.

(b) (6)

This is a 67-year-old white female, with ApoE genotype of ε3/ε4 randomized to receive LE10-M. On Study Day 69, the participant received the 6th dose of study drug. On Study Day 83 , 14 days after the 6th dose of study drug, the participant was diagnosed with cerebral microhemorrhages (ARIA-H) and vasogenic edema (ARIA-E) on MRI. There were several scattered new microhemorrhages (>10) and confluent foci of increased signal in the supratentorial white matter bilaterally on flair sequence (frontal, parietal and occipital lobes). The event of cerebral microhemorrhage (ARIA-H), was classified as severe in radiologic severity, and mild in clinical severity (by the investigator) and nonserious and the event of ARIA-E was classified as severe in radiographic severity and nonserious. On Study Day 84, MRI of brain showed mild generalized cerebral tissue loss and 10-15 scattered small signal voids consistent with hemosiderin deposits *(reviewer's note: these represent cerebral microhemorrhages)*, multifocal high signal lesions within the supratentorial white matter, and progression of white matter changes. It was noted that the participant had worsening migraine, which was not related to microhemorrhage and anxiety. On Study Day 90, the participant was asymptomatic and had her early termination visit and the study drug was permanently discontinued in response. On Study Day 121, a repeat MRI showed complete resolution of ARIA-E in both frontal and left parietal lobe region and new cerebral microhemorrhages were seen. The event of cerebral microhemorrhage (ARIA-H) was ongoing at the time of study discontinuation. On Study Day 189, MRI showed no significant changes and the cerebral microhemorrhages remained stable with no new findings.

Reviewer Comment: Given the proximity of worsening in underlying migraines in relation to the ARIA event (within one day after ARIA-E and ARIA-H was seen), it is possible that worsening headaches were related to ARIA-E.

(b) (6)

This is an 86-year-old white male, with an ApoE ε3/ε4 genotype randomized to receive LEC10-M . The participant received the 4th dose of study drug on Study Day 43. On Study Day 57 (~ week 8), 14 days after the 4th dose, the participant was diagnosed with ARIA-E in the right temporal, left frontal, and left parietal locations; and also had 3 new cerebral microhemorrhages [ARIA-H; 1st occurrence]) in the areas of vasogenic edema (ARIA-E) on MRI. The ARIA-E was radiographically rated as moderate in severity, and the ARIA-H was rated as mild. The participant remained asymptomatic. The participant was discontinued from study treatment on Study Day 64. On Study Day 91 the participant underwent an MRI, and the findings included 2 new cerebral microhemorrhages (asymptomatic ARIA-H; 2nd occurrence). mild in severity and nonserious. On Study Day 92, the participant experienced a right temporal-parietal headache, took paracetamol. On Study Day 98 headache was resolved. Headache was classified as mild and nonserious. The investigator considered that the headache was not related to the ARIA-H. The investigator classified the event of cerebral microhemorrhage (ARIA-H; 2nd occurrence) to be not related to study drug

Reviewer Comment: In this case, whether the second occurrence of cerebral microhemorrhages which occurred, 48 days after the last dose of the study drug, and 38 days after the first ARIA-E/ARIA-H event, was related to study drug cannot be clearly determined. This participant did not have baseline microhemorrhages to suggest that they had underlying amyloid angiopathy, and it is possible that the second occurrence was related to study drug. Additionally, because the intermittent headaches occurred within a day of the second occurrence of ARIA-H, it is possible that the headaches may be related to the microhemorrhages.

(b) (6)

Participant is a 60-year-old, white, female, with a ε4/ε4 allele, randomized to receive LE5-BW in 201 Core. On Study Day 43, the participant received the 4th dose of study drug. On Study Day 56 (week 8), 13 days after the 4th dose, the participant's MRI showed ARIA-E in the right temporal non-hippocampal, right parietal and right occipital region. However, the MRI abnormality of ARIA-E was initially missed by the central MRI reader. Therefore, the participant continued treatment with study drug. On Study Day 176 MRI showed ARIA-E of the right temporal non-hippocampal, right parietal and right occipital regions, and upon review of the MRI done on Study Day 56, it was recognized that ARIA-E was present at the time of the previous MRI. The ARIA-E on MRI on Study Day 176 was unchanged compared to that from Study Day 56 and was classified as radiographically moderate in severity. The participant was asymptomatic. The event was classified as moderate in severity and nonserious. On Study Day 184, the participant came in for her early termination visit and was discontinued from the study

treatment due to ARIA-E, with the last dose (13th dose) taken on study day 176. On Study Day 205, MRI results showed a decrease in the size of ARIA-E and on Study Day 260, MRI results showed complete resolution of ARIA-E.

(b) (6)

This is a 66-year-old white female, ApoE genotype ε4/ε4, randomized to LEC10-M in 201 Core. On Study Day 76, the participant received the 6th dose of study drug. On Study Day 85, ~ week 12, 9 days after the 6th dose, the participant was diagnosed with ARIA-E in the left occipital region, on MRI. The participant did not have neurological symptoms due to the ARIA-E. No treatment was reported for this event. On Study Day 182, an MRI showed increased size of ARIA-E, which was severe in radiographic severity in the bilateral frontal, parietal and occipital regions. On Study Day 195, the participant came in for her early termination visit and discontinued the study treatment due to the event of ARIA-E, with the 13th dose (last dose) of study drug taken on Study Day 174.

Reviewer Comment: This participant was dosed through the first ARIA-E event noticed on study day 85, and continued receiving study drug until day 174, with worsening noted on the ARIA-E on MRI on study day 195.

(b) (6)

This participant is a 77-year-old white female with ApoE ε3/ε4 genotype, who was randomized to receive LEC10-M in 201 Core. On Study Day 49, the participant received the 4th dose of study drug. On Study Day 56 (week 8), 7 days after the 4th dose, the participant's MRI showed a new ARIA-E event. However, ARIA-E was not recognized at that time and the participant continued treatment with study drug. The participant was asymptomatic. On Study Day 86, the participant was found to have ARIA-E on MRI and upon review of the MRI of Study Day 56 it was recognized that ARIA-E was present earlier. The event of (ARIA-E) was classified as radiographically mild in severity and nonserious. The study drug was permanently discontinued due to the event of ARIA-E, with the 6th dose (last dose) taken on Study Day 81. No treatment was reported for this event. The event of vasogenic edema (ARIA-E) resolved on Study Day 218.

(b) (6)

This participant is a 59-year-old, white, male, ε4/ε3 carrier on 100 mg of ASA. On Study Day 71, the participant received the 6th dose of study drug. On Study Day 77 (week 11), 6 days after the 6th dose of study drug, the participant was diagnosed with ARIA-E in the right temporal, nonhippocampal, right parietal and occipital lobes, based on MRI. It was classified as radiographically moderate in severity. The participant remained asymptomatic, with a normal neurological examination. On Study Day 85, the participant was discontinued from study treatment due to ARIA-E, with the last dose taken on Study Day 71. On Study Day 103, participant's MRI revealed a decrease in right occipital edema and residual hypersignal at T2 sequences with signs of discrete subarachnoid bleeding in adjacent right occipital grove (not reported as superficial siderosis by central read of the MRI of on Study Day 103). He remained

stable and asymptomatic. On Study Day 134, the participant was diagnosed by central and local read with superficial siderosis. The event was classified as mild in severity and nonserious. No treatment was reported for the event, and participant remained asymptomatic.

Reviewer Comment: This participant had a superficial siderosis in the area where the original ARIA-E occurred 28 days after the study drug administration, and 22 days after the onset of the ARIA-E event. It is likely that the superficial siderosis is related to study drug and related to the ARIA-E that occurred earlier.

(b) (6)

This participant is a 79-year-old white male, with ApoE ε4/ε4 genotype, randomized to LEC10-M in 201 Core. On Study Day 70, the participant received the 6th dose of study drug. On Study Day 77, week 11, 7 days after the 6th dose of study drug administration, the participant was diagnosed with 3 new cerebral microhemorrhages in the right frontal lobe and ARIA-E on MRI. The event of ARIA-H was classified as mild in radiologic severity and the ARIA-E was classified as moderate in radiologic severity. The participant remained asymptomatic. No treatment was reported for the events. On Study Day 99, the participant came in for his early termination visit and was discontinued from the study treatment due to the event of ARIA-H (1st occurrence) and ARIA-E, with the last dose taken on Study Day 70. On Study Day 133, the participant underwent an MRI, and the findings included 3 new cerebral microhemorrhages in the right frontal lobe (ARIA-H; 2nd occurrence) and superficial siderosis of central nervous system (left occipital lobe) [ARIA-H]). The events were classified as mild in severity and nonserious.

Reviewer Comment: In this participant's case, additional cerebral microhemorrhages and superficial siderosis were seen 60 days after last study drug dose.

<u>Narratives of Participants who had an ARIA event in 201 Core and participated in 201 OLE:</u>

4 participants (b) (6) who had an ARIA-E (with or without ARIA-H) in the 201 Core study were enrolled in the OLE study. Two of them, (b) (6) and (b) (6), continued to have multiple ARIA events in the OLE are described below.

(b) (6)

This participant is a 77-year-old white female with ApoE ε3/ε4 genotype, who was randomized to receive LEC10-M. On Study Day 49, the participant received the 4th dose of study drug. On Study Day 56 (week 8), 7 days after the 4th dose of study drug, the participant was diagnosed with ARIA-E, based on MRI results. The participant was asymptomatic. The ARIA-E event was classified as mild radiographically in severity and nonserious. However, his ARIA-E event was not recognized at that time and the participant continued treatment with study drug. On Study Day 86, the ARIA-E was discovered on MRI and it was recognized that it had been there since Study Day 56. The study drug was permanently discontinued due to the event of vasogenic

edema (ARIA-E), with the 6th dose (last dose) taken on Study Day 81. On Study Day 218, the event of ARIA-E resolved. The participant completed continued efficacy assessment visit 42, and discontinued from the 201 Core on Study Day 547 3 years and 4 months later this participant enrolled in the Extension Phase. On Extension Day 46, she received the 4th dose of study drug. On Extension Day 57, 8 days after the 4th extension study drug dose, she was diagnosed with vasogenic edema (ARIA-E) on the right and left frontal, right parietal areas classified as moderate radiographic severity on MRI. She remained asymptomatic. On Extension Day 74 she received the 5th dose of study drug. On Extension Day 83, 9 days after the 5th dose of study drug, the MRI showed increased size of ARIA-E to right temporal, left parietal, right and left occipital lobes. She remained asymptomatic. On Extension Day 158, the participant received the 9th dose of study drug. On Extension Day 169, 11 days after the 9th dose of extension study drug dose, the MRI showed 6 cerebral microhemorrhages, with no change in ARIA-E size. On Extension Day 186, her MMSE score was 11 (her baseline at the beginning of 201 Core was 22). She received 3 doses through ARIA H and 8 doses through ARIA-E. On Extension Day 201, the MRI report showed unchanged size of ARIA-H through 13 doses of ARIA-E. On Extension Day 278, she had complete resolution of ARIA-E. She received the 57th (last dose) of study drug on Extension Day 937, due to withdrawal by participant.

(b) (6)

This participant is a 75-year-old white female who is an ApoE ε3/ε4 carrier was randomized to receive LEC10-BW in 201 Core. On Study Day 51 (9 days after the 4th dose of study drug), she had a radiographically mild ARIA-E event, and came in for early termination visit and discontinued from study treatment. She then entered the extension study 3.5 years after she discontinued from the 201 Core study. On Extension Day 41, she received the 4th dose of study drug. On Extension Day 43, two days after the 4th dose of study drug, she was diagnosed with ARIA E (2nd occurrence) classified as moderate radiographic severity based on MRI. No symptoms were reported, and no action taken with study drug. On Extension Day 69, she received the 6th dose of study drug. On Extension Day 72, the ARIA-E increased in size in the right frontal, left frontal, right temporal non-hippocampal, right parietal left parietal and right occipital regions (severe radiographic severity). She remained asymptomatic. On Extension Day 100, the ARIA-E decreased in size in the left frontal, right parietal, right and left occipital regions but remained as moderate radiographic severity. Study drug was temporarily interrupted on week 13, 15 and 17, with reduction in the ARIA E size over time. On Extension Day 128, the ARIA-E (second occurrence) resolved. An area of left occipital superficial siderosis of the nervous system was also reported which persisted for the duration of follow-up. No treatment was reported for the event. On Extension Day 168, the participant received the 10th dose of study drug. On Extension Day 170, she was diagnosed with asymptomatic ARIA-E (3rd occurrence) in the left occipital region (mild radiographic severity). No action taken with study drug. On Extension Day 198, MRI showed increase in the ARIA-E size in the left occipital region (third occurrence) (still mild radiographic severity). The participant received 2 doses through ARIA-E. On Extension Day 274 the third occurrence of ARIA-E resolved. The participant received

the 53rd dose of study drug on Extension Day 841. As of data cut off day of 31 December 2021, participant still participating in the Extension Study.

Reviewer Comment: Despite multiple ARIA-E events starting in 201 Core, the participant remained asymptomatic, and has been dosed through the ARIA-E in the OLE study, and participation is ongoing.

Isolated ARIA-H in Core and participated in OLE

8 of the 9 participants (b) (6) who had one or more isolated ARIA-H event without ARIA-E during the Core continued to participate in the OLE study. Almost all of these participants either had another ARIA-H event or had no further ARIA events. Only participant (b) (6) who received LEC5 -M in core and had a cerebral microhemorrhage in the Core study, had 3 ARIA-E, 2 ARIA-H microhemorrhage, and one ARIA-H superficial siderosis occurrence during the OLE.

Drug interruptions in OLE due to ARIA

In Study 201 OLE there were no discontinuations because of ARIA, however study drug was interrupted in 10 participants (b) (6) who experienced an ARIA event. Participant (b) (6) who had a cerebral hemorrhage > 1cm is described under the SAE narratives above.

(b) (6)

Participant is a 79-year-old woman with ε3/ε3 genotype, who was randomized to receive LEC10-M in the 201 Core study. She did not experience ARIA in 201 Core. On Extension Day 164, she received the 13th dose of study drug. On Extension Study Day 176, she was diagnosed with one new cerebral microhemorrhage and symptomatic ARIA-E (first occurrence), in the right temporal (non-hippocampal), right parietal and occipital, and left occipital regions based on the MRI results. Her symptoms included intermittent left occipital headache for 9 days. No treatment was reported, and study drug was temporarily interrupted (2 doses, weeks 27 and 29). On Extension Day 185 she was noted to have a second occurrence of ARIA-E that was asymptomatic. The study drug remained interrupted until resolution of second occurrence on extension day 211. On extension day 211 the study drug was restarted. Participant received the 29th dose of study drug on Extension Day 871, and was discontinued from study on day 871, due to participant choice.

(b) (6)

Participant is a 62-year-old white female with ε3/ε4 genotype, randomized to receive placebo in the 201-core study. She did not have ARIA-E in 201 core. On Extension Day 166, she received the 13th dose of study drug. On Extension Day 180, she was diagnosed with ARIA-E in the right frontal lobe, classified as questionable radiographically and nonserious. She did not have any

symptoms. No action was taken with study drug. On Extension Day 216, she received the 16th dose of study drug. On Extension Day 229, ARIA-E further worsened radiologically and was present in the right frontal and left frontal lobes and was still considered mild. The ARIA-E was asymptomatic. No treatment was reported for the event. The participant's MMSE scores were 25 at Core Baseline, 14 at Extension Baseline, and 17 on Extension Day 188. She received 3 infusions through the ARIA-E. The 17th dose of the study drug was temporarily interrupted due to worsening in ARIA-E. On Extension Day 257, the ARIA-E resolved. On Extension Day 288 study drug was restarted. On Extension Day 579 she received the 39th dose of study drug and discontinued from study due to MRI compliance issues.

(b) (6)

Participant is a 76-year-old male, who was not a carrier of the ε4 allele, randomized to receive LEC10-BW in 201 Core. On Extension Day 177, the participant received the 13th dose of study drug. On the same day he was diagnosed with 1 new cerebral microhemorrhage on MRI, classified as asymptomatic, mild and non-serious. Study drug was interrupted due to this event and never restarted. Participant withdrew consent from the study due to MRI findings.

(b) (6)

Participant is a 72-year-old white male with ApoE ε4/ε4 allele, who was randomized to placebo in the core study. On 201 Core Study Day 1553, and Extension Day -51, there were 6 cerebral microhemorrhages present on MRI scan. On Extension Day 55, he received the 5th dose of study drug. Same day he was diagnosed with asymptomatic ARIA-E in the right and left temporal (nonhippocampal), and left occipital lobes and cerebellum. He had > 10 cerebral microhemorrhages on MRI. Both the ARIA-E and ARIA-H microhemorrhage was classified as severe radiographically. On Extension Day 79, he received the 7th dose of study drug. On Extension Day 84, 5 days after he received the 7th dose of study drug, he had > 10 cerebral microhemorrhages classified radiographically severe. On Extension Day 90, ARIA -E worsened to severe radiographic severity and was present in the right and left frontal, right temporal and left temporal, right and left parietal, right and left occipital hippocampus and cerebellum. The participant was treated with methylprednisolone 1000 mg iv daily. Both ARIA-H and ARIA-E were associated with symptomatic worsening dizziness. Study drug was temporarily interrupted on 8th, 9th, and 10th doses and never restarted. On Extension Day 272, ARIA-E decreased in size in the right and left occipital lobes and resolved radiologically on Extension Day 407. Participant discontinued from study per participant's choice.

Reviewer comment: In this participant's case continued dosing led to worsening in ARIA- E and ARIA-H, becoming severe, and symptomatic, and requiring treatment with iv methylprednisolone. Of note is that participant's TEAEs include dizziness and confusional state started on Day 79, the day he received the 7th dose and 5 days prior to the finding of severe ARIA-H and on imaging. The applicant identified dizziness as part of clinical symptoms due to ARIA-H, and ARIA-E but his narrative is silent to confusional state.

(b) (6)

Participant is an 83-year-old white female with ε3/ε4 genotype, who was randomized to receive LEC5-M in 201 core and has been taking baby aspirin through the study. She experienced a microhemorrhage on Study Day 168 in the core study, and continued wit study medication, receiving the last dose on Study Day 532. On Extension Day 44 she received the 4th dose of study drug on. On the same day she was diagnosed with one new cerebral microhemorrhage in the frontal lobe (radiographic severity mild) and ARA-E in the right and left temporal (nonhippocampal) and left frontal lobes (moderate radiographical severity.) Both were asymptomatic. No action was taken with study drug. On Extension Day 59 she received the 5th dose of study drug. On Extension Day 66, she experienced intermittent headache and ARIA-E effusion was considered symptomatic. The event of symptomatic ARIA-E effusion was classified as radiographically moderate in severity and the event of headache was classified as mild in severity; both of these events were considered nonserious. Study drug was temporarily interrupted for week 11, 13 and 15 doses due to ARIA-E effusion. On Extension Day 72 an unscheduled MRI showed increase in the size of the ARIA-E to right and left frontal lobe, right and left temporal lobe (non-hippocampal), right and left occipital lobe, and right parietal, with an unchanged area of cerebral microhemorrhage and noted superficial siderosis in right and left frontal lobe, right and left parietal, left temporal (non-hippocampal) and left occipital (which was form of ARIA-H) based on MRI result. The event of superficial siderosis of central nervous system was classified as severe radiographically and nonserious. No treatment was reported for the event. No new action was taken with the study drug due to this event as the study drug interruption continued. On Extension Day 86, MRI showed decrease in ARIA-E. On Extension Day 96, ARIA-E resolved. Study drug interruption continued. On Extension Day 101, MRI report revealed complete resolution of ARIA-E. On Extension Day 114, drug was restarted. On Extension Day 351, the participant received the 23rd dose of study drug. On the same day she was diagnosed with 3 new cerebral microhemorrhages and worsening of superficial siderosis. She received 17 doses through the ARIA-H. The participant received the 74th dose of study drug on extension day 1064. As of 31 Dec 2021, she is ongoing in the study.

(b) (6)

This participant is a 66-year-old white male with ApoE ε4/ε4 genotype who was randomized to receive LEC5-M in 201 Core. He was taking 100 mg of aspirin during his participation. On Extension Day 43, the participant received the 4th dose of study drug. Same day he was diagnosed with radiographically moderate ARIA-E in the right and left frontal, parietal and occipital lobes, left temporal (nonhippocampal), and left hippocampus. He remained asymptomatic. No action was taken with study drug. On Extension Day 74, he received the 6th dose of study drug. On the same day MRI showed 1 cerebral microhemorrhage and increased size of ARIE-E (now radiographically severe) which included the mid brain, right and left frontal, parietal, and occipital lobes; the left temporal lobe (non-hippocampal) and the left hippocampus (in midbrain, right and left frontal, left temporal (nonhippocampal), right and left occipital (hippocampus), and right and left parietal lobes. Study drug was interrupted on weeks 13, 15, 17, 19, 21, 23, 25, 27 with last dose taken on study day 74. The participant complained

of a headache (nonserious) and was treated with ibuprofen. On Extension Day 103, an MRI showed decrease in ARIA-E size, ARIA-H remained stable. On Extension Day 165, MRI showed reduction in size of ARIA-E and stable ARIA-H. Study drug interruption continued. On Extension Day 199, ARIA-E resolved, and ARIA-H remained stable. On Extension Day 206, study drug was restarted. On Extension Day 354, the participant received the 18th dose of study drug (this would be the 12th dose considering the missed doses). On Extension Day 354, the participant was diagnosed with a second occurrence of ARIA-E in the right frontal, right and left parietal, and right and left occipital lobes, moderate severity radiographically and noted with one 1 new cerebral microhemorrhage. The participant remained asymptomatic. On Extension Day 382, MRI showed reduction in ARIA-E size and stable ARIA-H. On Extension Day 455, MRI showed 3 new cerebral microhemorrhages (total of 5) and ARIA-E had increased in the right and left frontal, right and left temporal nonhippocampal), right and left parietal, right and left occipital lobes, hippocampus, and leptomeninges (and became radiographically severe). Participant remained asymptomatic. Study drug was temporarily interrupted (weeks 65, 69, 71 and 79) due to event of ARIA-E last taken on Study Day 435. The participant had received 19 doses of study drug through ARIA-H and 7 doses through ARIA-E. On Extension Day 477, the ARIA-E had decreased in size (right and left frontal, right temporal [non-hippocampal], right parietal), and ARIA-H was stable based on MRI report. The study drug remained interrupted. Extension Day 512, the ARIA-E had decreased in size (right frontal), and ARIA-H was stable based on MRI report. The study drug remained interrupted. On Extension Day 548, the ARIA-E resolved radiologically. On Extension Day 582, the study drug was restarted. The participant received 26 doses through the occurrence of ARIA-H. The event of cerebral microhemorrhage was ongoing at the time of data cutoff of 31 Dec 2021. As of data cutoff of 31 Dec 2021, the participant was ongoing in the Extension Phase of the study with 32 doses taken during the extension phase.

(b) (6)

This participant is a 70-year-old Asian female with a ε3/ε4 genotype, who was randomized to receive placebo in Study 201 Core. She did not have ARIA in 201 Core. On Extension Day 68, she received the 6th dose of study drug. On Extension Day 70 she was diagnosed with radiographically moderate ARIA-E in the right temporal (nonhippocampal), and right occipital lobes on MRI. The participant remained asymptomatic. No treatment was reported for this event. On Extension Day 99, the ARIA-E continued to increase in size and became radiographically severe. The 7th dose of study drug was interrupted due to this. On Extension Day 161, the ARIA-E resolved on MRI. On Extension Day 187, the 7th dose of study drug was administered. On Extension Day 994 the participant received the 65th dose of study drug. As of data cutoff of 31 Dec 2021, she is ongoing in the extension phase.

(b) (6)

This participant was randomized to receive LE10-M in the 201 Core study. This participant did not have ARIA in 201 core. A cerebral microhemorrhage was identified 49 days prior to the first dose of the study drug in the extension study. On Extension Study Day 75, 4 days after the 6th dose in the extension phase, the participant was diagnosed with ARIA-E in the right parietal,

occipital and non-hippocampal temporal lobes, which was radiographically rated as moderate in severity. The participant remained asymptomatic. While the narrative is silent to action taken with study drug, according to the ADAE dataset, the study drug was interrupted for 8 doses. On Extension Study Day 163, the vasogenic edema completely resolved radiographically. The participant received the 20th dose of study drug on Extension day 365 and withdrew from the study due to progression of AD symptoms.

Participants who were dosed through ARIA-E in 201 OLE without drug interruption

(b) (6)

This participant received LEC5-BW in 201 Core, had ApoE ε4/ε4 genotype, and no ARIA in 201 Core, had radiographically mild ARIA-E 1 day after the 22nd study dose in the extension study. She remained asymptomatic, and received 6 doses through ARIA-E until resolution of ARIA-E. She completed the 58th dose as of the 120-day cut off period in the Extension phase without further ARIA-E occurrence.

(b) (6)

This participant carried the ApoE ε4/ε4 genotype, received LEC5-M and did not have ARIA in in 201 Core. Eighteen days after the 12th dose of study drug in the extension phase had a radiographically mild ARIA-E and new superficial siderosis. She remained asymptomatic and received 3 doses through ARIA-E until radiographic resolution. She received a total of 15 doses in the extension study, and discontinued due to other health reasons.

(b) (6)

This participant carries a ApoE ε3/ε4 genotype, received placebo in 201 Core and did not have ARIA in 201 Core. The participant had ARIA- E 8 days after the 4th dose in the extension phase. She remained asymptomatic. The ARIA-E increased in size over 20 days, however continued to be dosed, and received 5 doses through the ARIA-E event, until radiographic resolution. As of the 120-day cut off, she has received 79 doses without any further ARIA-E events.

(b) (6)

This participant carried ApoE ε3/ε4 genotype, received LE10-M and did not have ARIA in 201 Core, and was discontinued from 201 Core early due to being started on apixaban. She experienced a radiographically moderately severe ARIA-E and ARIA-H microhemorrhage, diagnosed on the same day that she received the 6th dose. She remained asymptomatic and received two more doses until participant declined to continue participation

(b) (6)

Participant who carried an ε3/ε4 genotype, received LE10-M and did not have ARIA in 201 Core. This participant experienced a radiographically moderate ARIA-E event on Extension Day 72, one day after the 6th dose of study drug in the extension n phase. She remained asymptomatic and received three doses through the study drug. ARIA-E resolved on Extension Day 120. On

extension day 167, 9 days after the 13th dose of study drug, the participant had a second occurrence of ARIA-E, which was classified as mild radiographically. No action was taken with study drug, and participant was asymptomatic, and received 2 doses through ARIA-E. This resolved radiologically on Extension Day 199. The participant received the 66th dose of study drug without further instances of ARIA-E.

(b) (6)

Participant (b) (6), had an ApoE ε3/ε4 genotype received LE10-M . This participant had ARIA-E, of mild radiographic severity, after the 4th dose of study drug in 201 Core, and because it was not recognized initially, received 2 more doses before being discontinued per protocol in 201 Core. 8 days after the 4th dose on Extension Day 56 the participant had a mild radiographic severity ARIA-E, which was asymptomatic. She received the 5th dose of study drug on study day 74, and 9 days later there was an increase in the size of the ARIA-E (moderate radiographic severity), She received the 9th dose of study drug on Extension Day 158 and 11 days later MRI showed 6 ARIA-H microhemorrhages, and unchanged ARIA-E. No action was taken with study drug, and participant received 8 doses through ARIA-H and 13 doses through ARIA-E. On Extension Day 279 ARIA-E was resolved. The participant received 57 doses prior to withdrawing from the study.

Table 82 Multiple ARIA-E Events or worsening in original ARIA-E in 201 OLE

Participant ID ApoE status	201 Core study drug arm	# of recurrent ARIA-E events or worsening in first ARIA-E in the open label extension phase	Radiographic Severity	Action Taken with Study Drug	Symptomatic	Outcome
(b) (6) E3/E4	Placebo	First ARIA-E after 13th dose then radiographic worsening in existing ARIA-E after 16th dose	Questionable Mild	Dose not changed after 1st occurrence of ARIA-E (received 3 doses) Drug interrupted after radiographic worsening of existing ARIA-E	Asymptomatic	Discontinued per participant request after second ARIA-E
(b) (6) E3/E4	LE10-M (No ARIA-E in Core)	2 separate occurrences of ARIA-E (after the 6th and the 13th dose)	Moderate Mild	Dose not changed (received 3 doses through first ARIA-E and 2 doses through second ARIA-E)	Asymptomatic	Received 66 doses as of December 31, 2021, participation ongoing
(b) (6) E3/E4	LE10-M (Had ARIA-E in 201 Core)	First ARIA-E event after the 4th dose with radiographic worsening after the 5th dose	Moderate (Both)	Dose not changed1 dose through first ARIA-E and 12 doses through increased ARIA-E	Asymptomatic	Received 57 doses in the OLE and then discontinued from study.
(b) (6) E4/E4	Placebo (No ARIA-E in Core)	First ARIA-E event after the 5th dose then radiographic worsening after the 7th dose with new clinical symptoms	Moderate ARIA-E evolved to Severe	After 1st ARIA-E dose not changed received 2 doses then after worsening in existing ARIA-E with new occurrence of	Worsening Dizziness after worsening ARIA-E and occurrence severe ARIA-H microhemorrhage	Recovered after methyl prednisone treatment and holding dose. Drug not restarted

				severe ARIA-H and new clinical symptoms drug suspended		
(b) (6) E3/E4	LEC2.5-BW ARIA-H microhemorrhage in 201 Core)	First ARIA-E after the 4th dose, and after the 5th dose existing ARIA-E became symptomatic with headache and repeat imaging showed increase in size of ARIA-E	Moderate (All)	Study drug not interrupted after the 1st ARIA-E after the 5th dose with increase in ARIA-E size and new symptoms, study drug interrupted	Intermittent Headaches started with continued dosing after the 5th dose	Received 2 doses through initial ARIA-E/ARIA-H, then dose held for three doses, then resumed, as of cut of December 31, 2022 ongoing with 74 doses received.
(b) (6) E3/E4	LEC10-BW ARIA-E in 201 Core	First ARIA-E after the 4th dose, worsening in severity of existing ARIA-E after 6th dose, and Second occurrence of ARIA-E after 10th dose	1st ARIA-E moderate became severe after 6th dose) 2nd ARIA-E mild radiographic severity	1st ARIA-E dose not changed drug interrupted after worsening of existing ARIA-E after 6th dose, dose not changed for second ARIA-E after 10th dose	Asymptomatic	Received 2 doses through the first ARIA-E and 4 doses were held with worsening of existing ARIA-E. Dosing continued after the second ARIA-E. Participation ongoing with 53 doses received as of December 31, 2022.
(b) (6) E4/E4	LEC5-M No ARIA-E in Core	First ARIA-E after 4th dose, worsening in ARIA-E after 6th dose, Second occurrence of ARIA-E after 18th dose,	1st ARIA-E moderate and became severe after 6th dose, second occurrence of ARIA-E moderate severity after 18th dose which became severe on follow up MRI	After 1st ARIA-E dose not changed After worsening of the first ARIA-E drug interrupted, last ARIA-Es drug interrupted.	Headache after worsening of ARIA-E after the 6th dose	Dose continued after first ARIA-E, interrupted for 9 doses with worsening in ARIA-E after 6th dose, then resumed, Interrupted again after second occurrence of ARIA-E worsened Had received 32 doses and participation ongoing as of December 31, 2021.

12.1.4 Narratives of participants with low lymphocyte count in Study 201 Core

Of the participants who had low absolute lymphocyte counts at week 1 post-infusion, 6/62 (10%) had recurrent low lymphocyte count at subsequent visits: two participants had one more subsequent low lymphocyte count occurrence (b) (6) two had occurrence of two more low lymphocytes (b) (6) one participant had 5 occurrences (b) (6) and participant (b) (6) had ten additional low lymphocyte values. 2 of these participants had low lymphocyte counts at screening or baseline.

Of the participants receiving LEC10-BW, 4 (b) (6) had a low lymphocyte count at Visit 42 (week 79) which was 2 weeks after the last dose, and two participants had low lymphocyte count at the week 90 /follow up visit (b) (6) Participant (b) (6), had normal screening and baseline lymphocyte values, and only had a value under 0.9 at visit 42 week 79 (0.7). He ranged between 1.8 to 3.7 between visit 3 and visit 16, and between visit 16-visit 42 values dropped to ~1, with the visit 42 value being 0.7. Participant (b) (6) started out with normal lymphocyte count at screening and baseline, and dropped to 0.8 at the visit 3 week 1 visit (after the first infusion), and then ranged between 0.8-1.2 between visits 4-42, ending with a low value of 0.8 at visit 42, and 1 (normal) at the week 90 follow up. Participant (b) (6) had normal lymphocyte counts at screening and baseline, had a drop to 0.5 at the visit 3 week 1(after the first infusion), then ranged between 0.7 to 1.3 between visit 4 to visit 42, ending with low lymphocyte count of 0.7 at week 42, and 0.8 at the week 90 follow up visit .

Reviewer Comment: In summary of the 4 participants with low lymphocyte counts 2 weeks after the last dose of study drug only 2 had a normal baseline (b) (6), and (b) (6) had normal screening and baseline lymphocyte counts, with subsequent drop post infusion at visit 3, week 1 (after the first infusion) and afterwards ranged between ~0.7-1.3, between the week 3 to week 79 visit but ending with a low lymphocyte count. It is possible that in these two cases, the low lymphocyte count is related to study drug.

Of the total 160 participants in the LEC10-BW arm who had a hematology assessment for absolute neutrophil count at visit 3, post infusion 35/160 (22 %) had elevated neutrophil count. Of these 10/35 had recurrent neutrophilia, in 7/35 there was only one more subsequent occurrence of neutrophil elevation, in one participant (b) (6) there were two subsequent occurrences, and two participants participant (b) (6) had three occurrences. In all of these cases the elevation was mild ranging between 8-10.1 $x10^9$/L. Participant (b) (6) who had the highest value of neutrophil count (12.8 $x10^9$/L) at the visit 3 assessment, had normal neutrophil counts for the rest of their study participation.

Participant (b) (6) had a lymphocyte count of 1.3 at screening, 0.8 at baseline, 0.7 at visit 3 post infusion, and after visit 3 lymphocyte counts ranged between 0.6-1.2, ending with 1.2 at the week 90 follow up.

Participant (b) (6) had 10 separate occurrence of low lymphocytes through the study, and also was one of the two participants (in addition to (b) (6)) who had the lowest lymphocyte count at visit 3 (after first infusion). This participant had the following lymphocyte trajectory: a low lymphocyte count at 0.7 at screening (visit 1), 0.9 at baseline (visit 2), 0.1 post infusion on visit 3 (week 1), 1.2 at visit 4 (week 3), and ranged between 0.7-0.8 for the remainder of the time ending with a low lymphocyte count of 0.7 at visit 90.

Participant (b) (6), who started with a normal lymphocyte count, had a lymphocyte count of 1.2 at screening, 1.9 at baseline (visit 2 Day), and 0.1 on Visit 3 (week 1), followed by increase back up to 1.7 at visit 4 (week 4) and ranged between 1.6-2.4 for the rest of the study.

Reviewer Comment:
The two participants in the LEC10 BW arm, who had 5 or more occurrences of low lymphocytes during the 201 Core study both had a low lymphocyte value prior to study drug administration.

Participant (b) (6) who was randomized to receive LEC5-BW in 201 Core, had reduced lymphocyte count after the first infusion in 201 Core on Study Day 1 (baseline: 1.1 $x10^9$/L, post dose: 0.6 $x10^9$/L) which was identified as a TEAE and normalized by Day 7. She had two more occurrences of low lymphocytes during her participation in Study 201 Core (0.8 x 10^9 /L on Study Day 268, and Study Day 455, with normal values at all other times). She finished 201 Core with normal lymphocyte count (1.1 x 10^9 /L). During her participation in the 201 OLE, she had one incident of low lymphocyte count occurring on Study Day 85 at the time of her 7th infusion (0.8 x 10^9 /L) and remained in the normal range until visit 96 in the extension phase.

12.1.6. Management of Infusion Related Reactions in Study 201 Core

The following are treatment guidelines in the protocol for management of infusion reactions in 201 Core:

Grade 2: Stop the infusion. Administer diphenhydramine hydrochloride 25 to 50 mg orally (PO) or dexamethasone 10 mg intravenously (IV) and acetaminophen 650 mg to 1 g PO. (revised per Amendment 06) The investigator may also use other antihistamines, corticosteroids, and anti-inflammatory drugs as per local treatment guidelines. If the infusion reaction improves or resolves, infusion may be resumed if the investigator considers it safe to do so in his/her clinical judgment. If so, then resume the infusion at 50% of the prior rate once the infusion reaction has resolved; the infusion duration should not exceed 2 hours. Monitor for worsening of condition. (revised per Amendment 06).

For subsequent infusions, the investigator should consider premedicating with diphenhydramine hydrochloride 25 to 50 mg (PO or IV), dexamethasone (10 mg IV) and acetaminophen 650 mg to 1 g orally. Other antihistamines, corticosteroids, and anti-inflammatory drugs as per local treatment guidelines may be used as alternatives. Use of dexamethasone or any other corticosteroids for premedication should be done with caution. (revised per Amendment 06) The investigator should consider administering infusions at 50% of the original study rate. If a subject does not experience infusion reactions upon the next several administrations, the investigator may stop premedicating the subject and may increase the infusion as per original study rate for subsequent infusions.

Grade 3: Stop the infusion and disconnect the infusion tubing from the subject. Administer diphenhydramine hydrochloride 25 to 50 mg PO or IV, dexamethasone 10 mg IV (or equivalent), acetaminophen 650 mg to 1 g orally, bronchodilators for bronchospasms, and IV fluids for hypotension. Administer other medications/treatments as medically indicated. Hospital admission for observation may be indicated. (revised per Amendment 06) Discontinue subject from study drug and conduct an Early Termination Visit within 7 days of discontinuation and a Follow-up Visit 3 months later. (revised per Amendment 01)

Grade 4: Stop the infusion and disconnect the infusion tubing from the subject. Administer diphenhydramine hydrochloride 25 to 50 mg PO or IV dexamethasone 10 mg IV (or equivalent), and acetaminophen 650 mg to 1 g orally, bronchodilators for bronchospasm, IV fluids and IV adrenaline for hypotension. Administer other medications/treatments as medically indicated. Hospital admission for treatment is likely indicated. Discontinue subject from study drug and conduct an Early Termination Visit within 7 days of discontinuation and a Follow-up Visit 3 months later. (revised per Amendment 01)

12.2. References

See in text references

12.3. Financial Disclosure

See clinical efficacy review by Dr. Kevin Krudys for Financial Disclosures.

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/

DENIZ ERTEN-LYONS
01/05/2023 09:24:48 PM

RANJIT B MANI
01/06/2023 08:18:33 AM

SALLY U YASUDA
01/06/2023 08:54:42 AM

Clinical Review
Kevin Krudys, PhD
BLA 761269
Leqembi (lecanemab)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761269
Priority or Standard	Priority
Submit Date(s)	09/27/2021, 12/14/2021, 05/06/2022
Received Date(s)	05/06/2022
PDUFA Goal Date	01/06/2023
Division/Office	Division of Neurology 1/Office of Neuroscience
Reviewer Name(s)	Kevin Krudys, PhD
Review Completion Date	01/05/2023
Established/Proper Name	Lecanemab
(Proposed) Trade Name	Leqembi
Applicant	Eisai Inc.
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	10 mg/kg as an intravenous infusion every two weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of early Alzheimer's disease (mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s)	Treatment of Alzheimer's disease

Table of Contents

Table of Tables

Table of Figures

Glossary

Aβ	amyloid beta
AC	advisory committee
AD	Alzheimer's disease
AE	adverse event
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
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
CDER	Center for Drug Evaluation and Research
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
CSS	Controlled Substance Staff
DIAD	dominantly inherited Alzheimer's disease
DMC	data monitoring committee
DSMB	Data Safety Monitoring Board
eCTD	electronic common technical document
ED_{90}	dose regimen that achieves at least 90% of the treatment effect at the maximum effective dose
FAQ	Functional Assessment Questionnaire
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IgG1	immunoglobulin G1

IMC	Interim Monitoring Committee
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ITT	intent to treat
LS	least square
MCI	mild cognitive impairment
mITT	modified intent to treat
MMRM	mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NfL	neurofilament light chain
NIA-AA	National Institute on Aging at the National Institutes of Health and the Alzheimer's Association
NME	new molecular entity
OCS	Office of Computational Science
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PET	Positron Emission Tomography
PI	prescribing information or package insert
PK	pharmacokinetics
PKPD	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
RAR	response adaptive randomization
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
SUVR	standard uptake value ratio
vMRI	volumetric magnetic resonance imaging
WMS-IV LM II	Wechsler Memory Scale-IV Logical Memory (subscale) II

1. Executive Summary

1.1. Product Introduction

Lecanemab (previously BAN2401) is a humanized immunoglobulin G1 (IgG1) anti-amyloid beta (Aβ) monoclonal antibody targeting aggregated forms of Aβ. Extracellular deposits of Aβ are one of the two pathological hallmarks of Alzheimer's disease, along with intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Different Aβ species are defined by their size and structure and include monomers, oligomers and protofibrils, and insoluble fibrils and plaques. Accumulation of Aβ in the brain has been proposed to be an important part of the disease process which precedes neurodegeneration and clinical decline. Lecanemab reduces levels of brain Aβ plaque by targeting aggregated forms of Aβ, with highest affinity for large soluble protofibrils.

The applicant's proposed indication is for the treatment of early Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia, with confirmed amyloid pathology). The application is submitted for accelerated approval based on reduction of amyloid beta plaques. The dosing regimen is an intravenous infusion of 10 mg/kg lecanemab over approximately one hour, administered once every two weeks with no titration. Lecanemab is available as a 100 mg/mL solution in a single-dose vial for intravenous infusion.

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support accelerated approval. The applicant provided biomarker, efficacy, and safety data from a single adequate and well-controlled study that demonstrated that lecanemab, as compared to placebo, robustly reduced brain amyloid plaque in patients at the early stages of symptomatic Alzheimer's disease. The Division has previously determined in the review of aducanumab that such a reduction in amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. The observed effects of lecanemab on clinical endpoints in the study contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lecanemab is an anti-amyloid beta (Aβ) monoclonal antibody targeting aggregated forms of Aβ, with highest affinity for large soluble protofibrils, and developed to treat patients with Alzheimer's disease. This reviewer recommends accelerated approval based on biomarker, 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. Acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine are approved therapies, but they do not target the underlying pathology of the disease and their effects are modest and short-lived. Aducanumab is an amyloid beta-directed antibody that was approved under the accelerated approval pathway based on reduction of brain amyloid plaque as measured by ^{18}F-florbetapir positron emission tomography (PET) for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment (MCI) or mild dementia stage of disease, but its use to date is limited. There remains an urgent and unmet medical need for additional effective treatments for Alzheimer's disease, and a particular unmet need for effective therapies to delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease.

This submission contains biomarker, efficacy, and safety data from Study 201, 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 included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. For the placebo-controlled period, patients were randomized to placebo or one of 5 lecanemab dosing regimens, including the intended dosing

regimen of 10 mg/kg biweekly. The primary clinical endpoint was the change from baseline in a cognitive composite measure, Alzheimer's Disease Composite Score (ADCOMS), at Week 53. Change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of patients at Week 53 and Week 79 and serves as the endpoint to support accelerated approval.

Lecanemab reduced brain amyloid plaque in a dose- and time-dependent manner. The lecanemab 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$). The primary analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%. Prespecified analyses of data at Week 79 suggested reduced decline on clinical endpoints by approximately 20% to 40%.

The primary safety event identified in the clinical trial is amyloid-related imaging abnormalities (ARIA) which represent a spectrum of imaging findings on brain MRI, including 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 accelerated approval pathway is appropriate for lecanemab because Alzheimer's disease is clearly a serious and life-threatening disease, and lecanemab has the potential to address an unmet medical need and provide an advantage over available therapy. Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit. Lecanemab treatment results in a robust and statistically significant reduction in brain amyloid plaque with a magnitude that the Division has concluded to be reasonably likely to predict clinical benefit. The effects on amyloid are persuasive and consistent across doses and subgroups, supporting the ability of Study 201 to be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness.

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 years and older are currently living with Alzheimer's disease. • Alzheimer's disease is the sixth leading cause of death in the United States. • Almost two-thirds of Americans with Alzheimer's disease are women. Older African Americans and Latinos are disproportionately more likely to have Alzheimer's disease than White Americans.	Alzheimer's disease is a major public health issue which imposes an immense burden on patients and caregivers. The number of Americans with Alzheimer's disease dementia is expected to increase significantly in the next few decades.
Current Treatment Options	• FDA-approved therapies include the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate receptor antagonist memantine. Treatment effects of these therapies are modest and transitory. • Antipsychotics are commonly prescribed to treat behavioral	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	symptoms but are not approved for the treatment of Alzheimer's disease and are associated with increased mortality in older patients. • Aducanumab is an amyloid beta-directed antibody approved under the accelerated approval pathway and indicated for the treatment of Alzheimer's disease, specifically patients with mild cognitive impairment or mild dementia stage of disease.	reverse the pathophysiological processes that ultimately lead to the clinical deficits of Alzheimer's disease. Aducanumab is an effective treatment option in patients at earlier stages of the disease, but its use remains limited.
Benefit	• The efficacy of lecanemab in patients at the early stages of symptomatic Alzheimer's disease was evaluated in Study 201: ○ Participants were randomized to receive placebo or a range of lecanemab dosing regimens. ○ The trial enrolled 856 patients: 609 in lecanemab treatment arms and 247 in the placebo arm. ○ The primary endpoint was the change from baseline in ADCOMS. The ADCOMS is a weighted linear combination of items from 3 commonly used scales: ADAS-Cog, MMSE, and CDR-SB. ADAS-Cog and CDR-SB were key secondary endpoints. ○ Change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR was assessed in a subset of patients and listed as a key secondary endpoint in the protocol. • Lecanemab reduced brain amyloid plaque in a dose- and time-dependent manner. Brain amyloid plaque showed a reduction from 1.37 SUVR (78.0 Centiloids) at baseline to 1.07 SUVR (5.5 Centiloids) at Week 79 in the 10 mg/kg biweekly arm, compared to a value of 1.40 SUVR (84.8 Centiloids) at baseline and 1.40 SUVR (85.8	The applicant has demonstrated a robust and statistically significant treatment-related reduction in brain amyloid plaque in patients at the early stages of symptomatic Alzheimer's disease. The decrease in brain amyloid plaque demonstrated for lecanemab is consistent with the reduction established for aducanumab, a drug that received accelerated approval based on a conclusion that the decrease in brain amyloid plaque was reasonably likely to predict clinical benefit. The observed effects of lecanemab on clinical endpoints in the study contributed to the reasonable likelihood that a lowering of amyloid beta plaque will result in clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Centiloids) at Week 79 in the placebo arm. The lecanemab 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; p<0.001). • The primary Bayesian analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%. • The 10 mg/kg lecanemab treatment regimen demonstrated favorable numerical results for CDR-SB and nominal statistical significance for ADCOMS and ADAS-Cog 14 at Week 79.	
Risk and Risk Management	• Refer to safety review by Dr. Erton-Lyons.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		[Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☒	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)		
☒	Patient experience data that were not submitted in the application, but were considered in this review:			
		☒	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 years 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 noted 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 years 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 pathological 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 on 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 Aβ, or plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Accumulation of Aβ in the brain has been proposed to be the primary driver of the disease process and precedes the accumulation of tau pathology and neural degeneration. Consequently, therapies to inhibit Aβ production or enhance Aβ clearance have been investigated in an attempt to slow or halt the disease process. Importantly, "anti-amyloid" therapies are not a distinct class of drugs, but rather reflect many different modes of action. A careful examination of anti-Aβ therapies has revealed that for therapies targeting aggregated forms of Aβ there exists a relationship between reduction of brain amyloid plaque and reduction of clinical decline.

Some anti-Aβ monoclonal antibodies, including lecanemab, 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

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. Approved Alzheimer's disease treatments include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Aducanumab was approved using the accelerated approval pathway on June 7, 2021, and is the first approved therapy to target the underlying pathology of the disease.

There remains 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.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lecanemab 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 105081 for lecanemab (previously BAN2401) was opened in the United States on June 30, 2010, for the treatment of Alzheimer's disease following a pre-IND meeting between the applicant and FDA on June 12, 2009. Relevant regulatory interactions between FDA and the applicant include the following:

- November 6, 2012 – An End of Phase 2A Meeting was held. The meeting included a discussion of the proposed Study BAN2401-G000-201 (Study 201), including dosing, study population, the use of Bayesian analysis and response adaptive randomization, and the use of Alzheimer's Disease Composite Score (ADCOMS) as the primary clinical endpoint. The Division viewed Study 201 as proof-of-concept, but noted that it could, depending on the results, help provide confirmatory evidence.

- October 9, 2018 - The results of Study 201 were discussed at an End of Phase 2 Meeting. The Division expressed concerns with the applicant's interpretation of the clinical efficacy data and advised the applicant that the information at that time did not support accelerated or standard approval of lecanemab. The Division also expressed an openness to further discussion of the concerns raised at the meeting. There was little discussion of the Phase 3 study design, but the Division disagreed (b) (4)

- December 3, 2020 – In written responses, the Division agreed with the applicant's plan to increase enrollment in Study 301 in response to the impact of the COVID-19 pandemic. The applicant was also referred to the FDA 2020 Guidance for Industry entitled "Statistical Considerations for Clinical Trials During the Covid-19 Public Health Emergency."

- June 21, 2021 – Lecanemab was granted Breakthrough Therapy designation for the treatment of Alzheimer's disease.

- September 10, 2021 – A Type B meeting was held to discuss the contents of a BLA for accelerated approval. The Division agreed that a rolling submission was acceptable, and that Study 301 may serve as a confirmatory clinical trial to verify the clinical benefit of lecanemab.

- September 17, 2021 – The applicant opened BLA 761269 and submitted nonclinical information.

- May 6, 2022 – BLA submission complete.

3.3. Foreign Regulatory Actions and Marketing History

Lecanemab 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 three clinical sites. Site selection was based on risk ranking in the clinical investigator site selection tool, number of subjects with amyloid PET scan data, and history of prior inspections. The review concludes that Study 201 appears to have been conducted adequately and the data generated by the sites inspected appear acceptable in support of the respective indication.

4.2. Product Quality

Please see the Office of Pharmaceutical Quality (OPQ) review for any issues related to product quality.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

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

4.5. Clinical Pharmacology

The clinical pharmacology review team has concluded that the effectiveness of lecanemab is supported by exposure-response relationships from Study 201 on primary and secondary clinical endpoints and biomarkers. At 18 months after the initiation of treatment, higher lecanemab average plasma concentration at steady state (Cavg,ss) was correlated with larger magnitude of decrease in amyloid PET SUVR. In addition, an association was observed between lecanemab pharmacokinetic (PK) exposures and slowing of clinical decline.

No dose adjustment is recommended based on intrinsic and extrinsic factors. No significant effects of anti-drug antibody (ADA) titer, age, race, liver enzymes, creatinine clearance, and ApoE ε4 carrier status on lecanemab clearance were observed. Sex, body weight, albumin, and ADA status were found to impact lecanemab exposure, but not to a clinically significant extent to warrant dose adjustment.

The review notes that the assays used to measure anti-lecanemab antibodies were subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation and recommends that improved assays be developed. The review team also noted that the bioanalysis method validations for β-amyloid and p-tau 181 in plasma and cerebrospinal fluid (CSF) did not comply with recommendation in the FDA Bioanalytical Method Validation guidance, thus impacting the interpretability of biomarker data.

Based on internal discussion with OBP, it was concluded that the bridging between the clinical and commercial formulations is adequate.

The review team recommends accelerated approval.

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

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

One clinical study was pertinent to the evaluation of efficacy and is presented in Table 1.

Table 1: Tabular Presentation of the Clinical Study Contributing Efficacy Data 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
Controlled Studies to Support Efficacy and Safety							
BAN2401-G000-201 (Study 201)/NCT01767311	Bayesian adaptive randomization, double-blind, placebo-controlled, parallel group, dose ranging	IV infusion over one hour <u>Placebo</u> Saline infusion biweekly <u>Lecanemab</u> • 2.5 mg/kg biweekly • 5 mg/kg monthly* • 5 mg/kg biweekly • 10 mg/kg monthly* • 10 mg/kg biweekly *to maintain the blind, patients in the monthly dosing groups received blinded placebo infusions 2 weeks before and after administration of lecanemab	<u>Primary</u> Change from baseline in ADCOMS at 12 months <u>Secondary</u> Change from baseline in brain amyloid by PET, ADCOMS, CDR-SB, ADAS-Cog14, CSF biomarkers, and total hippocampal volume at 18 months	18-month treatment period 3-month follow-up period Enrollment in OLE after mean off-treatment period of 2 years	856	MCI due to Alzheimer's disease or mild Alzheimer's disease dementia CDR global score of 0.5 to 1.0 and memory box score ≥ 0.5 MMSE score ≥ 22 (except upper limit of 28 in certain countries) Positive amyloid load by PET or CSF 50 to 90 years of age	117 centers in 11 countries

5.2. Review Strategy

Study 201 serves as the single study to support the accelerated approval of lecanemab. Although listed as a key secondary endpoint in the protocol, change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR is proposed as the surrogate endpoint that is reasonably likely to predict clinical benefit, and is therefore the focus of this review. The clinical efficacy endpoint results are reviewed in the context of whether they support the likelihood of the surrogate to predict clinical benefit, rather than whether they directly provide substantial evidence of effectiveness of clinical benefit for full approval.

During the course of this review the topline results of the confirmatory study, Study 301, were publicly announced by the applicant. The data from Study 301 have not been submitted to this BLA and are not reviewed here. The topline results, however, certainly provide important context for this review and for the reasonable likelihood of reduction of brain amyloid plaque to predict clinical benefit. Specifically, the positive results of Study 301 appear to be consistent with the results of Study 201 and what is already known about the relationship between brain amyloid plaque reduction and effect on clinical endpoints.

The acceptability of a reduction in brain amyloid plaque to serve as a surrogate endpoint that is reasonably likely to predict clinical benefit has been addressed in the review of aducanumab and is therefore not reconsidered here. It is important to note, however, that the topline results from both the lecanemab and gantenerumab programs appear to be entirely consistent with the relationship between plaque reduction and change in clinical endpoints that was established in the aducanumab review.

This review focuses solely on clinical efficacy. This application is being reviewed separately for safety by Dr. Erten-Lyons.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 201 (BAN2401-G000-201) A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-Finding Study, with an Open-Label Extension Phase to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease

6.1.1. Study Design

Overview and Objective

Study 201 was a dose regimen-finding study in patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's disease dementia. The primary objective of the study was to evaluate the efficacy of lecanemab by establishing the simplest dose regimen that achieved at least 90% of the treatment effect at the maximum effective dose (ED_{90}) as assessed by the Alzheimer's Disease Composite Score (ADCOMS) at 12 months. Safety and tolerability of lecanemab in this patient population were also defined as primary objectives.

Trial Design

Study 201 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. A total of 117 centers across 11 countries in North America, Europe, and Asia enrolled patients into the trial. The study employed Bayesian response adaptive randomization, which allows for interim analyses during the study to update randomization allocation based on clinical endpoint results. Randomization was stratified by clinical subgroups (MCI due to Alzheimer's disease and mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), and ongoing treatment with concurrent medications for treatment of Alzheimer's disease. The study included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. For the placebo-controlled period, patients were randomized to placebo or one of 5 lecanemab dosing regimens according to the response adaptive randomization algorithm.

An open-label extension (OLE) phase of the study was initiated after analysis of the placebo-controlled portion of the study. Patients meeting the inclusion/exclusion criteria for the OLE and opting to enroll received lecanemab 10 mg/kg biweekly. The gap period in which patients were off treatment between the placebo-controlled portion and the OLE ranged from 9 to 59 months, with a mean of 24 months.

Diagnostic Criteria

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; McKhann et al. 2011) and were required to have evidence of brain Aβ pathology by either visual read of a positron emission tomography (PET) scan or CSF assessment of $A\beta_{1-42}$.

Key Inclusion Criteria

1. Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory (subscale)

II (WMS-IV LMII), as follows:
   a. ≤15 for age 50 to 64 years
   b. ≤12 for age 65 to 69 years
   c. ≤11 for age 70 to 74 years
   d. ≤9 for age 75 to 79 years
   e. ≤7 for age 80 to 90 years
2. CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater
3. Male or female patients age 50 to ≤90 years
4. Positive amyloid pathology by either visual read of PET or CSF assessment
5. Mini-Mental State Examination (MMSE) score ≥22 (except in the United Kingdom, Spain, Germany, Sweden, France, and the Netherlands where MMSE was to be ≥22 and ≤28)
6. Patients receiving cholinesterase inhibitors or memantine or both must be on stable dose for at least 12 weeks
7. Must have a caregiver/informant who spends at least 8 hours per week with the patient and is available for the duration of the study

Key Exclusion Criteria

1. Any neurological condition (other than Alzheimer's disease) which may be contributing to cognitive impairment
2. History of transient ischemic attacks, stroke, or seizures within the previous year of screening
3. Any psychiatric diagnosis or symptoms that could interfere with study procedures
4. Contraindications to MRI scanning
5. Evidence of clinically significant lesions that could indicate a dementia diagnosis other than Alzheimer's disease on brain MRI
6. Brain MRI performed at screening that shows evidence of any of the following: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, vasogenic edema, cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease or space occupying lesions or brain tumors
7. Any immunological disease which is not adequately controlled or requires treatment with biological drugs
8. Bleeding disorder that is not under control
9. Uncontrolled Type 1 or Type 2 diabetes or hypertension
10. History of uncontrolled cardiovascular disease within 6 months of screening
11. Participation in a clinical study involving any new chemical entities for Alzheimer's disease within 6 months of screening
12. Use of anticoagulants

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

Dose selection was based on pharmacokinetic-pharmacodynamic (PKPD) modeling of Aβ aggregate brain reduction in mice and safety and PK data from the initial combined single ascending dose and multiple ascending dose study. Briefly, PKPD analysis relating CSF concentrations to Aβ aggregate reduction in Tg-APP ArcSwe mice was used to derive a CSF IC_{50} value. PK data from the single ascending and multiple ascending dose cohorts were used to predict doses which would produce CSF exposure in excess of the IC_{50}. Biweekly dosing (2.5 mg/kg, 5 mg/kg, and 10 mg/kg) appeared to be the focus of exploration, but more convenient monthly dosing regimens (5 mg/kg and 10 mg/kg) were also included in the study.

Study Treatments

IV infusions of lecanemab or placebo were administered over approximately 60 minutes. Patients were randomized to receive placebo or 1 of 5 lecanemab treatment regimens, including 3 arms with biweekly (once every 2 weeks) dosing (2.5, 5, and 10 mg/kg) and 2 arms with monthly (once every 4 weeks) dosing (5 and 10 mg/kg). To maintain the blind, patients assigned to once every 4-week dosing regimens also received placebo infusions at intervening 2-week time points.

Initially, infusions were to take place at the clinical site followed by an option for home infusion. Due to logistical reasons, the home infusion option was no longer allowed under Protocol Amendment 7.

During the study the Data Safety Monitoring Board (DSMB) recommended that the 10 mg/kg biweekly dose no longer be administered to homozygous ApoE ε4 carriers due to emerging data from the study indicating a higher risk of ARIA in these patients. This modification was implemented in Protocol Amendment 4. Following discussion with European Health Authorities, it was decided that all ApoE ε4 carriers (homozygous and heterozygous) should no longer be administered lecanemab 10 mg/kg biweekly. Per Protocol Amendment 5 all ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg biweekly for 6 months or less were discontinued from study drug and newly enrolled ApoE ε4 carriers were randomized to placebo or a lecanemab dose other than 10 mg/kg biweekly. Patients who were randomized to the 10 mg/kg biweekly dosing regimen and had been on treatment for more than 6 months were allowed to continue in the study at that dose.

All patients in the OLE received open-label lecanemab 10 mg/kg biweekly, including patients who were ApoE ε4 carriers.

Reviewer Comment: The modifications implemented in Protocol Amendments 4 and 5 led to the discontinuation of study drug in 25 patients and resulted in a stark imbalance in the proportion of ApoE ε4 carriers in the 10 mg/kg biweekly arm compared to other arms, thus complicating the interpretation of clinical endpoint results in this treatment arm.

Assignment to Treatment

Bayesian response adaptive randomization (RAR) was used to allocate patients to placebo or lecanemab treatment. The first 196 patients were randomized with a ratio of 4 to placebo and 2 to each of the 5 active lecanemab treatment arms (4:2:2:2:2:2). After the first 196 patients were randomized, an interim analysis was conducted on the primary endpoint and RAR guided subsequent randomization allocation. Interim analyses and RAR were repeated after 250 patients were randomized and again after each additional 50 patients were randomized until 800 patients were randomized. Following each interim analysis, randomization probabilities were updated such that the probability of being randomized to placebo or a treatment arm likely representing the target dose was increased. The RAR was revised before the interim analysis of 350 patients to account for the protocol modifications precluding randomization of ApoE ε4 carriers to the lecanemab 10 mg/kg biweekly treatment arm. Interim analyses and RAR were conducted by an external, unblinded, and independent data analysis group.

An Interactive Voice Response System was used to manage randomization and treatment assignment. Randomization was stratified by ApoE ε4 carrier status (carrier or non-carrier), clinical disease stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), and presence or absence of treatment with cholinesterase inhibitors and/or memantine. Enrollment was monitored such that at least 60% of the population included patients with a baseline clinical stage of MCI due to Alzheimer's disease.

Blinding

Study drug was dispensed by an unblinded pharmacist at each site. All other study site staff and patients were blinded to treatment assignment during the placebo-controlled period. To maintain the blind across all treatment arms, patients assigned to once every 4-week dosing regimens also received placebo infusions at intervening 2-week time points. Imaging analyses were to be performed blinded to clinical information. Although the primary endpoint was assessed at Week 53, the blind was continued for the entire 79 weeks of the study. Although each site had separate personnel responsible for collection of efficacy assessments and collection and review of MRIs, the protocol did not specify that raters were to be blinded from safety assessments.

Dose Modification/Dose Discontinuation

Study drug was discontinued in all patients with ARIA-E and in patients who developed any macrohemorrhages, an area of superficial siderosis, or symptomatic treatment-emergent microhemorrhages. There were no dose reductions and no resumption of dosing after resolution of ARIA-E or ARIA-H. Administration of study drug was also to be terminated for infusion reactions of Grade 3 severity or above as defined in the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), clinical features indicating meningoencephalitis, or hypersensitivity reactions with clinical features of tissue injury.

Per Protocol Amendment 5 all ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg biweekly for 6 months or less were discontinued from study drug and newly enrolled ApoE ε4 carriers were randomized to placebo or a lecanemab dose other than 10 mg/kg biweekly.

Administrative Structure

An independent Interim Monitoring Committee (IMC) external to the applicant was established to oversee and ensure the integrity of interim analyses and RAR. The IMC consisted of 3 members with expertise in Bayesian adaptive design of clinical trials. An independent data analysis group conducted the analyses and provided the results to the IMC. The IMC also monitored the Bayesian interim analysis outcomes and informed the applicant if criteria for early success or futility were met.

A separate unblinded DSMB was established to review the safety and efficacy data on an ongoing basis and advise the applicant on issues related to safety. The DSMB consisted of up to 3 members with clinical training in neurology, neuroradiology, or immunology and one statistician.

An independent centralized imaging laboratory was selected to analyze PET scans. The central laboratory was to provide visual assessments of amyloid positivity and quantitative analyses of standard uptake values (SUVs) and ratios (SUVRs).

Procedures and Schedule

The schedule for key assessments is provided in Table 2. The pre-randomization period consisted of screening and baseline visits within a 60-day period before administration of the first dose. Eligible subjects reported to the study site every 2 weeks for 78 weeks with a follow-up visit 3 months after the last dose of the study drug.

Table 2: Study 201 Schedule of Key Assessments

Assessment	Schedule
Eligibility Criteria	Screening and Baseline
ApoE Genotyping	Baseline
Physical Examination	Screening, Baseline, Weeks 9, 17, 27, 39, 53, 65, 79, Follow-up, Early Termination
Safety Brain MRI	Screening, Weeks 9, 13, 27, 39, 53, 65, 79, Follow-up, Early Termination
Study Drug Administration	Weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77
Anti-Lecanemab Ab	Weeks 1, 13, 27, 39, 53, 65, 79, Follow-up, Early Termination
Lecanemab Concentration	Weeks 1, 13, 27, 39, 53, 65, 77, Early Termination
Blood for Biomarker Analysis	Baseline, Weeks 53, 79
CSF Collection (optional)	Baseline, Weeks 53, 77/79
Amyloid PET (optional)	Baseline, Weeks 53, 79
Volumetric MRI	Screening, Weeks 9, 13, 27, 39, 53, 65, 79, Follow-up, Early Termination
MMSE, CDR	Screening, Baseline, Weeks 13, 27, 39, 53, 65, 79, Follow-up, Early Termination
ADAS-Cog14, FAQ	Baseline, Weeks 13, 27, 39, 53, 65, 79, Follow-up, Early Termination

Created by reviewer, modified from Table 7 and Table 8 in Study 201 protocol
Note: The Screening visit was to occur 31 to 60 days prior to randomization; the Baseline visit was to occur 1 to 30 days prior to randomization
Note: Longitudinal PET and CSF substudies were optional

Patients enrolling in the OLE had the option to participate in a longitudinal PET substudy. Patients who consented to the substudy were stratified into two cohorts for amyloid PET assessments. Cohort 1 had assessments at baseline (OLE screening), Weeks 13 and 53 and annually thereafter and Cohort 2 had assessments at baseline (OLE screening), Weeks 27 and 53, and annually thereafter.

Concurrent Medications

Treatment of Alzheimer's disease with cholinesterase inhibitors and/or memantine was allowed if patients were on a stable dose for at least 12 weeks prior to Baseline. If a patient started, changed dose, or stopped any of these medications, study visits were to continue, but data from the patient was censored. Patients taking other medications were required to be on stable doses for at least 4 weeks before Baseline.

The following restrictions and limitations were also implemented in the protocol:

- Anticoagulants were not permitted and patients who needed to start chronic (defined as greater than 4 weeks) anticoagulant treatment during the study were withdrawn from study drug.

- Immunoglobulin therapy and therapy with biologics were not permitted for 6 months prior to Baseline until the follow-up visit.
- Medications needed as short courses of treatment, and which are central nervous system-active were not permitted for 72 hours before cognitive testing.

Subject Completion, Discontinuation, or Withdrawal

Patients who completed the scheduled visits, including the follow-up visit, were considered to have completed the study.

Patients who discontinued the study or study drug were to have an early termination visit within 7 days after the last dose of study drug and were to return for each scheduled visit when clinical assessments of efficacy were to be conducted, including the 3-month follow-up visit. The clinical assessments to be conducted at the early termination visit include those outlined in Table 2. Drug specific reactions that led to protocol-driven discontinuation include ARIA, infusion reactions, and hypersensitivity reactions as described earlier. Reasons for study discontinuation captured by the case report form (CRF) include AEs, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study termination by the sponsor, or other.

Patients withdrawn from the study were not replaced.

Study Endpoints

Surrogate Endpoint

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. Change from baseline in brain amyloid plaque as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR was assessed in a subset of patients at Week 53 and Week 79 and listed as a key secondary endpoint in the protocol. The primary amyloid PET analysis was the SUVR calculated for a composite cortical region of interest with whole cerebellum mask as a reference region. Different reference regions (subcortical white matter, derived whole cerebellum and adjusted by subcortical white matter, whole cerebellum mask and adjusted by subcortical white matter, derived whole cerebellum, cerebellar gray matter, and composite reference region) were also assessed and used for sensitivity analyses. A negative change from baseline in SUVR indicates a reduction in amyloid burden and a negative treatment difference (lecanemab minus placebo) favors lecanemab. SUVR values were also converted to the Centiloid scale (Klunk et al. 2015). Centiloid is a 100-point scale independent of tracer or method which has an average value of 0 in high certainty amyloid negative individuals and 100 in typical Alzheimer's disease patients.

An independent centralized imaging laboratory was selected to analyze PET scans. Image

processing and quantitative assessment of SUVR were performed by readers blinded to treatment status and clinical information.

The Division has previously determined in the review of aducanumab that a reduction in amyloid plaque burden measured by PET imaging is reasonably likely to predict clinical benefit. Amyloid plaque is an underlying, fundamental, and defining pathophysiological feature of Alzheimer's disease. Although the role of amyloid and its relationship to other pathophysiological features of Alzheimer's disease, such as tau and neurodegeneration, is complicated, the presence of amyloid plaques is a primary and essential finding in Alzheimer's disease, including early in the disease. It is reasonable to conclude that treatment that is targeted at reducing amyloid plaque, and that successfully accomplishes that reduction, has the potential to convey clinical benefit.

Primary Endpoint

The primary endpoint was the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at Week 53. Change from baseline in ADCOMS at Week 79 was included as a key secondary endpoint. The ADCOMS is a weighted linear combination of selected items from 3 commonly used scales: 4 items from the ADAS-Cog (delayed word recall, orientation, word recognition, and word finding), two items from the MMSE (orientation to time and drawing), and all 6 items from the CDR-SB. ADAS-Cog 14 and CDR-SB were included as secondary endpoints and are described below. MMSE is a widely used performance-based assessment of cognitive ability consisting of 11 tasks evaluating orientation, word recall, attention and calculation, and visuospatial functions. ADCOMS scores range from 0 to 1.97 with a higher composite score indicating greater disease severity. ADCOMS was developed to provide an assessment more sensitive to change and treatment effects in patients at the early stages of disease (Wang et al. 2016).

Secondary Endpoints

CDR-SB

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.

ADAS-Cog

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, three additional tasks were added to create the ADAS-Cog 14 for use in this earlier disease population. The ADAS-Cog 14 scale ranges from 0 to 90, with higher scores indicating greater disease severity.

Pharmacodynamic Endpoints

Key biomarker and pharmacodynamic endpoints included the following:

- Change from baseline in CSF levels of $A\beta_{1-42}$, phosphorylated tau at residue 181 (p-tau), and total tau (t-tau) at Week 53 and Week 79
- Change from baseline in brain volumes (total hippocampus, left and right hippocampus, whole brain, and total ventricle) as measured by vMRI at Weeks 27, 52, and 79
- Change from baseline in plasma levels of p-tau 181, $A\beta_{42/40}$ ratio, and neurofilament light chain (NfL) at Week 53 and Week 79

Statistical Analysis Plan

The original Statistical Analysis Plan (SAP) was drafted in January 2014, and was amended three times with the final version implemented in June 2018, prior to study completion.

Interim Analyses – Bayesian RAR

Frequent Bayesian interim analyses were conducted to update randomization allocation based on results on the ADCOMS and to allow for ongoing assessment of evidence of early success or futility. Interim analyses were conducted after the first 196 patients were randomized, after 250 patients were randomized and again after each additional 50 patients were randomized until 800 patients were randomized. Three additional interim analyses were subsequently performed at 3 month-intervals and a final Bayesian analysis was conducted when all patients had completed 12 months of treatment. Early success was defined as a probability of at least 0.95 that the target dose was superior to placebo by 25%. Futility was defined as a probability of less than 0.05 (with ≤300 patients randomized) or 0.075 (with ≥ 350 patients randomized) that the target dose was superior to placebo by 25% after 12 months of treatment. Neither criterion was met, and the study continued to completion.

Definitions of Statistical Analysis Populations

The following analysis populations were defined in the SAP:

- Randomized Set – all patients who were randomized to study drug
- Full Analysis Set – randomized patients who received at least one dose of study drug and had baseline and at least one post-dose primary efficacy measurement
- Pharmacodynamic (PD) Analysis Set – patients with sufficient PD data to derive at least one PD parameter (used for analyses of amyloid PET, CSF biomarkers, and vMRI)

Analysis Method for Amyloid PET

Change from baseline in brain amyloid plaque as measured by PET was analyzed with a mixed effects model with repeated measures (MMRM) with treatment group, visit, clinical subgroup (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), presence or absence of Alzheimer's disease medication use at baseline, ApoE ε4 status (carrier or non-carrier), region (North America, Western Europe, and Asia), and treatment group-by-visit interaction as fixed effects and baseline amyloid plaque level as a covariate. The adjusted p-value based on the Dunnett-Hsu method with 1-sided alpha of 0.05 was provided in addition to the p-value corresponding to pairwise comparison.

For the OLE period, change from OLE baseline in brain amyloid was analyzed with MMRM with OLE baseline amyloid and treatment gap duration as covariates and double-blind treatment group, visit, ApoE ε4 status, and double-blind treatment group-by-visit interaction as fixed effects.

Analysis Methods for Clinical Endpoints

The analyses of clinical endpoints used the Full Analysis Set and censored patients at the time of initiation of new Alzheimer's disease medication or dose adjustment of an existing stable treatment of an Alzheimer's disease medication.

Bayesian Analysis

The primary analysis of the change from baseline to Week 53 in the ADCOMS was based on Bayesian statistics using a two-dimensional first-order normal dynamic linear model of dose-response with normal and inverse-gamma priors. For each dose the probability of being superior to placebo was determined by comparing the posterior distribution of the mean

change from baseline to Week 53 between the lecanemab treatment arm and placebo. The threshold for success of the primary endpoint was a probability of at least 0.80 that the target dose was superior to placebo by 25%. The same Bayesian analysis was repeated for change from baseline in ADCOMS to Week 79 as well as for CDR-SB and ADAS-Cog 14. Bayesian imputation method was used in the case of missing or censored endpoint data.

Conventional Analysis

Change from baseline in clinical endpoints was also assessed with MMRM with treatment group, visit, clinical subgroup, presence or absence of Alzheimer's disease medication use at baseline, ApoE ε4 status, region, and treatment group-by-visit interaction as fixed effects and clinical scale at baseline as a covariate. These analyses were not performed at the interim analyses.

Adjustments for Multiplicity

There was no adjustment for multiplicity. See the statistical review for additional details.

Subgroup Analyses

Subgroup analyses for amyloid PET and clinical endpoints were planned for the following pre-defined groups:

- Age (≤64, 65-79, ≥80)
- Gender (male, female)
- Ethnicity
- Race
- Region (North America, Western Europe, and Asia)
- Clinical subgroup (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia)
- ApoE ε4 carrier status (carrier or non-carrier)
- Presence or absence of Alzheimer's disease medication use

Change from baseline in amyloid PET, vMRI, and CSF biomarkers were also to be analyzed by baseline PET SUVR subgroups (≥ median and < median).

Protocol Amendments

The original protocol (Version 2) was issued in November 2012. Protocol Amendment 4 modified the randomization algorithm such that ApoE ε4 homozygous patients were no longer randomized to the lecanemab 10 mg/kg biweekly treatment arm due to concerns about the risk

for ARIA. Shortly thereafter, Protocol Amendment 5 stipulated that ApoE ε4 heterozygous patients were also not to be randomized to the lecanemab 10 mg/kg biweekly treatment arm. In response to a request by another regulatory authority, patients who were ApoE ε4 carriers and who had not reached 6 months of treatment with 10 mg/kg biweekly were to be discontinued from treatment. Protocol Amendment 7 increased the amyloid PET substudy sample size from 260 to 306 patients. The open-label extension phase was initiated in September 2018 via Protocol Amendment 11.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in accordance with GCP and 21 CFR parts 50, 56 and 312.

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

Of the 3267 patients who signed the informed consent form at screening, a total of 856 continued in the study to randomization. The most common reason for screen failure was failure to meet inclusion or exclusion criteria. There were 2 patients who were randomized, both to the placebo arm, but did not receive study treatment. Patient disposition is summarized in Table 3. It is important to note the uneven distribution of patients randomized to the different treatment arms with more patients randomized to the 10 mg/kg arms and placebo in accordance with the Bayesian RAR. The greater percentage of discontinuations at the higher lecanemab dose levels is primarily driven by considerations regarding ARIA-E. All ARIA-E cases resulted in per-protocol discontinuation of treatment (25 and 16 patients in lecanemab 10 mg/kg monthly and 10 mg/kg biweekly, respectively). Also, 25 patients who were ApoE ε4 carriers and who were on 10 mg/kg biweekly for less than 6 months were discontinued from treatment according to a request by another regulatory authority.

Table 3: Study 201 Patient Disposition

Disposition	Study 201					
No. of patients screened	3267					
No. of patients not randomized	2411					
	Lecanemab					
	2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly	Placebo N=247

	N=52 n (%)	N=51 n (%)	N=92 n (%)	N=253 n (%)	N=161 n (%)	n (%)
Patients randomized	52 (100%)	51 (100%)	92 (100%)	253 (100%)	161 (100%)	247 (100%)
Full Analysis Set	52 (100%)	48 (94%)	89 (97%)	246 (97%)	152 (94%)	238 (96%)
Per-protocol population	50 (96%)	46 (90%)	89 (97%)	242 (96%)	152 (94%)	236 (96%)
PD Analysis Set (PET SUVR)	28 (54%)	28 (55%)	27 (29%)	89 (35%)	44 (27%)	99 (40%)
Discontinued treatment*+	18 (35%)	11 (22%)	28 (30%)	94 (37%)	74 (46%)	59 (24%)
Adverse event	5 (10%)	3 (6%)	9 (10%)	42 (17%)	22 (14%)	15 (6%)
Subject choice	7 (13%)	6 (12%)	13 (14%)	34 (13%)	18 (11%)	23 (9%)
Other reasons	6 (12%)	2 (4%)	6 (6%)	18 (7%)	34 (21%)	21 (9%)
Discontinued study+	17 (33%)	14 (28%)	31 (34%)	98 (39%)	74 (46%)	68 (28%)
Adverse event	4 (8%)	2 (4%)	5 (5%)	23 (9%)	12 (8%)	10 (4%)
Withdrawal by Participant	6 (12%)	8 (16%)	22 (24%)	55 (22%)	31 (19%)	45 (18%)
Other reasons	7 (13%)	4 (8%)	4 (4%)	20 (8%)	31 (19%)	13 (5%)

Created by the reviewer using adds.xpt and Tables 12 and 13 in Study 201 CSR
*Defined as patients who did not complete study treatment (i.e., did not receive last dose of study drug at Week 77)
+Percentages are based on number of patients treated (i.e., excluding the two patients randomized to placebo who did not receive treatment)

Protocol Violations/Deviations

A total of 12 patients in the Full Analysis Set had major protocol violations. The most common reason for protocol violation was deviation from eligibility criteria. These deviations are not expected to affect interpretation of the results.

Table of Demographic Characteristics

Table 4 contains information regarding demographic characteristics for each treatment arm in the Full Analysis Set. Demographic characteristics were reasonably balanced across the treatment arms except for a larger proportion of male patients in the 10 mg/kg monthly and 10 mg/kg biweekly treatment arms compared to placebo. The population enrolled in the study is generally representative of the patient population except for an under-representation of African American and Hispanic patients. There is no reason to expect that efficacy would be different based on race/ethnicity. Overall, 80% of patients were enrolled in the United States.

Table 4: Study 201 Baseline Demographics (Full Analysis Set)

Demographic Parameters	**Placebo** (N=238) n (%)	**Treatment Group**					
		2.5 mg/kg biweekly (N=52) n (%)	**5 mg/kg monthly** (N=48) n (%)	**5 mg/kg biweekly** (N=89) n (%)	**10 mg/kg monthly** (N=246) n (%)	**10 mg/kg biweekly** (N=152) n (%)	**Total** (N=825) n (%)
Sex							
Male	101 (42%)	26 (50%)	24 (50%)	41 (46%)	136 (55%)	88 (58%)	416 (50%)
Female	137 (58%)	26 (50%)	24 (50%)	48 (54%)	110 (45%)	64 (42%)	409 (50%)
Age							
Mean years (SD)	71.1 (8.9)	70.5 (8.3)	70.4 (7.5)	70.6 (7.4)	71.3 (7.5)	72.6 (8.8)	71.3 (8.2)
Median (years)	72	70.5	71	72	71	73	72
Min, max (years)	50, 89	50, 86	55, 84	52, 87	53, 90	51, 88	50, 90
Age Group							
≤ 64 years	55 (23%)	11 (21%)	9 (19%)	20 (23%)	44 (18%)	27 (18%)	166 (20%)
> 64 - < 80 years	144 (61%)	35 (67%)	35 (73%)	60 (67%)	168 (68%)	94 (62%)	536 (65%)
≥ 80 years	39 (16%)	6 (12%)	4 (8%)	9 (10%)	34 (14%)	31 (20%)	123 (15%)
Race							
White	216 (91%)	48 (92%)	46 (96%)	73 (82%)	222 (90%)	141 (93%)	746 (90%)
Black or African American	5 (2%)	2 (4%)	1 (2%)	4 (5%)	4 (2%)	4 (3%)	20 (2%)
Asian	16 (7%)	2 (4%)	1 (2%)	9 (10%)	17 (7%)	7 (5%)	52 (6%)
American Indian or Alaska Native	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
Other[1]	1 (<1%)	0	0	3 (3%)	3 (1%)	0	7 (<1%)
Ethnicity							
Hispanic or Latino	9 (4%)	4 (8%)	1 (2%)	3 (3%)	9 (4%)	9 (6%)	35 (4%)
Not Hispanic or Latino	229 (96%)	48 (92%)	47 (98%)	86 (97%)	237 (96%)	143 (94%)	790 (96%)
Region							
United States	183 (77%)	46 (88%)	39 (81%)	63 (71%)	201 (82%)	130 (86%)	662 (80%)
Canada	12 (5%)	1 (2%)	2 (4%)	7 (8%)	14 (6%)	5 (3%)	41 (5%)
Western Europe	28 (12%)	4 (8%)	6 (13%)	7 (8%)	15 (6%)	10 (6%)	70 (9%)
Asia	15 (6%)	1 (2%)	1 (2%)	12 (13%)	16 (6%)	7 (5%)	52 (6%)

Source: Table 14.1.4.1.1 in Study 201 CSR

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

Other Baseline Characteristics (disease characteristics, important concomitant drugs)

Table 5 contains a summary of baseline disease characteristics and baseline use of concomitant Alzheimer's disease medications. The proportion of ApoE ε4 carriers was unbalanced due to the protocol amendments restricting enrollment of ApoE ε4 carriers in the 10 mg/kg biweekly lecanemab treatment arm. ApoE ε4 carriers were more likely to be allocated by the Bayesian RAR to the next most likely efficacious doses of 10 mg/kg monthly and 5 mg/kg biweekly. There was also a higher proportion of patients with mild Alzheimer's disease dementia in the 10 mg/kg biweekly treatment arm compared to placebo. Otherwise, disease characteristics are mostly balanced across treatment arms and reflect a population of patients who are early in the course of Alzheimer's disease. The percentage of the population who were ApoE ε4 carriers (71%) is consistent with previous reports as is the proportion of patients receiving concomitant medications for Alzheimer's disease (54%). Additionally, 6% of patients received any Alzheimer's disease medication and stopped prior to entering the study.

Table 5: Study 201 Disease Characteristics (Full Analysis Set)

Disease Characteristic	**Placebo** (N=238) n (%)	**Treatment Group**					
		2.5 mg/kg biweekly (N=52) n (%)	**5 mg/kg monthly** (N=48) n (%)	**5 mg/kg biweekly** (N=89) n (%)	**10 mg/kg monthly** (N=246) n (%)	**10 mg/kg biweekly** (N=152) n (%)	**Total** (N=825) n (%)
Baseline Clinical Stage							
MCI due to AD	154 (65%)	34 (65%)	33 (69%)	52 (58%)	166 (68%)	90 (59%)	529 (64%)
Mild AD	84 (35%)	18 (35%)	15 (31%)	37 (42%)	80 (32%)	62 (41%)	296 (36%)
Laboratory ApoE ε4 Status							
Carrier	169 (71%)	38 (73%)	37 (77%)	81 (91%)	218 (89%)	46 (30%)	589 (71%)
Heterozygote	129 (54%)	33 (64%)	26 (54%)	67 (75%)	160 (65%)	38 (25%)	453 (55%)
Homozygote	40 (17%)	5 (10%)	11 (23%)	14 (16%)	58 (24%)	8 (5%)	136 (17%)
Non-carrier	69 (29%)	14 (27%)	11 (23%)	8 (9%)	28 (11%)	106 (70%)	236 (29%)
Number of Years Since Diagnosis of AD	237	52	48	89	245	152	823
Mean years (SD)	2.4 (1.7)	2.3 (1.7)	2.1 (1.2)	2.2 (1.2)	2.2 (1.6)	2.2 (1.5)	2. 3 (1.5)
Median (years)	2	2	2	2	2	2	2
Min, Max (years)	1, 11	1, 7	1, 6	1, 6	1, 12	1, 9	1, 12
Concomitant AD medication							
Cholinesterase inhibitors and/or memantine at baseline	128 (54%)	28 (54%)	25 (52%)	56 (63%)	131 (53%)	79 (52%)	447 (54%)
Baseline CDR-SB							

Mean (SD)	2.9 (1.5)	3.0 (1.6)	2.9 (1.4)	3.0 (1.3)	2.9 (1.3)	3.0 (1.4)	2.9 (1.4)
Median	3	3	2.5	3	2.5	3	3
Min, Max	0.5, 9	0.5, 7	1, 6	0.5, 6.5	0.5, 8	0.5, 8.5	0.5, 9
Baseline CDR global score							
0.5	200 (84%)	44 (85%)	40 (83%)	77 (87%)	210 (85%)	133 (88%)	704 (85%)
1.0	38 (16%)	8 (15%)	8 (17%)	12 (13%)	36 (15%)	19 (12%)	121 (15%)
Baseline MMSE							
<22	0	0	0	0	1 (<1%)	0	1 (<1%)
≥22 - <27	135 (57%)	32 (62%)	32 (67%)	55 (62%)	150 (61%)	88 (58%)	492 (60%)
≥27 - ≤30	103 (43%)	20 (38%)	16 (33%)	34 (38%)	95 (39%)	64 (42%)	332 (40%)
Baseline ADAS-Cog 14	237	52	47	89	246	152	823
Mean (SD)	22.6 (7.7)	22.7 (8.1)	22.9 (7.7)	22.8 (6.7)	21.9 (7.3)	22.1 (7.7)	22.3 (7.5)
Median	22.0	22.5	22.3	23.7	21.3	22.7	22
Min, Max	6.0, 46.7	10.0, 42.3	8.7, 47.3	8.7, 39.0	3.7, 48.3	4.3, 42.0	3.7, 48.3
Baseline ADCOMS							
Mean (SD)	0.37 (0.17)	0.39 (0.20)	0.40 (0.17)	0.39 (0.16)	0.37 (0.15)	0.37 (0.15)	0.38 (0.16)
Median	0.36	0.38	0.36	0.39	0.36	0.37	0.36
Min, Max	0.05, 0.94	0.07, 0.87	0.10, 0.78	0.11, 0.78	0.06, 0.89	0.04, 0.87	0.04, 0.94

Source: Tables 14.1.4.1.1 and 14.1.4.1.2 in Study 201 CSR and adcdr.xpt, admmse.xpt, adadas.xpt, and adcss.xpt

Key baseline demographics and disease characteristics for the PD Analysis Set (amyloid PET) are provided in Table 6 and are largely consistent with patients in the full analysis set.

Table 6: Study 201 Key Baseline Demographics and Disease Characteristics (PD Analysis Set)

Demographic Parameters	**Placebo** (N=99) n (%)	**Treatment Group**					
		2.5 mg/kg biweekly (N=28) n (%)	**5 mg/kg monthly** (N=28) n (%)	**5 mg/kg biweekly** (N=27) n (%)	**10 mg/kg monthly** (N=89) n (%)	**10 mg/kg biweekly** (N=44) n (%)	**Total** (N=315) n (%)
Sex							
Male	41 (41%)	14 (50%)	16 (57%)	14 (52%)	52 (58%)	25 (55%)	162 (51%)
Female	58 (59%)	14 (50%)	12 (43%)	13 (48%)	37 (42%)	19 (43%)	153 (49%)
Age							
Mean years (SD)	71.4 (8.6)	72.3 (7.9)	69.7 (8.5)	71.5 (8.3)	72.2 (6.9)	72.9 (8.1)	71.8 (8.0)
Median (years)	72	71.5	70.5	73	72	73	72
Min, max (years)	50, 89	54, 86	55, 84	52, 87	55, 85	52, 88	50, 89
Baseline Clinical Stage							
MCI due to AD	73 (74%)	20 (71%)	20 (71%)	18 (67%)	67 (75%)	27 (61%)	225 (71%)
Mild AD	26 (26%)	8 (29%)	8 (29%)	9 (33%)	22 (25%)	17 (39%)	90 (29%)
Laboratory ApoE ε4 Status							
Carrier	74 (75%)	20 (71%)	19 (68%)	23 (85%)	74 (83%)	9 (20%)	219 (70%)

Heterozygote	60 (61%)	17 (61%)	15 (54%)	21 (78%)	59 (66%)	8 (18%)	180 (57%)
Homozygote	14 (14%)	3 (11%)	4 (14%)	2 (7%)	15 (17%)	1 (2%)	39 (12%)
Non-carrier	25 (25%)	8 (29%)	9 (32%)	4 (15%)	15 (17%)	35 (80%)	96 (30%)
Concomitant AD medication							
Cholinesterase inhibitors and/or memantine at baseline	44 (44%)	16 (57%)	15 (54%)	17 (63%)	45 (51%)	20 (45%)	157 (50%)

Source: addm.xpt and adls.xpt

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance, defined as total number of infusions patients received divided by the total number of infusions patients could have received, was >97% for placebo and all treatment arms. Although compliance was high, protocol-mandated discontinuation of study treatment due to ARIA-E meant that some patients received fewer target doses. For example, the mean duration of exposure to treatment was 12.0 months in the 10 mg/kg biweekly lecanemab treatment arm compared to 15.6 months in the placebo arm.

Overall, 2% of study participants started a new concomitant Alzheimer's disease medication at some point during the study and 6% changed the dose of an existing Alzheimer's disease medication. The percentages were similar across placebo and lecanemab treatment arms.

Efficacy Results – Surrogate Endpoint

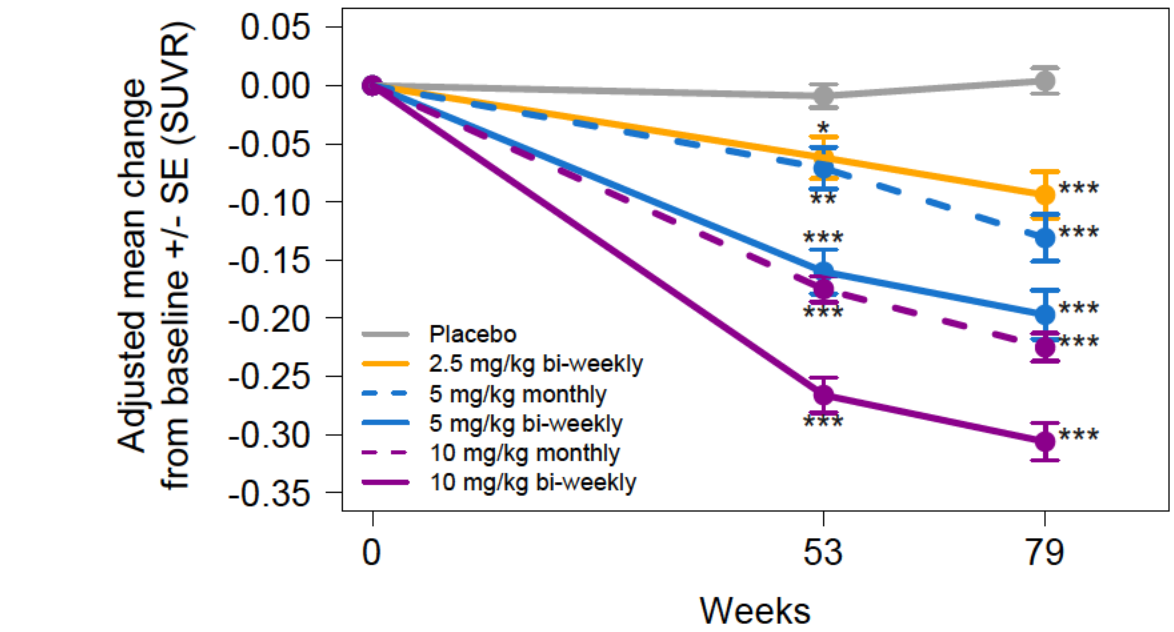
Lecanemab treatment demonstrated a statistically significant treatment effect on the surrogate endpoint of change from baseline in brain amyloid as measured by ^{18}F-florbetapir PET and quantified by a composite SUVR at Week 79 for all regimens, including the proposed dosing regimen of 10 mg/kg biweekly (-0.310, $p<0.001$) (Table 7). The results indicate time- and dose-dependent relationships for reduction of brain amyloid with lecanemab treatment (Figure 1). The median [25th – 75th percentile] value of SUVR in the lecanemab 10 mg/kg biweekly treatment arm at Week 79 was 1.05 [0.97 – 1.14]. Consistent and statistically significant findings were observed using all other reference regions (subcortical white matter, derived whole cerebellum and adjusted by subcortical white matter, whole cerebellum mask and adjusted by subcortical white matter, derived whole cerebellum, and composite reference region).

Table 7: Study 201 Surrogate Endpoint Analysis (SUVR)

	Placebo (N=99)	**2.5 mg/kg biweekly** (N=28)	**5 mg/kg monthly** (N=28)	**5 mg/kg biweekly** (N=27)	**10 mg/kg monthly** (N=89)	**10 mg/kg biweekly** (N=44)
Baseline SUVR						
n	98	28	27	27	88	44
Mean (SD)	1.40 (0.16)	1.41 (0.11)	1.42 (0.17)	1.40 (0.12)	1.42 (0.18)	1.37 (0.16)
Min, max	0.91, 1.73	1.11, 1.60	1.09, 1.72	1.23, 1.70	1.04, 1.84	0.99, 1.77
Change from Baseline in SUVR at Week 53						
n	96	27	27	25	88	43
Least square mean	-0.009	-0.062	-0.071	-0.160	-0.175	-0.266
Standard error	0.010	0.018	0.018	0.019	0.011	0.015
Difference from placebo		-0.053	-0.062	-0.151	-0.167	-0.257
90% CI for difference		(-0.086, -0.019)	(-0.096, -0.029)	(-0.185, -0.117)	(-0.189, -0.144)	(-0.287, -0.227)
p-value (compared with placebo)		0.010	0.002	<0.001	<0.001	<0.001
Dunnett p-value		0.100	0.027	0.000	0.000	0.000
Change from Baseline in SUVR at Week 79						
N	88	23	23	24	82	37
Least square mean	0.004	-0.094	-0.131	-0.197	-0.225	-0.306
Standard error	0.011	0.020	0.020	0.021	0.012	0.016
Difference from placebo		-0.099	-0.136	-0.201	-0.229	-0.310
90% CI for difference		(-0.136, -0.061)	(-0.173, -0.098)	(-0.238, -0.164)	(-0.254, -0.204)	(-0.344, -0.277)
p-value (compared with placebo)		<0.001	<0.001	<0.001	<0.001	<0.001
Dunnett p-value		0.000	0.000	0.000	0.000	0.000

Source: Tables 25 and 14.2.2.3.2e in Study 201 CSR

Figure 1: Study 201 Change from Baseline in Brain Amyloid (SUVR)



Placebo	n=98	96	88
2.5 mg/kg bi-weekly	n=28	27	23
5 mg/kg monthly	n=27	27	23
5 mg/kg bi-weekly	n=27	25	24
10 mg/kg monthly	n=88	88	82
10 mg/kg bi-weekly	n=44	43	37

Created by the reviewer from 14.2.2.3.2e in Study 201 CSR
*p<0.05, **p<0.01. ***p<0.001

Changes in brain amyloid as measured by PET were also calculated using the Centiloid scale and are represented in Table 8 and Figure 2. The results are consistent with those reported for the SUVR analysis. The change from baseline in brain amyloid at Week 79 compared to placebo for the 10 mg/kg biweekly regimen was -73.5 (p<0.001) and the median [25th – 75th percentile] Centiloid value was 2.06 [-17.0 – 23.3].

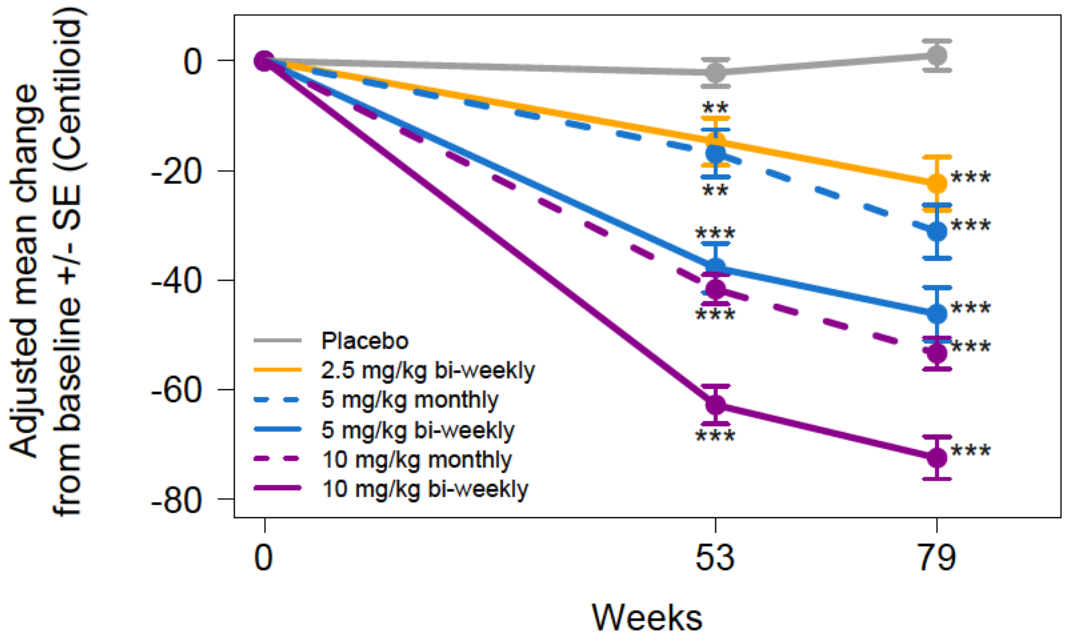
Table 8: Study 201 Surrogate Endpoint Analysis (Centiloids)

	Placebo (N=99)	**2.5 mg/kg biweekly** (N=28)	**5 mg/kg monthly** (N=28)	**5 mg/kg biweekly** (N=27)	**10 mg/kg monthly** (N=89)	**10 mg/kg biweekly** (N=44)
Baseline Centiloid						
n	98	28	27	27	88	44
Mean (SD)	84.8 (37.4)	87.7 (26.4)	89.4 (39.7)	84.9 (28.0)	90.3 (41.5)	78.0 (38.0)
Min, max	-31.4, 161.8	16.2, 131.4	10.2, 159.5	43.9, 155.1	-0.28, 189.0	-12.0, 171.1

Change from Baseline in Centiloid at Week 53						
n	96	27	27	25	88	43
Least square mean	-2.2	-14.7	-16.9	-37.8	-41.7	-62.8
Standard error	2.5	4.3	4.4	4.5	2.7	3.5
Difference from placebo		-12.6	-14.7	-35.6	-39.5	-60.7
90% CI for difference		(-20.5, -4.7)	(-22.7, -6.8)	(-43.8, -27.5)	(-45.0, -34.1)	(-67.9, -53.5)
p-value (compared with placebo)		0.009	0.003	<0.001	<0.001	<0.001
Dunnett p-value		0.096	0.027	0.000	0.000	0.000
Change from Baseline in Centiloid at Week 79						
N	88	23	23	24	82	37
Least square mean	1.0	-22.4	-31.2	-46.2	-53.4	-72.5
Standard error	2.7	4.8	4.8	4.9	2.9	3.9
Difference from placebo		-23.4	-32.2	-47.2	-54.4	-73.5
90% CI for difference		(-32.2, -14.6)	(-41.0, -23.3)	(-56.0, -38.4)	(-60.3, -48.5)	(-81.4, -65.6)
p-value (compared with placebo)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dunnett p-value	0.000	0.000	0.000	0.000	0.000	0.000

Source: Tables 14.2.2.3.5 and 14.2.2.3.2h in Study 201 CSR

Figure 2: Study 201 Change from Baseline in Brain Amyloid (Centiloid)



Placebo	n=98	96	88
2.5 mg/kg bi-weekly	n=28	27	23
5 mg/kg monthly	n=27	27	23
5 mg/kg bi-weekly	n=27	25	24
10 mg/kg monthly	n=88	88	82
10 mg/kg bi-weekly	n=44	43	37

Created by the reviewer from Table 14.2.2.3.2h in Study 201 CSR
**p<0.01 ***p<0.001

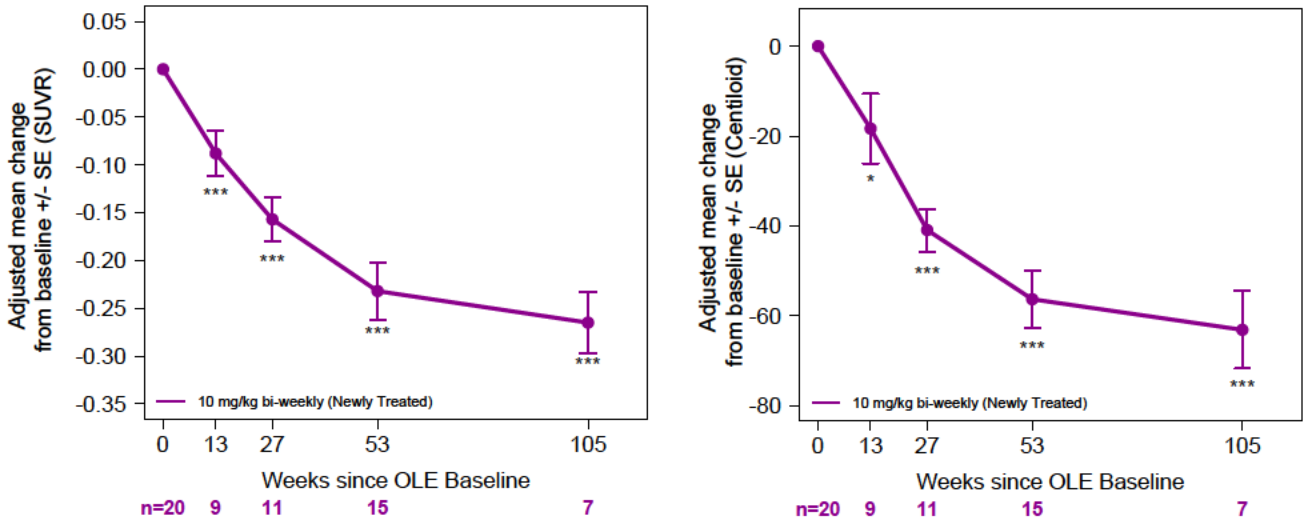
The proportion of patients who converted from having a positive amyloid PET scan by visual read at baseline to a negative scan by visual read at Week 79 was 22% for the placebo arm compared to 81% for the 10 mg/kg biweekly lecanemab treatment arm. The 22% conversion rate in the placebo arm is clearly at odds with the small numerical increase in brain amyloid observed with quantitative assessment (Figure 1 and Figure 2). This discrepancy can largely be explained by the fact that baseline visual assessments were performed at study inclusion whereas readings of post-baseline scans were conducted after all patients completed 18 months of treatment. Although blinded to treatment assignment, readers might have been more likely to judge borderline post-baseline scans as negative in expectation of a treatment effect. Despite the complication introduced by this apparent bias, the visual read findings are still consistent with a treatment effect of lecanemab and the percentage of negative scans by visual read at Week 79 in the 10 mg/kg biweekly lecanemab treatment arm is similar to the percentage of negative scans determined by quantitative assessment (Centiloid value less than 24.1). Caution should also be exercised when considering amyloid negativity at Week 79 by

SUVR or Centiloid cutoffs because approximately 6% of baseline amyloid scans were negative by quantitative assessment despite being classified as positive by visual read.

Reviewer Comment: For the reasons outlined above, (b) (4)

Reduction of brain amyloid plaque with lecanemab treatment was also demonstrated in patients who were randomized to placebo in the double-blind portion of the study and subsequently treated with lecanemab 10 mg/kg biweekly in the open-label extension (Figure 3). Mean brain amyloid at the open-label baseline visit in this group of patients was 1.37 (SUVR) and 77.2 (Centiloid). Overall, the trend in this smaller population is similar to the one observed in the double-blind portion of the study. The PET measurements at Weeks 13 and 27 in the open-label extension, however, provide additional insight into the initial time course of brain amyloid reduction. Adjusted mean changes from baseline at Weeks 13 and 27 were -0.088 and -0.157, respectively for SUVR and -18.3 and -40.9 for Centiloids.

Figure 3: Study 201 OLE Change from Baseline in Brain Amyloid in Patients Newly Treated with 10 mg/kg Lecanemab (Left – SUVR; Right – Centiloids)



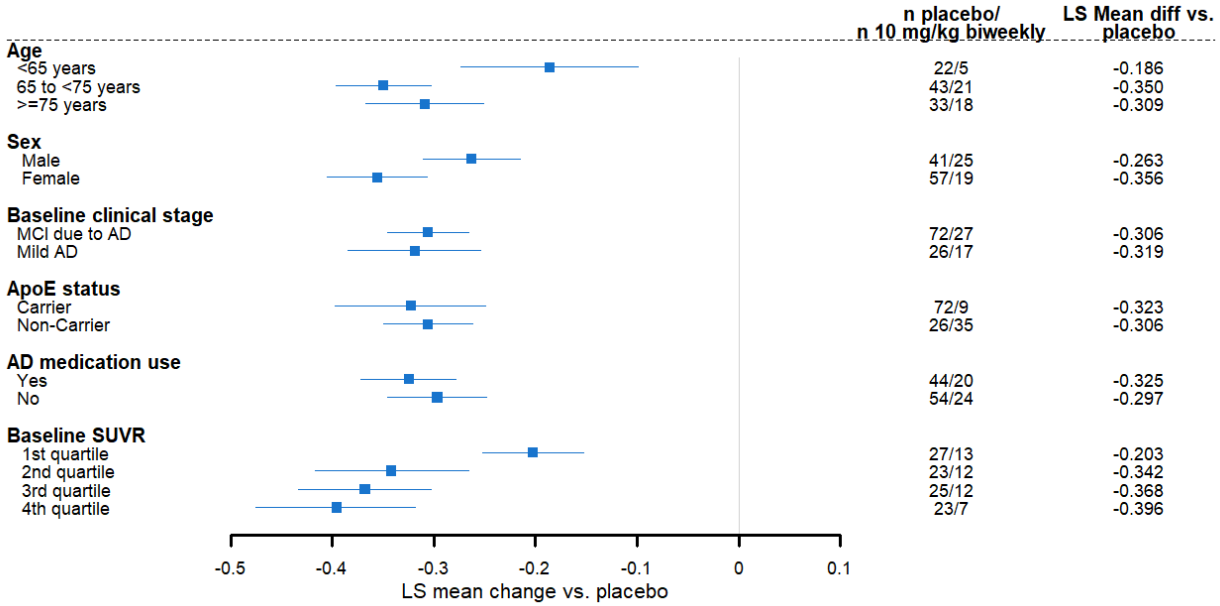
Created by the reviewer from Tables 14.2.2.1.4 and 14.2.2.2.4 in Study 201 OLE CSR
*p<0.05 **p<0.01 ***p<0.001

Subgroup Analysis of the Surrogate Endpoint

Subgroup analyses for the surrogate endpoint are summarized in Figure 4 and demonstrate that significant amyloid plaque reduction is observed across patient demographics and disease characteristics. There were too few patients for meaningful subgroup analysis by race or region.

Higher baseline SUVR was associated with a greater SUVR reduction. A PKPD model which incorporated longitudinal data from all dose levels indicated that ApoE ε4 carriers had higher baseline SUVR and older patients had greater SUVR reduction compared to younger patients. See the clinical pharmacology review for more information. The statistical review performed subgroup analyses by adding interactions to the MMRM model and found similar results to those presented in Figure 4.

Figure 4: Study 201 Subgroup Analysis of Amyloid PET SUVR (Week 79)



Created by the reviewer using analyses presented in Figures 15.1.4.1a and 15.1.4.1b in the ISE.

Given the size of the study, subgroup analyses for clinical endpoints are not presented in this review. Of the 8 subgroups defined in the SAP, the statistical review presents one (ApoE ε4 carrier status) to raise uncertainty regarding the impact of amyloid reduction on clinical endpoints because there is no apparent treatment effect on the clinical endpoint in ApoE ε4 non-carriers. Subgroup analyses on clinical endpoints are better suited for the larger confirmatory Study 301. It is worth noting that in the topline results for that study, ApoE ε4 non-carriers appeared to demonstrate a treatment effect on clinical endpoints (van Dyck et al. 2022).

Data Quality and Integrity

There were no major data quality issues identified during the review of Study 201.

Efficacy Results – Primary Endpoint

The primary Bayesian analysis of ADCOMS at Week 53 indicated that the lecanemab 10 mg/kg

biweekly dosing regimen had a 64% probability of being superior to placebo by 25%. This did not meet the prespecified criterion for success of 80% probability. The probability of lecanemab 10 mg/kg biweekly being superior to placebo by any amount at Week 53 was 98%.

The original clinical study report included a table suggesting there was a (b) (4)% probability of the 10 mg/kg biweekly dosing regimen being superior to placebo by 25% on ADCOMS at Week 53. An addendum to the clinical study report clarified that this table, which presented results of a sensitivity analysis without censoring efficacy data based on initiation or dose adjustment of Alzheimer's disease medications, was incorrectly inserted in the original report. According to the SAP, the primary analysis was to be performed censoring efficacy data based on initiation or dose adjustment of Alzheimer's disease medications. This primary analysis resulted in a probability of 64% of the 10 mg/kg biweekly regimen being superior to placebo by 25%.

Reviewer Comment: The fact that the primary result was not successful according to the prespecified threshold should not be incorrectly interpreted as evidence of ineffectiveness of lecanemab. On face, this result suggests that lecanemab is very likely to be effective and more likely than not to be effective by at least 25%.

Efficacy Results – Secondary clinical endpoints

The primary endpoint was at Week 53, but the blind continued to Week 79 and assessments of clinical endpoints at this time point were prespecified as key secondary objectives of the study. A summary of the MMRM analysis results for the key secondary endpoints at Week 79 is provided in Table 9 and longitudinal results for the placebo and lecanemab 10 mg/kg biweekly arms are illustrated in Figure 5. The 10 mg/kg biweekly lecanemab treatment regimen demonstrated favorable numerical results for CDR-SB and nominal statistical significance for ADCOMS and ADAS-Cog 14 at Week 79. MMSE and Functional Assessment Questionnaire were also included as exploratory endpoints. A favorable numerical result was observed for MMSE in the 10 mg/kg lecanemab treatment arm, but the Functional Assessment Questionnaire (FAQ) was similar to placebo.

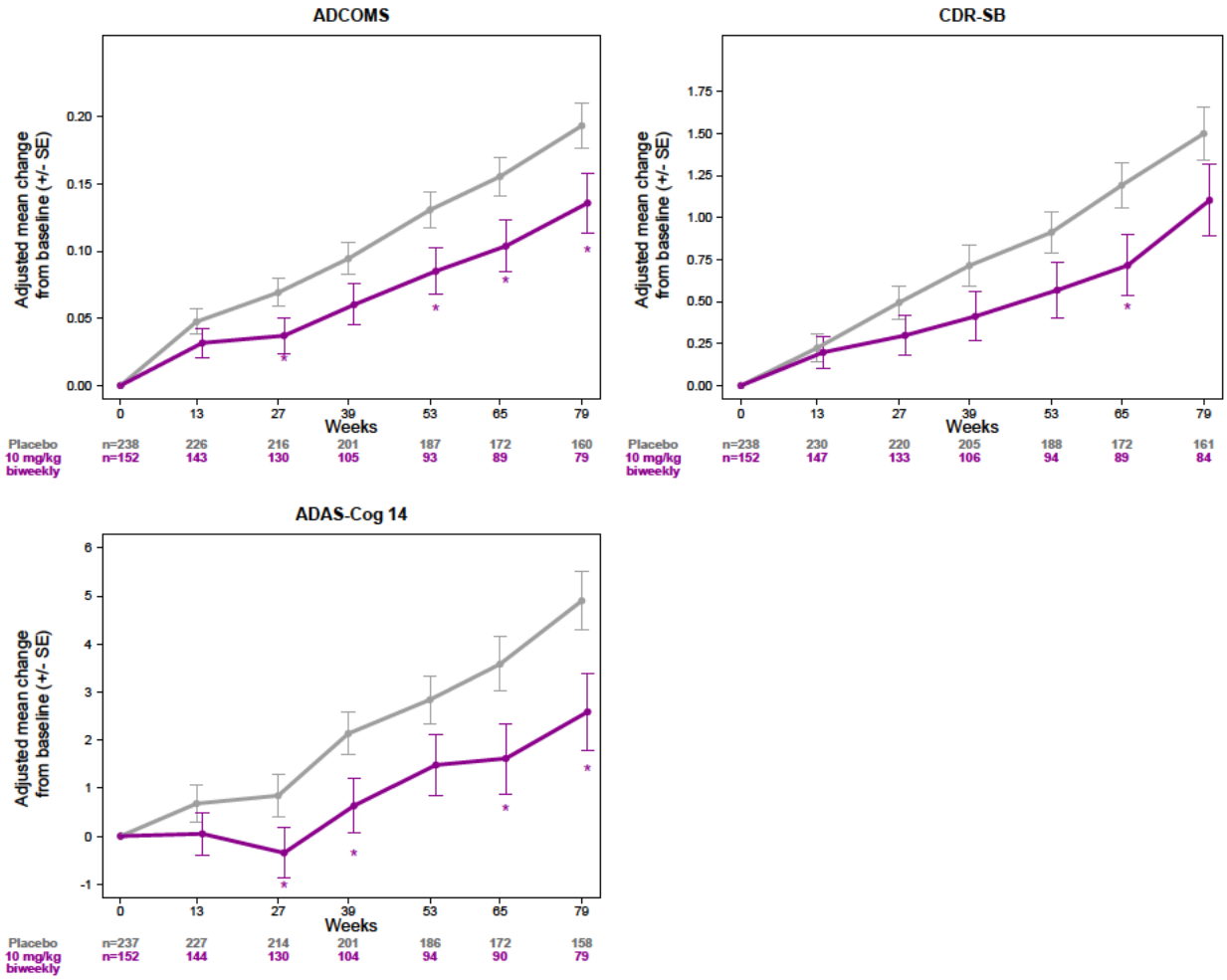
Table 9: Study 201 Secondary Endpoint Analysis (Full Analysis Set, Week 79)

	Placebo (N=238)	**2.5 mg/kg biweekly** (N=52)	**5 mg/kg monthly** (N=48)	**5 mg/kg biweekly** (N=89)	**10 mg/kg monthly** (N=246)	**10 mg/kg biweekly** (N=152)
Baseline ADCOMS						
N	238	52	48	89	246	152
Mean	0.370	0.386	0.395	0.390	0.373	0.373
Change from Baseline in ADCOMS at Week 79						
n	160	33	35	61	146	79
LS mean	0.193	0.173	0.192	0.199	0.166	0.136
Standard error	0.017	0.035	0.035	0.026	0.018	0.022

Difference from placebo		-0.020	-0.001	0.006	-0.028	-0.057
90% CI for difference		(-0.083, 0.042)	(-0.064, 0.061)	(-0.044, 0.055)	(-0.065, 0.010)	(-0.102, -0.013)
p-value (compared with placebo)		0.59	0.97	0.86	0.23	0.03
Baseline CDR-SB						
n	238	52	48	89	246	152
Mean	2.89	2.98	2.94	3.03	2.91	2.97
Change from Baseline in CDR-SB at Week 79						
n	161	34	36	67	149	84
LS mean	1.50	1.23	1.71	1.46	1.25	1.10
Standard error	0.16	0.34	0.33	0.25	0.17	0.21
Difference from placebo		-0.27	0.21	-0.04	-0.25	-0.40
90% CI for difference		(-0.88, 0.33)	(-0.38, 0.81)	(-0.51, 0.44)	(-0.61, 0.11)	(-0.82, 0.03)
p-value (compared with placebo)		0.46	0.56	0.90	0.26	0.13
Baseline ADAS-Cog 14						
n	237	52	47	89	246	152
Mean	22.56	22.72	22.94	22.75	21.90	22.06
Change from Baseline in ADAS-Cog 14 at Week 79						
n	158	33	34	61	146	79
LS mean	4.90	5.57	5.75	4.51	4.62	2.59
Standard error	0.62	1.28	1.28	0.96	0.65	0.81
Difference from placebo		0.67	0.84	-0.40	-0.28	-2.31
90% CI for difference		(-1.59, 2.93)	(-1.42, 3.11)	(-2.20, 1.40)	(-1.64, 1.08)	(-3.91, -0.72)
p-value (compared with placebo)		0.62	0.54	0.72	0.74	0.02

Source: Tables 27, 30, 36, 38, 43, and 45 in Study 201 CSR
All p-values are nominal.

Figure 5: Study 201 Longitudinal Change from Baseline for Clinical Endpoints (MMRM) for Placebo and Lecanemab 10 mg/kg Biweekly Treatment Arms



Created by the reviewer.
Source: Tables 27, 30, 36, 38, 43, and 45 in Study 201 CSR
* p<0.05

The results from Bayesian analyses were consistent with MMRM results. At Week 79, the lecanemab 10 mg/kg biweekly treatment arm demonstrated 27% less decline in ADCOMS and a probability of 98% of being superior to placebo. The probability of the 10 mg/kg biweekly dose to be superior to placebo by 25% was 76%. For CDR-SB and ADAS-Cog 14, the 10 mg/kg biweekly arm demonstrated 33% and 56% less decline, respectively, at Week 79 compared to placebo with probabilities of 96% and 99% of being superior to placebo.

The Division communicated concerns about the interpretation of the clinical efficacy data at the 2018 End of Phase 2 Meeting, including the proportion of patients with missing efficacy data, the use of ADCOMS as the primary endpoint, statistical issues with multiplicity, and the

disproportion in ApoE ε4 carriers between the lecanemab 10 mg/kg biweekly arm and placebo. These concerns remain valid when considering Study 201 in isolation. This application, however, is being considered for accelerated approval based on whether the surrogate endpoint of reduction in brain amyloid plaque is reasonably likely to predict a clinical benefit to patients. Since 2018, accumulating data on the association between amyloid plaque reduction and treatment effects on clinical endpoints provide important context for the favorable clinical endpoint observations in Study 201.

It is important, however, to specifically address the concern about the imbalance in ApoE ε4 carriers in the placebo and 10 mg/kg biweekly lecanemab treatment arms. One might reasonably hypothesize that the apparent treatment effect observed in the lecanemab 10 mg/kg biweekly arm is driven by the preponderance of ApoE ε4 non-carriers, who presumably have slower disease progression. And, in fact, ApoE ε4 non-carriers were observed to have slower progression than ApoE ε4 carriers for ADCOMS in the placebo arm of Study 201 (LS means at Week 79 of 0.174 and 0.202, respectively). But there are other observations and results which caution against drawing such a conclusion. First, it should be noted that slower progression in ApoE ε4 non-carriers is not a universal finding across clinical trials. Second, the progression in ADAS-Cog 14 was greater in ApoE ε4 non-carriers than carriers in the placebo arm (LS means at Week 79 of 5.96 vs. 4.32, respectively), yet this endpoint demonstrated the largest overall treatment effect with the smallest nominal p-value. Third, analyses using only patients randomized before the change in randomization scheme result in consistent findings. Finally, the 10 mg/kg biweekly data were combined with the 10 mg/kg monthly data to create a group with comparable proportions of ApoE ε4 non-carriers and carriers to the placebo arm. In this combined group, the trends were consistent with the overall results. For example, in the combined group the difference vs. placebo (90% CI) at Week 79 was -0.30 (-0.62 to 0.02). Notwithstanding these lines of reasoning, the decision to cease randomization of ApoE ε4 carriers to the 10 mg/kg biweekly regimen introduced uncertainty which can only be fully addressed with a larger dataset.

Efficacy Results – Pharmacodynamic endpoints

CSF Biomarkers

A total of 92 patients (including 24 in the placebo arm and 12 in the 10 mg/kg biweekly lecanemab treatment arm) contributed CSF data for biomarker analysis. The applicant reports that in this population, lecanemab treatment was associated with an increase in $A\beta_{1-42}$ and a decrease in p-tau 181. For $A\beta_{1-42}$, the LS mean changes at Week 77/79 for placebo and 10 mg/kg lecanemab biweekly were -3.6 pg/ml and 392.4 pg/ml, respectively (LS mean difference of 396.1 pg/ml, $p<0.001$). For p-tau 181, the LS mean changes at Week 77/79 for placebo and 10 mg/kg lecanemab biweekly were 1.4 pg/ml and -10.9 pg/ml, respectively (LS mean difference of -12.3 pg/ml, $p=0.04$). There was no notable treatment difference in total tau, NfL, or neurogranin associated with lecanemab.

Plasma Biomarkers

Plasma $A\beta_{42/40}$ ratio was evaluated in 284 patients (including 88 in the placebo arm and 43 in the 10 mg/kg biweekly lecanemab treatment arm). The applicant reports a dose- and time-dependent increase in plasma $A\beta_{42/40}$ ratio with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 0.0021 and 0.0075, respectively (LS mean difference of 0.0054, $p<0.004$).

Plasma p-tau 181 was evaluated in 562 patients (including 179 in the placebo arm and 84 in the 10 mg/kg biweekly lecanemab treatment arm). The applicant reports a dose-dependent decrease in plasma p-tau 181 with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 0.083 pg/ml and -1.11 pg/ml, respectively (LS mean difference of -1.20 pg/ml, $p<0.001$). No effect was observed on plasma NfL.

See the Clinical Pharmacology review for further consideration of fluid biomarker data.

vMRI

A total of 656 patients (including 209 in the placebo arm and 99 in the 10 mg/kg biweekly lecanemab treatment arm) had sufficient vMRI data to derive at least one parameter. There was no notable treatment difference in change from baseline in total hippocampus volume. The LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly were -257 mm^3 and -277 mm^3 (LS mean difference of -19 mm^3, $p=0.24$).

Lecanemab treatment was associated with a decrease in whole brain volume with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of -21776 mm^3 and -29894 mm^3 (LS mean difference of -8118 mm^3, $p<0.001$) and an increase in total ventricular volume with LS mean changes at Week 79 for placebo and 10 mg/kg lecanemab biweekly of 5345 mm^3 and 7662 mm^3 (LS mean difference of 2318 mm^3, $p<0.001$). Given the favorable results on clinical endpoints observed in Study 201 and the clinical benefit publicly reported in Study 301, the clinical relevance of these changes to whole brain volume and total ventricular volume is unclear. It is also important to note that fluid biomarkers of neurodegeneration, including plasma NfL in Study 201 and reported markers in Study 301, do not suggest a greater extent of neurodegeneration with lecanemab treatment. It will be important to collect longer-term data in a larger number of patients to further understand the clinical implications, if any, of these observations.

Dose/Dose Response

The results displayed in Figure 1 clearly demonstrate that greater amyloid plaque reduction is associated with higher doses of lecanemab. See the Clinical Pharmacology review for further information, including exposure-response relationships.

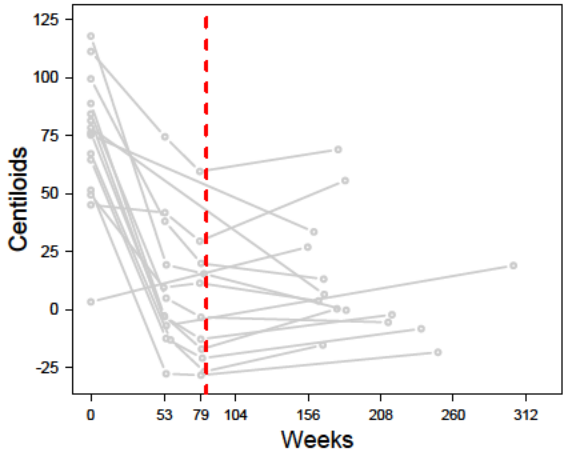
Durability of Response

There was a significant gap of approximately 2 years between the placebo-controlled portion of the study and the OLE, thereby limiting the duration for which patients were continuously treated with lecanemab. The data from the placebo-controlled period suggest that amyloid plaque continues to decrease to levels consistent with amyloid negativity following dosing with lecanemab 10 mg/kg biweekly.

Persistence of Effect

The gap period between the placebo-controlled portion of the trial and the OLE provides an opportunity to gain insight into the effect of lecanemab after treatment is stopped. The individual profiles for patients who were treated with lecanemab 10 mg/kg biweekly in the placebo-controlled portion of the trial and subsequently had PET assessments at baseline in the OLE are plotted in Figure 6. For the 11 patients who had PET assessments at both Week 79 and OLE baseline, the mean increase in brain amyloid as measured by SUVR was 0.25 (5.9 Centiloids) and the mean rate of increase was 0.11/year (2.6 Centiloids/year). This rate of increase is consistent with the small increase in brain amyloid observed in patients treated with placebo in the double-blind portion of Study 201.

Figure 6: Individual Amyloid Plaque Time Profiles (Centiloids) in Patients Randomized to Lecanemab 10 mg/kg Biweekly in Study 201 Who Also Had PET Assessment at OLE Baseline



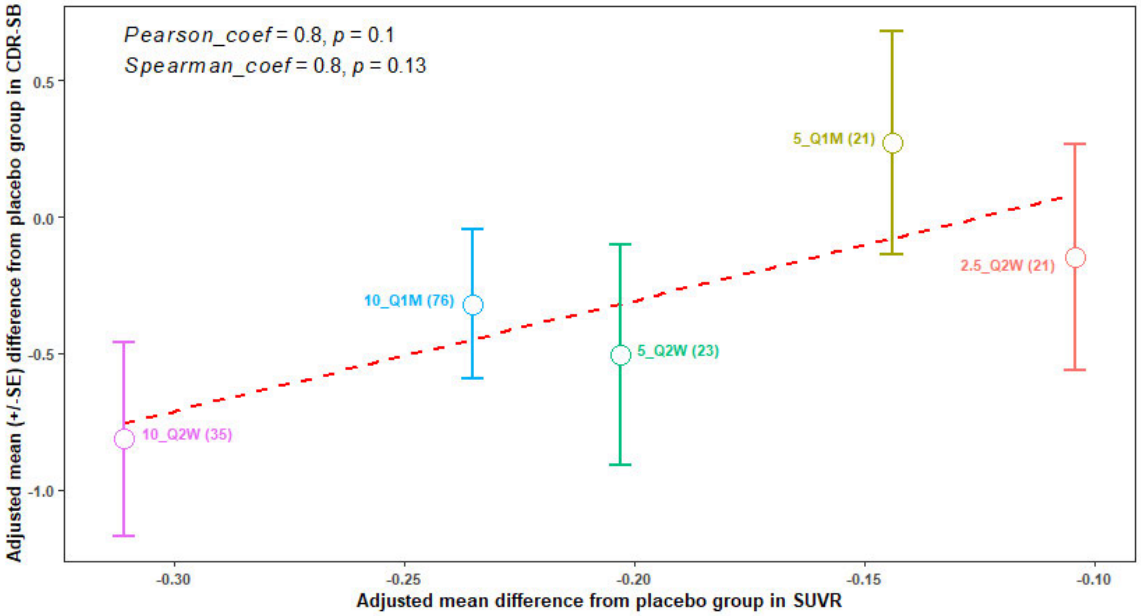
Created by the reviewer using adca.xpt
Dashed red line represents the end of the lecanemab treatment period in Study 201

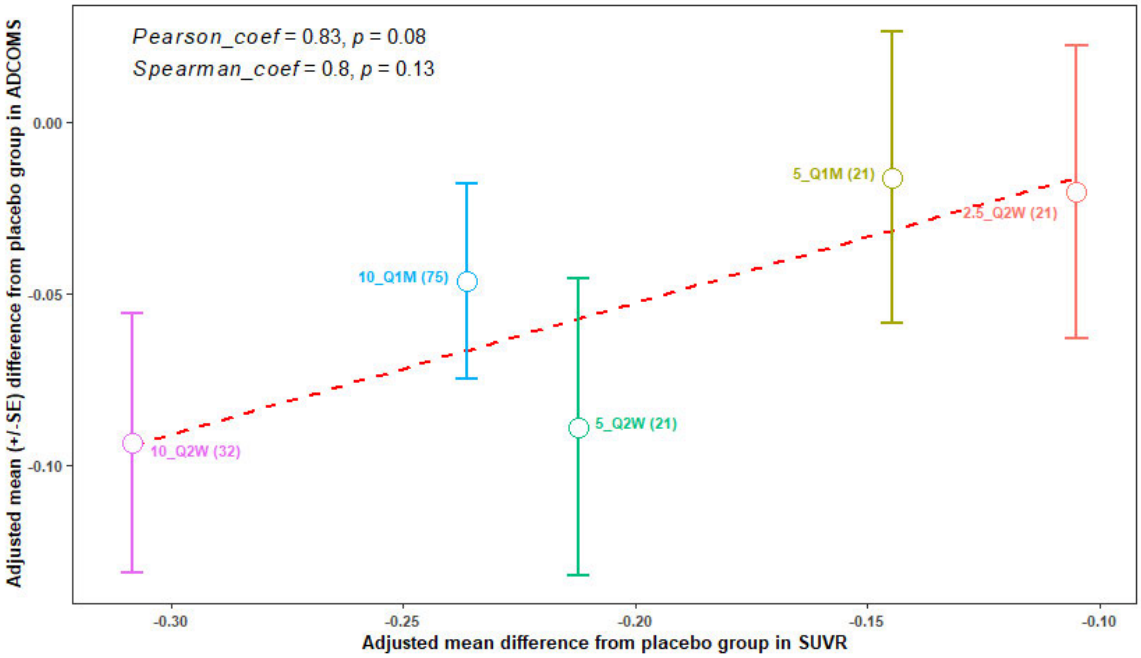
Additional Analyses Conducted on the Individual Trial

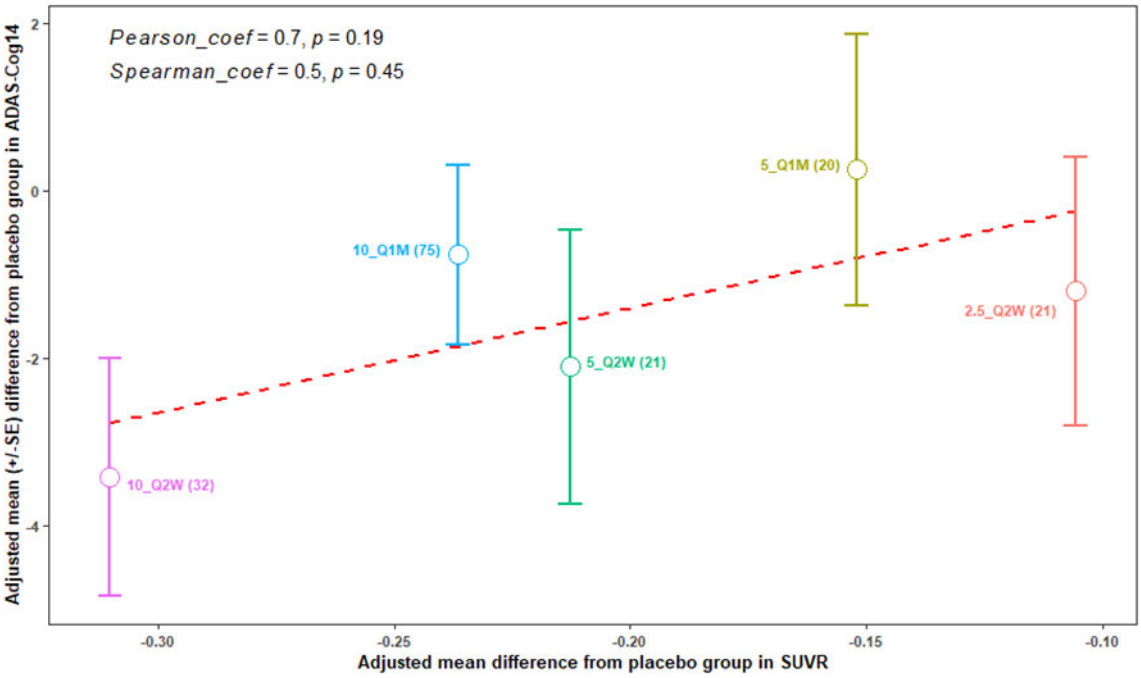
<u>Correlation between Amyloid PET and Clinical Endpoints</u>

The correlation between the effect on amyloid PET and the effect on clinical endpoints was explored at the dose level in the subpopulation of patients who had post-baseline assessments for both endpoints (approximately 37% of patients). Note that this population is different than the Full Analysis Set and more closely approximates a per protocol population. A decrease in brain amyloid was associated with treatment effects at the population level for ADCOMS (Pearson correlation coefficient=0.832, p=0.08), CDR-SB (Person correlation coefficient=0.805, p=0.10), and ADAS-Cog14 (Person correlation coefficient=0.699, p=0.189) (Figure 7).

Figure 7: Correlation between Change from Baseline in Clinical Endpoints and Amyloid PET SUVR at Week 79







Source: Clinical Pharmacology Review

Mediation Analysis

A mediation analysis was also performed by the applicant to investigate the link between the effect of lecanemab on brain amyloid and clinical endpoints. In the mediation analysis, the

proportion of treatment effect explained by amyloid PET SUVR was defined as the percentage change of treatment effects estimated from two ANCOVA models with or without adjusting for amyloid PET SUVR. For the 10 mg/kg biweekly dose arm, the estimated treatment effect on CDR-SB changed from -0.63 (p=0.11) to -0.03 (p=0.95) after adjusting for the change from baseline in amyloid PET SUVR. The proportion of the treatment effect explained by amyloid PET SUVR in this analysis is 95%, suggesting a relationship between amyloid PET SUVR and the treatment effect on CDR-SB.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review because only one trial is reviewed.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The population enrolled in Study 201 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 lecanemab earlier in the disease may provide the best opportunity to delay or halt the pathophysiological processes that lead to the clinical deficits of Alzheimer's disease. The ongoing study (Study 303) of lecanemab in individuals in Stages 1 and 2 of Alzheimer's disease should shed light on potential benefit in this population. Intervention with lecanemab later in the disease may be expected to provide less benefit, as downstream pathological processes may dominate. The application does not contain clinical data to directly assess the effectiveness of lecanemab 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 lecanemab on reduction of brain amyloid plaque should occur across the disease continuum, providing the potential for clinical benefit.

Individuals with Down syndrome represent another important population at risk for Alzheimer's disease who might also benefit from treatment with lecanemab. Alzheimer's disease 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

The effect of lecanemab on brain amyloid plaque demonstrated in Study 201 meets the statutory standard for substantial evidence of effectiveness to support accelerated approval. The intended lecanemab dosing regimen, 10 mg/kg biweekly, demonstrated a reduction in brain amyloid plaque from 1.37 SUVR (78 Centiloids) at baseline to 1.07 SUVR (5.5 Centiloids) at Week 79 with a statistically significant difference from placebo of -0.31 SUVR (-73.5 Centiloid); $p<0.001$. The magnitude of the reduction is consistent with the observed reduction that supported the accelerated approval of aducanumab.

Although the reduction of brain amyloid plaque was observed in only a subset of patients in a single study, the results are highly persuasive. As observed in the placebo arm of Study 201, amyloid plaque does not spontaneously disappear in patients with Alzheimer's disease. The reduction observed in the lecanemab 10 mg/kg biweekly arm is thus incompatible with variability or chance. Also, the results demonstrated a clear dose- and concentration-response relationship over the dosing regimens included in the study. The effects on amyloid are persuasive and consistent across doses and subgroups, supporting the ability of Study 201 to be considered a single adequate and well-controlled trial that is capable of providing substantial evidence of effectiveness.

The clinical endpoint results from Study 201 provide context for the amyloid reduction observed in the study and inform the reasonable likelihood of the reduction in brain amyloid plaque to predict clinical benefit. Despite limitations introduced by the under-enrollment of ApoE ε4 carriers in the lecanemab 10 mg/kg biweekly arm and the adaptive design of the trial, the estimates of the treatment effect at Week 79 across clinical endpoints are consistent with a modest reduction of clinical decline. Importantly, a similar degree of reduction (approximately 20% to 40%) in the decline of clinical endpoints has been observed in other studies in which brain amyloid was reduced to a similar extent. This reduction corresponds to a delay in progression of several months over the 18 months of the study. Patients and caregivers have clearly expressed that a delay of several months at this stage of the disease is clinically important.

Although the results of the confirmatory study, Study 301, have not been reviewed, the topline results provide important context for the reasonable likelihood of reduction of brain amyloid plaque to predict clinical benefit. It is worth noting that the positive results of Study 301 appear to be consistent with the results of Study 201 and what is already known about the relationship between brain amyloid plaque reduction and effect on clinical endpoints. The topline results for the gantenerumab studies, although negative, are entirely consistent with the known relationship between amyloid plaque reduction and clinical endpoints.

8. Review of Safety

Please see the separate safety review by Dr. Erten-Lyons.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not deemed necessary for this submission.

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 review by Dr. Erten-Lyons for considerations regarding a REMS.

12. Postmarketing Requirements and Commitments

In order to verify the clinical benefit of lecanemab, the applicant will be required to conduct a randomized, controlled trial to evaluate the efficacy of lecanemab compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of a sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The recently completed Study 301 is intended to address this requirement.

13. Appendices

13.1. References

Albert, MS, ST DeKosky, D Dickson, B Dubois, HH Feldman, NC Fox, A Gamst, DM Holtzman, WJ Jagust, RC Petersen, PJ Snyder, MC Carrillo, B Thies, and CH Phelps, 2011, The Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease, Alzheimers Dement., 7(3): 270-279.

Alzheimer's Association, 2021, 2021 Alzheimer's Disease Facts and Figures, Special Report: Race, Ethnicity and Alzheimer's in America.
https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Klunk, WE, RA Koeppe, JC Price, TL Benzinger, MD Devous Sr., WJ Jagust, KA Johnson, CA Mathis, D Minhas, MJ Pontecorvo, CC Rowe, DM Skovronsky, and MA Mintun, 2015, The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET, Alzheimers Dement., Jan;11(1):1-15.e1-4

McKhann, GM, DS Knopman, H Chertkow, BT Hyman, CR Jack Jr., CH Kawas, WE Klunk, WJ Koroshetz, JJ Manly, R Mayeux, RC Mohs, JC Morris, MN Rossor, P Scheltens, MC Carrillo, B Thies, S Weintraub, and CH Phelps, 2011, The Diagnosis of Dementia due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease, Alzheimers Dement., 7(3):263-269.

van Dyck, CH, CJ Swanson, P aisen, RJ Bateman, C Chen, M Gee, M Kanekiyo, D Li, L Reyderman, S Cohen, L Froelich, S Katayama, M Sabbagh, B Vellas, D Watson, S Dhadda, M Irizarry, LD Kramer, and T Iwatsubo, Nov 29 2022, Lecanemab in Early Alzheimer's Disease, N Eng J Med

Vermunt, L, SAM Sikkes, A van den Hout, R Handels, I Bos, WM van der Flier, S Kern, PJ Ousset, P Maruff, I Skoog, FRJ Verhey, Y Freund-Levi, M Tsolaki, AK Wallin, MO Rikkert, H Soininen, L Spiru, H Zetterberg, K Blennow, P Scheltens, G Muniz-Terrera, PJ Visser, for the Alzheimer Disease Neuroimaging Initiative, AIBL Research Group, ICTUS/DSA study groups, 2019, Duration of Preclinical, Prodromal, and Dementia Stages of Alzheimer's Disease in Relation to Age, Sex, and APOE Genotype, Alzheimer's & Dementia, 15:888-898.

Wang, J, V Logovinsky, SB Hendrix, SH Stanworth, C Perdomo, L Xu, S Dhadda, I Do, M Rabe, J Luthman, J Cummings, and A Satlin, 2016, ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials, J Neurol Neurosurg Psychiatry, Sep;87(9):993-9.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 201

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: >1000		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐

APPEARS THIS WAY ON ORIGINAL

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
01/05/2023 05:30:35 PM