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Rev.2.0.1 accompanying GVP Module V Rev.2
Human Medicines Evaluation

EUROPEAN UNION RISK MANAGEMENT PLAN

Lecanemab/LEQEMBI®

Version 1.0

Date of this Plan: 11 Dec 2024

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Risk Management Plan (RMP) Version to Be Assessed as Part of This Application:

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a: For ongoing studies, the data cut-off date was 15 Apr 2022; for postmarketing data, the data cut-off date was 05 Jul 2024.

Qualified Person for Pharmacovigilance (QPPV) Name:	[redacted], Family Physician ([redacted]) EU QPPV and General Safety Officer Eisai GmBH Edmund Rumpler Straβe 3 60549 Frankfurt Deutschland Bus: +49 (0) [redacted]
QPPV oversight declaration	The content of this RMP has been reviewed and approved by Eisai's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADR	adverse drug reaction
AE	adverse event
APOE	apolipoprotein E
APP	amyloid precursor protein
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormalities oedema/effusion
ARIA-H	amyloid-related imaging abnormalities- microhaemorrhage and hemosiderin deposit
ATC	Anatomic Therapeutic Classification
CAA	cerebral amyloid angiopathy
CSF	cerebrospinal fluid
DIAD	dominantly inherited Alzheimer's disease
DLP	data lock point
EAD	early Alzheimer's disease
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GDS	Geriatric Depression Scale
HCP	Healthcare Professional
ICH	International Council for Harmonisation
IgG	immunoglobulin G
INN	international nonproprietary name
IV	intravenous
LEC10-BW	lecanemab 10 mg/kg biweekly (every 2 weeks)
LEC10-M	lecanemab 10 mg/kg monthly
mAb	monoclonal antibody
mAb158	murine homologous antibody of BAN2401
MAD	multiple ascending dose
MAH	Marketing Authorisation Holder

Abbreviation	Definition of Term
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NHP	nonhuman primate
NOAEL	no observed adverse effect level
OLE	open-label extension
PBO	placebo
PET	positron emission tomography
PI	Product Information
PL	Package Leaflet
PSEN	presenilin
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAD	single ascending dose
SAE	serious adverse event
SD	Sprague Dawley
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	treatment-emergent adverse event
Tg2576	transgenic mice expressing human APP with Swedish mutation
WHO	World Health Organization

PART I PRODUCT OVERVIEW

Table 1 Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Lecanemab
Pharmacotherapeutic group(s) (Anatomic Therapeutic Classification [ATC] Code)	N06DX04 - Nervous system, psychoanaleptics, anti-dementia drugs, other anti-dementia drugs
Name of marketing authorisation holder (MAH)	Eisai GmbH
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	LEQEMBI®
Marketing authorisation procedure	Centralised
Brief description of the product	
Chemical class	Lecanemab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb).
Summary of mode of action	Lecanemab is a humanized IgG1 (IgG1) monoclonal antibody (mAb) which demonstrates low affinity for amyloid beta (Aβ) monomers, while it binds with high selectivity to Aβ aggregate species, with preferential activity for toxic soluble Aβ protofibrils. Lecanemab binds these aggregate Aβ species to neutralize and clear them from the brain. Lecanemab has been shown to produce a robust reduction in brain amyloid with effects on downstream cerebrospinal fluid biomarkers such as phosphorylated tau (CSF p-Tau), suggesting that lecanemab may have an indirect influence on tau pathology.
Important information about its composition	Each millilitre of concentrate for solution for infusion contains 100 mg of lecanemab. Lecanemab is a recombinant humanised IgG1 mAb produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	The proposed Summary of Product Characteristics (SmPC) is provided in Module 1.3.1.

Table 1 Product Overview

Indication(s) in the EEA	
Current	Lecanemab is indicated for adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (see section 5.1).
Proposed (if applicable)	Not applicable.
Dosage in the EEA	
Current	The recommended dose of lecanemab is 10 mg/kg. Lecanemab is administered as an intravenous (IV) infusion over approximately 1 hour, once every 2 weeks.
Proposed (if applicable)	Not applicable.
Pharmaceutical form(s) and strengths	
Current (if applicable)	Lecanemab concentrate for solution for infusion (100 mg/mL active) drug product is in a 2 mL and 5 mL fill volume per vial. Clear to opalescent, colourless to pale yellow liquid.
Proposed (if applicable)	Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Aβ = amyloid beta, AD = Alzheimer's disease, ApoE ε4 = apolipoprotein E ε4, ATC = Anatomic Therapeutic Classification, CSF = cerebrospinal fluid, EEA = European Economic Area, IgG1 = immunoglobulin G1, INN = international nonproprietary name, IV = intravenous, mAb = monoclonal antibody, MAH = marketing authorisation holder, RMP = Risk Management Plan, SmPC = Summary of Product Characteristics.

PART II SAFETY SPECIFICATION

Part II Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2 Summary of Epidemiology of Alzheimer's Disease

Incidence	Alzheimer's disease (AD) is a progressive, neurodegenerative disorder of unknown aetiology and the most common form of dementia among older people. Globally, it is estimated that approximately 50 million people are affected by AD and other types of dementia which is predicted to more than triple by 2050 (World Health Organization [WHO], 2022; Alzheimer's Disease International, 2021; Maciejewska, et al., 2021; Lane, et al., 2018). AD is the single most common cause of dementia, accounting for 50% to 75% (Lane, et al., 2018). In a meta-analysis conducted in 2017, the incidence rate of AD in Europe was found to be 11.08 cases per 1000 person-years (95% CI: 10.30-11.89). Broken down by sex, the incidence rate was 7.02 per 1000 person-years (95% CI: 6.06-8.05) in men and 13.25 per 1000 person-years (95% CI: 12.05-14.51) in women. Incidence rates in southern European countries (Greece, Italy, and Spain) and northern European countries (France, United Kingdom, Sweden, and Denmark) were 8.97 cases per 1000 person-years (95% CI: 8.13-9.86) and 15.94 cases per 1000 person-years (95% CI: 14.25-17.72), respectively (Niu, et al., 2017). Estimating the incidence of AD in epidemiological studies is challenging because of the difficulty in accurately establishing the time of onset of the disease and in accessing diagnostics (via positron emission tomography [PET] or CSF) to confirm AD biomarkers. Estimation of the incidence of the earlier stage of disease – mild cognitive impairment (MCI) due to AD – is similarly challenging. The heterogeneity of incidence estimates across studies of MCI is substantial, and most studies do not contain data in which the aetiology of MCI is known or in which AD pathology has been confirmed, given the limitations in the availability of diagnostic testing for AD (Gillis, et al., 2019). Accepting these limitations, a meta-analysis estimated the incidence of MCI per 1000 person-years as 22.5 (95% CI: 5.1-51.4) for patients aged 75 to 79 years, 40.9 (95% CI: 7.7-97.5) for patients aged 80 to 84 years, and 60.1 (95% CI: 6.7-159.0) for patients aged ≥85 years (Gillis, et al., 2019). Because not all dementia is due to AD, it would follow that not all MCI is due to AD; hence, these incidences (or numbers) may be overestimates.

Table 2 Summary of Epidemiology of Alzheimer's Disease

Prevalence	By the year 2050, the worldwide prevalence of AD is predicted to grow to greater than 139 million (Alzheimer's Disease International, 2021), while in the US alone, the prevalence is projected to reach to 13.8 million individuals 65 years of age or older by 2060 (WHO, 2022). AD is primarily a condition of later life, roughly doubling in prevalence every 5 years after age 65 (Lane, et al., 2018). AD is now most common in Western Europe and the US; in the US, an estimated 6.5 million people aged 65 years and older are living with AD in 2022 and 73% are age 75 or older (Alzheimer's Association, 2022). In a meta-analysis conducted in 2017, the prevalence of AD in Europe was 5.05% (95% CI: 4.73-5.39) (Niu, et al., 2017). A large amount of literature explores the prevalence of AD; however, the insidious nature of the disease combined with different methods of operationalising the disease definition makes precise estimates of the prevalence challenging. The prevalence of the earlier stage of MCI due to AD is also challenging to estimate. A meta-analysis of the prevalence of MCI, regardless of aetiology, found that the prevalence increased from 6.7% in patients aged 60 to 64 years to 25.2% in patients aged 80 to 84 years (Petersen, et al., 2018). Approximately half of patients with MCI have shown abnormal amyloid levels indicating AD aetiology, with amyloid positivity increasing with age – from 37% at age 60 years to 66% at age 85 years (Jansen, et al., 2015).
Demographics of target population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:	The main risk factor for AD is advanced age (Alzheimer's Association, 2022; Maciejewska, et al., 2021; Qiu, et al., 2009). AD is primarily a condition of later life, roughly doubling in prevalence every 5 years after age 65 (Lane, et al., 2018). The percentage of people with AD increases with age: 5.0% of people aged 65 to 74 years, 13.1% of people aged 75 to 84 years, and 33.2% of people aged 85 years and older have AD (Alzheimer's Association, 2022). The prevalence of AD is greater in women than in men and greater among black people and Hispanics than among non-Hispanic whites (Alzheimer's Association, 2022; Hebert, et al., 2001). Other known risk factors are family history and genetics (the presence of variant 4 of apolipoprotein E [APOE], and gene mutations of amyloid precursor protein [APP], presenilin 1 [PSEN1], and presenilin 2 [PSEN2]) (Maciejewska, et al., 2021; Lane, et al., 2018). Compared with the most common APOE genotype of E3/E3, E4 heterozygosity increases risk of AD by about 3 times, and E4 homozygosity increases risk by 8 to 12 times (Alzheimer's Association, 2022). Approximately two-thirds of pathology confirmed AD cases are *APOE4* carriers (heterozygous or homozygous), compared with about 15% to 20% of the general population (Mattsson, et al., 2018). Comorbidities such as hypertension, hypercholesterolaemia, type 2 diabetes mellitus, atherosclerosis, and Down's syndrome are also risk factors for developing AD. Other environmental and lifestyle factors which may also have a general impact on human mental health include traumatic brain injury, smoking, pesticides, heavy metal pollution, low physical activity, low Mediterranean diet adherence, and a lower education attainment (Alzheimer's Association, 2022; Maciejewska, et al., 2021; Rajamaki, et al., 2021; Lane, et al., 2018).

Table 2 Summary of Epidemiology of Alzheimer's Disease

The main existing treatment options	Current therapeutic agents for patients with mild, moderate, and severe AD consist of symptomatic therapies that include acetylcholinesterase inhibitors (AChEIs), such as donepezil, and the N-methyl-D-aspartate receptor antagonist, memantine. These agents provide symptomatic benefit and do not prevent progression of the disease process (Thoe, et al., 2021; Birks, 2006; McShane, et al., 2006). Antipsychotics are commonly prescribed to treat behavioural symptoms but are not approved for the treatment of AD and are associated with increased mortality in older patients. There remains an urgent unmet medical need for effective treatments that target the underlying pathology of AD, thus slow the progression of the disease.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	-Alzheimer's Association, 2022; In England and Wales, AD is the leading cause of death overall, accounting for 11.6% of all deaths registered in 2015 (Lane, et al., 2018). AD is the sixth-leading cause of death in the US and the 5th leading cause for people aged 65 years and older (Xu, et al., 2020). A rapid increase in morbidity is predicted in low- and middle-income countries in the near future, especially African countries and India (Maciejewska, et al., 2021), which show patterns of increasing cardiovascular disease, hypertension, and diabetes. AD lies on a continuum, which progresses from preclinical AD, MCI to mild, moderate, and severe stages of AD. Individuals with MCI due to AD can still perform adequately and independently in daily life activities. In earlier stage AD, they begin to require occasional assistance with complex activities, later progressing to needing frequent help with basic needs. Patients with severe AD require full-time care with the most basic feeding, toileting, and ambulating needs (Alzheimer's Association, 2022; Herring, et al., 2021). Over a lifetime horizon, the probability of transitioning to each severity level and the median time to reach each AD health state (the time when 50% of those alive had progressed) in patients treated with standard of care is 89.4% and 2.77 years to mild AD or worse, 80.0% and 4.92 years to moderate AD or worse, and 67.2% and 7.44 years to severe AD. From a baseline cohort of patients treated with standard of care, the estimated median survival in MCI due to AD, median survival in mild AD or better, and median survival in moderate AD or better health states are 2.54 years, 4.29 years, and 6.12 years, respectively. The predicted lifetime probability of transitioning to institutionalization is 29.4% and the median survival in the community (of the baseline cohort) is 8.85 years (Herring, et al., 2021).

Table 2 Summary of Epidemiology of Alzheimer's Disease

Important co-morbidities	• AD mostly affects the elderly. Comorbidities associated with age which frequently accompany AD include the following (Maclejewska, et al., 2021, Rajamaki, et al., 2021; Bergland, et al., 2017; Browne, et al., 2017; Poblador-Plou, et al., 2014): o Type 2 diabetes mellitus o Hypercholesterolaemia and atherosclerosis o Cardiovascular disease/Hypertension • AD as a consequence of other diseases (Maclejewska, et al., 2021): o Down's syndrome • Comorbidities triggered by AD (Maclejewska, et al., 2021; Rajamaki, et al., 2021; Greenberg, et al., 2020; Waziry, et al., 2020; Poblador-Plou, et al., 2014): o Cerebrovascular disease, including intracerebral haemorrhage or haemorrhagic stroke o Cerebral amyloid angiopathy (CAA) and cerebral microbleeds o Psychosis o Depression/Apathy o Insomnia o Sleep disorders o Epilepsy/Seizures

AChEIs = acetylcholinesterase inhibitors, AD = Alzheimer's Disease, *APOE4* = apolipoprotein E4 variant, APP = amyloid precursor protein, CAA = cerebral amyloid angiopathy, CSF = cerebrospinal fluid, MCI = mild cognitive impairment, PET = positron emission tomography, PSEN = presenilin, WHO = World Health Organization.

Part II Module SII - Nonclinical Part of the Safety Specification

The key nonclinical safety findings for lecanemab are shown in Table 3.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
Key issues identified from acute or repeat-dose toxicity studies	No toxicologically relevant adverse effects were observed after a single dose of lecanemab in Sprague Dawley (SD) rats up to 100 mg/kg IV or in cynomolgus monkeys up to 50 mg/kg IV. In addition, mAb 158 showed no toxicologically relevant effects after 18 weekly doses up to 50 mg/kg in Tg2576 mice. No microhaemorrhages or other adverse histopathologic effects were observed in the brains of Tg2576 mice (transgenic mice expressing human amyloid precursor protein [APP] with Swedish mutation) in the 50 mg/kg dose group that had a) significant pharmacodynamic effects on protofibrils, and b) the presence of adequate systemic plasma levels of mAb158.	Magnetic resonance imaging (MRI) signal changes, mostly interpreted as ARIA-E and ARIA-H, have been observed in studies with lecanemab, as well as with other amyloid modifying therapies, particularly N -terminal mAb of IgG1 type that target Aβ, such as bapineuzumab (Salloway, et al., 2009; Sperling, et al., 2012) and gantenerumab (Panza, et al., 2014; Ostrowitzki, et al., 2012). Amyloid -related imaging abnormalities, including ARIA-E, an anti-Aβ antibody class effect, is included in Table 20 as an important identified risk. ARIA (cerebral microhaemorrhage, superficial siderosis) and intracerebral haemorrhage > 1 cm is included as an important identified risk in Table 21.
	In the 4- and 39-week, repeated -dose, nonhuman primate (NHP) toxicity studies, the only findings were increasing trends in mean absolute and related spleen weights and size and number of germinal centres in the spleen. These findings were reversible and are believed to be related to a low -level immune response to a foreign protein or to the anticipated pharmacologic activity of lecanemab binding to a soluble Aβ target in the peripheral circulation followed by clearance through known immune -mediated mechanisms. There was no clear correlation of increase in spleen weights with the increases in germinal centres in the spleen in individual monkeys.	Given the lack of any other lecanemab -related observations, the relevance of the spleen findings to humans is expected to be of limited significance and the no -observed -adverse-effect level (NOAEL) has been determined to be ≥100 mg/kg in the 39-week repeated -dose NHP toxicity study.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive/Developmental toxicity	No developmental or reproductive toxicity studies have been conducted to date.	There are no data on the use of lecanemab in pregnant women and there are no data on the presence of lecanemab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Due to the age range of expected use for lecanemab for the approved indication, use of lecanemab in premenopausal women is expected to be low. The age range of the early Alzheimer's disease (EAD) patient population means it is not possible to perform studies in women who are breastfeeding or pregnant.
Genotoxicity	Lecanemab is a mAb and is not expected to induce direct genotoxicity or form active or genotoxic metabolites. Therefore, no genotoxicity studies with lecanemab were conducted according to the ICH S6(R1) guideline.	Not applicable.
Carcinogenicity	Carcinogenicity studies with lecanemab were not conducted. A weight-of-evidence assessment of carcinogenicity risk was conducted considering the factors specified in the ICH S6(R1) guideline. There is a lack of genotoxic concern, a plausible link between the mechanism of action (i.e., soluble Aβ modulation) and carcinogenesis, histopathologic signals in a chronic toxicology study, or evidence of immunosuppression in nonclinical studies. In addition, carcinogenicity studies in rodents would not produce meaningful data due to the potential immunogenicity of lecanemab and studies with the murine homologues are not considered valuable. This weight-of-evidence is sufficient to indicate a minimal or no potential for cancer risk in humans of this therapeutic protein and that additional nonclinical studies or carcinogenicity studies with lecanemab to address this risk were not warranted.	No safety risk has been identified.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Other Toxicity-Related Information or Data	In single-dose IV toxicity studies in rats and cynomolgus monkeys, and 4- and 39-week intermittent IV repeated -dose toxicity studies in cynomolgus monkeys, there were no findings suggesting local irritation at the injection site at any dose level.	No safety risk has been identified.
	Local tolerance was assessed in a 4-week subcutaneous local irritation study in monkeys. Lecanemab showed no local irritation at the injection site in NHPs after 28 daily subcutaneous doses of the 200 mg/mL formulation at 10 mg/kg. No anti-lecanemab antibodies were detected in this study.	
	In vitro tissue cross reactivity of lecanemab was evaluated using a full panel of -freshfrozen rat, monkey, and human tissues. Lecanemab reacted with endocrine cells in intermediate lobe (pituitary), proximal tubular epithelial cells (kidney), and pia mater and subpial/perivascular space (cerebrum, cerebellum, and spinal cord) among the cynomolgus monkey tissues examined. No lecanemab -specific staining was present in any of the SD rat tissues examined. In the human tissues examined, lecanemab reacted with extracellular Aβ plaques in cerebrum, neurons and glial cells, epithelium, and mononuclear cells in some organs/tissues, and pancreatic islet cells, but did not react with intravascular serum. The binding to cytoplasmic compartments may not be toxicologically relevant under in vivo conditions due to the inability of mAbs to gain access to the cytoplasmic compartment.	No safety risk has been identified.

Aβ = amyloid beta, APP = amyloid precursor protein, ARIA-E = amyloid related imaging abnormalities - oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit, EAD = early Alzheimer's disease, ICH = International Council for Harmonisation, IgG1 = immunoglobulin G1, IV = intravenous, mAb = monoclonal antibody, mAb158 = murine homologous antibody of BAN2401, MRI = magnetic resonance imaging, NHP = nonhuman primate, NOAEL = no observed- adverse- -effect level, SD = Sprague Dawley, Tg2576 = transgenic mice expressing human APP with Swedish mutation.

Part II Module SIII - Clinical Trial Exposure

The lecanemab clinical development programme comprises a total of 8 ongoing or completed studies: Three studies in subjects with early AD (BAN2401-G000-201 Core [Phase 2/completed]/Open-label extension [Phase 2/ongoing], BAN2401-G000-301 Core [Phase 3/completed]/Open-label extension [Phase 3/ongoing], BAN2401-J081-104 [Phase 1/completed], 1 study in preclinical AD (BAN2401-G000-303 [Phase 3/ongoing]), 1 study in mild to moderate AD (BAN2401-A001-101 [Phase 1/completed]) and 2 studies in healthy volunteers (BAN2401-A001-004 [Phase 1/completed]) and BAN2401-A001-005 [Phase 1/ongoing]). Finally, there is a Phase 2/3 study (DIAN-TU-001) evaluating potential disease modifying therapies in dominantly inherited Alzheimer's disease (DIAD) where lecanemab is used as a background therapy, which is also ongoing.

In Study 201 there was a Gap Period between the end of the Core and the start of the Extension Phase where subjects were off lecanemab (i.e., untreated) for 9 to 59 months (mean 24 months).

Cumulatively, as of 13 Sep 2022 for Study 301 Core and 15 Apr 2022 for all ongoing studies, a total of 2341 participants (59 healthy volunteers and 2282 subjects [79 subjects from Phase 1 studies and 2203 subjects from Phase 2/3 studies] with AD from the 8 studies) were exposed to lecanemab. For DIAN-TU-001 and Study BAN2401-A001-005, as of the cut-off date for ongoing studies (15 Apr 2022), no subjects had received lecanemab.

Exposure data for lecanemab Phase 1 studies are provided in Table 4 as individual studies and cumulative exposure by duration for lecanemab Phase 2/3 studies are provided in Table 5. Exposure data for Study 301 ApoE ε4 non-carriers or heterozygotes (i.e. the 'indicated population') are provided in Table 6. Exposure data stratified by age and gender are presented in Table 7, Table 8 and Table 9 (Phase 1, Phase 2/3 studies and the indicated population, respectively), by dose in Table 10, Table 11 and Table 12 (Phase 1, Phase 2/3 studies and the indicated population, respectively), and race/ethnicity in Table 13, Table 14 and Table 15 (Phase 1, Phase 2/3 studies and the indicated population, respectively).

Table 4 Exposure to Lecanemab in Phase 1 Studies (Studies 101, 104, and 004)

Population	Subjects	Subject-months[a]
Phase 1 Studies		
Healthy Subjects		
Study BAN2401-A001-004[b]	59	1.9
Alzheimer's Disease		
Study BAN2401-A001-101[c]	60	80.5
Study BAN2401-J081-104[d]	19	43.6
Total	138	126.0

AD = Alzheimer's disease, MAD = Multiple Ascending Dose, MCI = mild cognitive impairment, SAD = Single Ascending Dose.

a: Subject-months = total duration of exposure (days)/30.417.

b: Duration of exposure is defined as 1 day for subjects receiving a single dose of lecanemab.

c: Study BAN2401-A001-101 includes subjects with mild or moderate AD. For subjects in the SAD phase, duration of exposure is defined as 1 day. For subjects in the MAD phase, duration of exposure is defined as [date of last dose – date of first dose +1] +1 treatment cycle (14 days for 10 mg/kg and 28 days for other groups).

d: Study BAN2401-J081-104 includes subjects with MCI or mild AD. Duration of exposure is defined as 1 day for the first dose + [date of last dose – date of second dose +1] + 1 treatment cycle (14 days).

Table 5 Cumulative Exposure to Lecanemab in Phase 2/3 Clinical Studies by Duration (Studies 301, 201, and 303)

Population Duration of Exposure	Subjects	Subject-years[a]
Early Alzheimer's Disease[b]		
≥1 day	2045	2738.2
≥6 weeks	1920	2730.3
≥3 months	1731	2696.9
≥6 months	1549	2630.5
≥9 months	1369	2520.5
≥12 months	1247	2414.4
≥15 months	1185	2344.3
≥18 months	895	1918.4
≥24 months	377	1067.4
≥30 months	171	610.9
≥36 months	105	434.0
Total	2045	2738.2
Preclinical Alzheimer's Disease[c]		
≥1 day	158	85.1
≥6 weeks	144	84.2
≥3 months	109	77.8
≥6 months	72	63.4
≥9 months	45	46.5
≥12 months	21	25.8
≥15 months	10	13.4
≥18 months	3	3.9
≥24 months	0	0.0
≥30 months	0	0.0
≥36 months	0	0.0
Total	158	85.1

Table 5 Cumulative Exposure to Lecanemab in Phase 2/3 Clinical Studies by Duration (Studies 301, 201, and 303)

Population Duration of Exposure	Subjects	Subject-years[a]
Total Phase 2/3 Studies		
≥1 day	2203	2823.3
≥6 weeks	2064	2814.5
≥3 months	1840	2774.6
≥6 months	1621	2693.9
≥9 months	1414	2567.0
≥12 months	1268	2440.2
≥15 months	1195	2357.7
≥18 months	898	1922.2
≥24 months	377	1067.4
≥30 months	171	610.9
≥36 months	105	434.0
Total	2203	2823.3

BAN2401-G000-201: Duration of core exposure (weeks) is defined as ([date of last core dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly).

Duration of extension exposure (weeks) is defined as [date of last dose – date of first extension dose + 1]/7 + 1 treatment cycle (2 weeks).

Total exposure is core exposure + extension exposure, ignoring gap period.

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks).

BAN2401-G000-303: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly). Study 303 is blinded and exposure includes subjects who are randomized to placebo. 1:1 randomization is used to estimate lecanemab exposure.

a: Subject-years = total duration of exposure (weeks)/52.

b: Includes Phase 2/3 Studies BAN2401-G000-201 (Core and Extension) and BAN2401-G000-301 (Core and Extension).

c: Includes Phase 3 Study BAN2401-G000-303. This study is blinded and the number of lecanemab subjects have been estimated (total number/2).

Table 6 Cumulative Exposure to Lecanemab in the Study 301 Indicated Population by Duration

Population **Duration of Exposure**[b]	Subjects	Subject-years[a]
≥1 day	757	996.8
≥6 weeks	729	995.4
≥3 months	705	991.0
≥6 months	685	983.4
≥9 months	660	967.9
≥12 months	638	948.1
≥15 months	618	925.8
≥18 months	190	288.0
Total	757	996.8

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks).

a: Subject years = total duration of exposure (weeks)/52.

b: Includes Phase 3 Study BAN2401-G000-301 (Core)

Table 7 Exposure to Lecanemab in Clinical Trials by Age Group and Gender - Phase 1 Studies (Studies 101, 104, and 004)

Population Age Group	Subjects		Subject-months[a]	
	Male	Female	Male	Female
Healthy Subjects[b]				
Adults (<65 years)	38	21	1.2	0.7
Elderly (≥65 years)	0	0	0.0	0.0
Elderly (≥65 to <75 years)	0	0	0.0	0.0
Elderly (≥75 years)	0	0	0.0	0.0
Alzheimer's Disease[c]				
Adults (<65 years)	11	10	19.7	15.5
Elderly (≥65 years)	30	28	45.1	43.9
Elderly (≥65 to <75 years)	13	18	26.3	28.0
Elderly (≥75 years)	17	10	18.8	15.8

AD = Alzheimer's disease, MAD = multiple ascending dose, MCI = mild cognitive impairment, SAD = single ascending dose.

BAN2401-A001-101: Subjects had mild or moderate AD. For subjects in the SAD phase, duration of exposure is defined as 1 day. For subjects in the MAD phase, duration of exposure is defined as [date of last dose – date of first dose +1] +1 treatment cycle (14 days for 10 mg/kg and 28 days for other groups).

BAN2401-J081-104: Subjects had MCI + mild AD. Duration of exposure is defined as 1 day for the first dose + [date of last dose – date of second dose+1] + 1 treatment cycle (14 days).

a: Subject months = total duration of exposure (days)/30.417.

b: Includes Phase 1 Study BAN2401-A001-004. Duration of exposure is defined as 1 day for subjects receiving a single dose of lecanemab.

c: Includes Phase 1 Studies BAN2401-A001-101 and BAN2401-J081-104.

Table 8 Exposure to Lecanemab in Phase 2/3 Clinical Trials by Age Group and Gender (Studies 301, 201, and 303)

Population Age Group	Subjects		Subject-years[a]	
	Male	Female	Male	Female
Early Alzheimer's Disease[b]				
Adults (<65 years)	200	207	261.3	288.2
Elderly (≥65 years)	815	823	1119.6	1069.1
Elderly (≥65 to <75 years)	415	472	572.6	607.4
Elderly (≥75 years)	400	351	547.0	461.7
Preclinical Alzheimer's Disease[c]				
Adults (<65 years)	6	17	4.5	6.7
Elderly (≥65 years)	52	84	30.3	43.6
Elderly (≥65 to <75 years)	41	65	24.5	34.1
Elderly (≥75 years)	12	19	5.9	9.5

BAN2401-G000-201: Duration of core exposure (weeks) is defined as [date of last core dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly).

Duration of extension exposure (weeks) is defined as [date of last dose – date of first extension dose + 1]/7 +1 treatment cycle (2 weeks).

Total exposure is core exposure + extension exposure, ignoring gap period.

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks)

BAN2401-G000-303: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly). Study 303 is blinded, and exposure includes subjects who are randomized to placebo. 1:1 randomization is used to estimate lecanemab exposure.

a: Subject-years = total duration of exposure (weeks)/52.

b: Includes Phase 2/3 Studies BAN2401-G000-201 (Core and OLE Phase) and BAN2401-G000-301 (Core and OLE Phase).

c: Includes Phase 3 Study BAN2401-G000-303. This study is blinded and the number of lecanemab subjects have been estimated (total number/2).

Table 9 Exposure to Lecanemab in the Study 301 Indicated Population by Age Group and Gender

Table 10 Exposure to Lecanemab in Clinical Trials by Dose - Phase 1 Studies (Studies 101, 104, and 004)

Population Dose Level	Subjects	Subject-months[a]
Healthy Subjects[b]		
10 mg/kg single dose	30	1.0
All other dose regimens or routes of administration[c]	29	1.0
Alzheimer's Disease[d]		
10 mg/kg biweekly	19	35.5
All other doses[c]	60	88.6

AD = Alzheimer's disease, IV = intravenous, MAD = multiple ascending dose, MCI = mild cognitive impairment, SAD = single ascending dose.

BAN2401-A001-101: Subjects had mild or moderate AD. For subjects in the SAD phase, duration of exposure is defined as 1 day. For subjects in the MAD phase, duration of exposure is defined as [date of last dose – date of first dose +1] +1 treatment cycle (14 days for 10 mg/kg and 28 days for other groups).

BAN2401-J081-104: Subjects had MCI + mild AD. Duration of exposure is defined as 1 day for the first dose + [date of last dose – date of second dose+1] + 1 treatment cycle (14 days).

a: Subject months = total duration of exposure (days)/30.417.

b: Includes Phase 1 Study BAN2401A001004. Duration of exposure is defined as 1 day for subjects receiving a single dose of lecanemab.

c: Subject who received only protocol specified doses other that '10 mg/kg IV biweekly' are counted in the 'All other doses' category.

d: Includes Phase 1 Studies BAN2401-A001-101 and BAN2401-J081-104.

Table 11 Exposure to Lecanemab in Phase 2/3 Clinical Trials by Dose (Studies 301, 201, and 303)

Population Dose Level	Subjects	Subject-years[a]
Early Alzheimer's Disease[b]		
10 mg/kg biweekly[c]	1694	2334.5
All other doses	351	403.7
Preclinical Alzheimer's Disease[d]		
10 mg/kg biweekly[c]	88	56.9
All other doses	71	28.2

IV = intravenous.

BAN2401-G000-201: Duration of core exposure (weeks) is defined as ([date of last core dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly).

Duration of extension exposure (weeks) is defined as [date of last dose – date of first extension dose + 1]/7 +1 treatment cycle (2 weeks).

Total exposure is core exposure + extension exposure, ignoring gap period.

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks)

BAN2401-G000-303: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly). Study 303 is blinded, and exposure includes subjects who are randomized to placebo. 1:1 randomization is used to estimate lecanemab exposure.

a: Subject years = total duration of exposure (weeks)/52.

b: Includes Phase 2/3 Studies BAN2401-G000-201 (Core and OLE Phase) and BAN2401-G000-301 (Core and OLE Phase).

c: Subjects who received at least 1 dose of 10 mg/kg IV biweekly are counted in the 10 mg/kg biweekly group. Subjects who received only other protocol specified doses are counted in the 'All other doses' category.

d: Includes Phase 3 Study BAN2401-G000-303. This study is blinded and the number of lecanemab subjects have been estimated (total number/2).

Table 12 Exposure to Lecanemab in the Study 301 Indicated Population by Dose

Population **Dose Level**	Subjects	Subject-years[a]
Early Alzheimer's Disease[b]		
10 mg/kg biweekly	757	996.8

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks)

a: Subject-years = total duration of exposure (weeks)/52.

b: Includes Phase 3 Study BAN2401-G000-301 (Core)

Table 13 Exposure to Lecanemab in Clinical Trials by Race/Ethnicity - Phase 1 Studies (Studies 101, 104, and 004)

Population	Healthy Subjects[a]		Alzheimer's Disease[b]	
	Subjects	Subject months[c]	Subjects	Subject months[c]
Race				
White	33	1.1	46	62.2
Black or African American	12	0.4	12	14.6
Asian	14	0.5	20	43.6
Chinese	0	0.0	0	0.0
Japanese	5	0.2	19	43.6
Other Asian	9	0.3	0	0.0
Not recorded	0	0.0	1	0.0
Other	0	0.0	1	3.7
Missing	0	0.0	0	0.0
Total	59	1.9	79	124.1
Ethnicity				
Hispanic or Latino	22	0.7	8	13.5
Not Hispanic or Latino[d]	37	1.2	71	110.5
Missing	0	0.0	0	0.0
Total	59	1.9	79	124.1

AD = Alzheimer's disease, MAD = multiple ascending dose, MCI = mild cognitive impairment, SAD = single ascending dose.

BAN2401-A001-101: Subjects had mild or moderate AD. For subjects in the SAD phase, duration of exposure is defined as 1 day. For subjects in the MAD phase, duration of exposure is defined as [date of last dose – date of first dose +1] +1 treatment cycle (14 days for 10 mg/kg and 28 days for other groups).

BAN2401-J081-104: Subjects had MCI + mild AD. Duration of exposure is defined as 1 day for the first dose + [date of last dose – date of second dose+1] + 1 treatment cycle (14 days).

a: Includes Phase 1 Study BAN2401-A001-004. Duration of exposure is defined as 1 day for subjects receiving a single dose of lecanemab.

b: Includes Phase 1 Studies BAN2401-A001-101 and BAN2401-J081-104.

c: Subject months = total duration of exposure (days)/30.417.

d: Ethnicity was not recorded in Study BAN2401-J081-104; therefore, all subjects are reported under 'Not Hispanic or Latino'.

Table 14 Exposure to Lecanemab in Clinical Trials by Race/Ethnicity - Phase 2/3 Studies (Studies 301, 201, and 303)

Population	Early Alzheimer's Disease[a]		Preclinical Alzheimer's Disease[b]	
	Subjects	Subject years[c]	Subjects	Subject years[c]
Race				
White	1642	2180.4	147	80.7
Black or African American	51	62.7	2	0.2
Asian	295	417.7	9	3.1
Chinese	6	8.7	0	0.0
Japanese	167	272.3	0	0.0
Other Asian	122	136.8	0	0.0
Not recorded	0	0.0	9	3.1
Other	36	49.8	2	1.0
Missing	21	27.6	0	0.0
Total	2045	2738.2	158	85.1
Ethnicity				
Hispanic or Latino	202	236.9	9	5.1
Not Hispanic or Latino	1794	2443.4	149	79.9
Missing	49	57.9	0	0.0
Total	2045	2738.2	158	85.1

BAN2401-G000-201: Duration of core exposure (weeks) is defined as [date of last core dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly).

Duration of extension exposure (weeks) is defined as [date of last dose – date of first extension dose + 1]/7 +1 treatment cycle (2 weeks).

Total exposure is core exposure + extension exposure, ignoring gap period.

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks).

BAN2401-G000-303: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks for biweekly and 4 weeks for monthly). Study 303 is blinded, and exposure includes subjects who are randomized to placebo. 1:1 randomization is used to estimate lecanemab exposure.

a: Includes Phase 2/3 Studies BAN2401-G000-201 (Core and OLE Phase) and BAN2401-G000-301 (Core and OLE Phase).

b: Includes Phase 3 Study BAN2401-G000-303. This study is blinded and the number of lecanemab subjects have been estimated (total number/2).

c: Subject years = total duration of exposure (weeks)/52.

Table 15 Exposure to Lecanemab in the Study 301 Indicated Population by Race/Ethnicity

Population	Subjects	Subject years[a]
Early Alzheimer's Disease[b]		
Race		
White	582	758.9
Black or African American	18	22.3
Asian	126	175.8
Chinese	4	4.5
Japanese	74	107.2
Other Asian	48	64.0
Other	18	20.6
Missing	13	19.3
Total	757	996.8
Ethnicity		
Hispanic or Latino	111	132.3
Not Hispanic or Latino	616	824.8
Missing	30	39.8
Total	757	996.8

BAN2401-G000-301: Duration of exposure (weeks) is defined as [date of last dose – date of first dose + 1]/7 + 1 treatment cycle (2 weeks).

a: Subject years = total duration of exposure (weeks)/52.

b: Includes Phase 3 Study BAN2401-G000-301 (Core)

Part II Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 16 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion[a]	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subjects who are breastfeeding or pregnant or subjects planning on becoming pregnant.	No reproductive or development toxicity studies have been conducted and there has been no experience of pregnancy or lactation during the use of lecanemab.	No	Due to the age range of expected use for lecanemab for the approved indication, use of lecanemab in premenopausal women is expected to be very low. The age range of the EAD patient population means it is not possible to perform studies in women who are breastfeeding or pregnant.
• Neurological condition that may contribute to cognitive impairment above and beyond that caused by the subject's AD. • Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject. • Geriatric Depression Scale (GDS) score ≥8 at screening.	To ensure that the efficacy evaluation of subjects with AD was not confounded by underlying condition.	No	The safety profile of lecanemab does not suggest there would be an increased risk if used in these populations.
Suicidal ideation or suicidal behaviour within 6 months before screening, at screening or baseline or been hospitalized or treated for suicidal behaviour in the past 5 years before screening.	This is a standard exclusion criterion for neurological therapies.	No	The safety profile of lecanemab does not suggest there would be an increased risk if used in these populations.

Table 16 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion[a]	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Other significant pathological findings on brain MRI at screening including >4 microhaemorrhages, macrohaemorrhage, superficial siderosis and other findings.	To ensure patient safety as subjects with AD with baseline superficial siderosis, microhaemorrhages, and macrohaemorrhages are at increased risk of developing ARIA-H spontaneously; therefore, their inclusion would have impacted the ability of the trial to detect ARIA-H related to the study therapy.	No	While this was an exclusion criterion for Study 301 and Study 201 Core, individuals who experienced these events were allowed to continue in the Open -label Extension (OLE) Phases; therefore, the safety profile is characterized and no difference in the safety profile was observed. ARIA-H is included in Table 21 as an important identified risk.
History of transient ischemic attacks, stroke, or seizures within 12 months of screening.	To ensure that the efficacy evaluation of subjects with AD was not confounded by underlying condition.	No	While this was an exclusion criterion for Study 301 and Study 201 Core, individuals who experienced these events were allowed to continue in the OLE Phases and the data do not suggest an increased risk with the use of lecanemab in these individuals.
Any immunological disease which is not adequately controlled, or that requires treatment with biological drugs during the study.	To ensure that the safety and efficacy evaluation of subjects with AD was not confounded by underlying condition or other biological drugs.	No	The safety profile of lecanemab does not suggest there would be an increased risk if used in these populations.
Subjects with malignant neoplasms within 3 years of screening (except for basal or squamous cell carcinoma in situ of the skin, or localised prostate cancer in male subjects).	This is a standard exclusion criterion for clinical studies.	No	While this was an exclusion criterion for Study 301 and Study 201 Core, individuals who experienced these events were allowed to continue in the OLE Phases and the data do not suggest an increased risk with the use of lecanemab in these individuals.

Table 16 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion[a]	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Medical conditions (e.g., cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the subject's safety or interfere with the study assessments.	To ensure that the safety evaluation of subjects with AD was not confounded by underlying condition.	No	While patients are generally not started on a disease-modifying therapy for a chronic condition when they are not stable, some participants in the clinical studies developed acute conditions during the lecanemab clinical studies, and the safety profile did not differ.
Subjects with a bleeding disorder that is not under adequate control.	To ensure patient safety as subjects with a bleeding disorder may be at an increased risk of haemorrhage. A concomitant bleeding disorder that is not under adequate control may represent an additional risk for brain haemorrhage in early AD patients.	No	It is contraindicated for patients to start therapy while a bleeding disorder is not under adequate control. If lecanemab therapy were to be used in these conditions, the concern is for ARIA (specifically, ARIA intracerebral haemorrhage >1 cm in diameter) which is an important identified risk (Table 22).
Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or electrocardiogram (ECG) at screening or baseline.	To ensure that the safety evaluation of subjects with AD was not confounded by underlying condition.	No	Participants in the clinical studies developed acute conditions during the lecanemab clinical studies, and the safety profile did not differ.

AD = Alzheimer's Disease, ARIA = amyloid-related imaging abnormalities, GDS = Geriatric Depression Scale, EAD = early Alzheimer's disease, ECG = electrocardiogram, MRI = magnetic resonance imaging, OLE = open-label extension.

a: Important exclusion criteria from EAD Studies BAN2401-G000-201 Core/OLE Phase, BAN2401-G000-301 Core/OLE Phase, or BAN2401-J081-104.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The lecanemab clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programme

Table 17 Exposure of Special Populations Included or Not in Clinical Trial Development Programme

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	In Study 301 Core, 8.1% of lecanemab -treated subjects had a medical history coding to the SOC of Hepatobiliary disorders.
Patients with renal impairment	In Study 301 Core, 19.3% of lecanemab -treated subjects had a medical history coding to the SOC of Renal and urinary disorders.
Patients with cardiovascular impairment	In Study 301 Core, 26.9% of lecanemab -treated subjects had a medical history coding to the SOC of Cardiac disorders.
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	
Severe Alzheimer's disease	Subjects with preclinical and moderate AD have been included in the lecanemab clinical trial programme. Subjects with severe AD were excluded from the clinical development programme.
Population with relevant different ethnic origin	Over half of subjects in the lecanemab Phase 1 studies were White (57.2%; 55.9% healthy subjects and 58.2% subjects with AD). A total of 17.4% of Black or African American subjects (20.3% healthy subjects and 15.2% subjects with AD) and 24.6% of Asian subjects (23.7% healthy subjects and 25.3 subjects with AD) enrolled in lecanemab Phase 1 studies. Most subjects in the lecanemab Phase 2/3 clinical studies were White (81.2%; 80.3% of subjects with early AD and 93.0% of subjects with preclinical AD). A total of 2.4% of subjects were Black or African American (2.5% of subjects with early AD and 1.3% of subjects with preclinical AD) and 13.8% of subjects were Asian (14.4% of subjects with early AD and 5.7% of subjects with preclinical AD) in the Phase 2/3 lecanemab studies.

Table 17 Exposure of Special Populations Included or Not in Clinical Trial Development Programme

Subpopulations carrying relevant genetic polymorphisms • *APOE4* carrier status	Most subjects in Study 301 Core were *APOE4* carriers (68.6%). Of these, 53.3% were heterozygous carriers and 15.3% were homozygous *APOE4* carriers. In Study 201 Core, the proportion of *APOE4* carriers (heterozygous and homozygous) was higher in the placebo (PBO) (71.0%) than lecanemab 10 mg/kg biweekly (every 2 weeks) (LEC10-BW) group (30.3%). This was a consequence of a protocol amendment required by European Heath Authorities early in the study whereby *APOE4* carriers could no longer be randomized to the LEC10-BW dose, and any *APOE4* carriers at this dose were discontinued if they had less than 6 months of exposure. These actions resulted in an imbalance of *APOE4* carriers at the dose of LEC10-BW (30% *APOE4* carriers), as the response-adaptive randomization allocated most of the *APOE4* carriers to the next most efficacious groups, LEC10-M (88.6% of subjects who were *APOE4* carriers).

AD = Alzheimer's disease, *APOE4* = apolipoprotein E4 variant, LEC10-BW = lecanemab 10 mg/kg biweekly (every 2 weeks), LEC10-M = lecanemab 10 mg/kg monthly, PBO = placebo, SOC = System Organ Class.

Part II Module SV - Postauthorisation Experience

SV.1 Postauthorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Exposure has been calculated based on number of vials of lecanemab dispensed and the number of individual prescriptions.

SV.1.2 Exposure

As of 05 Jul 2024, over [redacted] patients treated with lecanemab with an estimated exposure is more than [redacted] patient-years (in the United States and a small number from China). In addition, there were approximately [redacted] patients treated with lecanemab who have been enrolled in the Japan postmarketing observational study, Study BAN2401-J081-401.

Part II Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

Lecanemab is administered under healthcare professional oversight. In Study 301 Core, incidence of treatment-emergent adverse events (TEAEs) that were reviewed for possible abuse potential were higher in PBO (18 [2.0%]) than LEC10-BW (8 [0.9%]). Overall, incidence was low and included abnormal dreams (PBO 0.7%; LEC10-BW 0.4%), apathy (0.1% each), feeling abnormal, (0.1% each), hallucinations (PBO 0.6%; LEC10-BW 0.2%), auditory hallucinations (PBO 0.3%; LEC10-BW 0.0%) and visual hallucinations (PBO 0.4%; LEC10-BW 0.0%). Based on these results, lecanemab is not anticipated to be a drug with abuse potential. Similar drugs in this class are not known to have abuse potential.

Part II Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 18 Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated). Headache is a very common and unspecific symptom in the elderly and may or may not occur in the setting of ARIA. TEAEs reported in Study 301 were in subjects who did not have ARIA concurrent with (or shortly after) the headache. In Study 301, headache reported after 6 months of exposure has a low probability to be related to ARIA. Therefore, a typical headache episode in a subject with previous positive history for headaches may not be indicative of ARIA if it follows the usual clinical course and is not accompanied by other neurologic features. The risk was generally nonserious and clinically manageable.	Headache
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated. The difference between lecanemab and placebo was small in Study 301 Core and rates of serious events were low (PBO 0.3%; LEC10-BW 0.7%).	Atrial fibrillation
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the PI are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized). Infusion related reactions are typically of lower grades of severity, have onset with first infusion, have low rates of discontinuation, and have a low recurrence rate (regardless of use of preventative medications). In both Study 301 Core and 201 Core, there was no difference in use of preventative medications for preventing subsequent infusion reactions nor in severity of subsequent infusion reactions, and regardless of use of preventative medications, most subjects did not report further infusion-related reactions. The proposed SmPC contains the following language “In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, corticosteroids, or anti-inflammatory drugs prior to future infusions may be considered.”	Infusion-related reactions

ADR = adverse drug reaction, EU = European Union, PI = Product Information, RMP = Risk Management Plan, SmPC = Summary of Product Characteristics.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 19 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact
Important Identified Risks	
ARIA-E/vasogenic cerebral oedema	ARIA can occur in patients with AD treated with Aβ-targeting antibodies, including lecanemab. ARIA-E most commonly presents as brain oedema or sulcal effusion (Greenberg, et al.,2020). In epidemiologic studies and AD clinical studies, the background rates of ARIA-E rate in PBO arms of clinical trials ranges from 1.7% – 2.7% over 18 months (Honig, et al., 2024). MRI signal changes, mostly interpreted as vasogenic cerebral oedema and cerebral microhaemorrhages, have been observed in studies with lecanemab, as well as with other amyloid modifying therapies, particularly N-terminal mAbs of IgG1 type that target Aβ, such as bapineuzumab (Sperling, et al., 2012; Salloway, et al., 2009), gantenerumab (Panza, et al., 2014; Ostrowitzki, et al., 2012), and aducanumab (Salloway, et al., 2022). **Overall Population** In Study 301 Core, ARIA-E was observed more frequently in LEC10-BW subjects than PBO subjects (overall incidence of ARIA-E was 113 [12.6%] in LEC10-BW and 15 [1.7%] in PBO). ARIA-E occurs early in treatment, is mostly asymptomatic, resolves spontaneously regardless of radiographic severity, and asymptomatic radiographically mild ARIA-E can be dosed through without interruption. Increasing number of E4 alleles is a risk factor for ARIA-E; however, the clinical course of ARIA-E remains unchanged. The incidence of symptomatic ARIA-E was low, with no subjects in PBO and 25 (2.8%) subjects in LEC10-BW. **Indicated Population** ARIA-E was observed more frequently in LEC10-BW subjects than PBO subjects (overall incidence of ARIA-E was 67 [8.9%] in LEC10-BW and 10 [1.3%] in PBO). ARIA-E occurs early in treatment, is mostly asymptomatic, resolves spontaneously regardless of radiographic severity, and asymptomatic radiographically mild ARIA-E can be dosed through without interruption. Increasing number of E4 alleles is a risk factor for ARIA-E; however, the clinical course of ARIA-E remains unchanged. The incidence of symptomatic ARIA-E was low, with no subjects in PBO and 12 (1.6%) subjects in LEC10-BW. Consistent with risk minimisation measures implemented in clinical studies, patients treated with lecanemab require MRI monitoring for the potential occurrence of ARIA-E and for dosing management in whom ARIA-E is detected. ARIA-E management includes dose suspension and follow-up MRI assessments in patients with symptomatic or asymptomatic, radiographically moderate or severe ARIA-E until resolution of the ARIA-E episode. Dosing can be resumed following resolution of the ARIA-E episode. Dosing can be continued

Table 19 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact
	uninterrupted for asymptomatic, radiographically mild ARIA-E, with spontaneous resolution.
ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)	ARIA-H represent as a spectrum of haemorrhagic events which can be seen spontaneously as well as in patients treated with anti-amyloid therapies. ARIA-H includes cerebral microhaemorrhage, and superficial siderosis (Greenberg, et al., 2020). In epidemiologic studies and AD clinical studies, the background rates of ARIA-H rate in PBO arms of clinical trials ranges from 8.6% – 13.6% over 18 months (Honig, et al., 2024).ARIA-H can occur in 2 settings: 1) isolated ARIA-H events not associated with ARIA-E and 2) concurrent with ARIA-E. Note that incidences given below are at event level, some subjects may have both ARIA-H microhaemorrhage and superficial siderosis. ***Isolated ARIA-H*** **Overall Population** In Study 301 Core, the incidence of isolated ARIA-H was similar in LEC10-BW and PBO (ARIA-H microhaemorrhage: 60 [6.7%] and 63 [7.0%], respectively; ARIA-H superficial siderosis: 23 [2.6%] and 13 [1.4%], respectively) and both type of events occurred throughout the course of treatment. **Indicated Population** In Study 301 Core, the incidence of isolated ARIA-H was similar in LEC10-BW and PBO (ARIA-H microhaemorrhage: 48 [6.3%] and 40 [5.2%], respectively; ARIA-H superficial siderosis: 17 [2.2%] and 10 [1.3%], respectively) and both type of events occurred throughout the course of treatment. ***Concurrent ARIA-H and ARIA-E*** **Overall Population** The incidence of concurrent ARIA-H and ARIA-E was higher in LEC10-BW compared with PBO (ARIA-H microhaemorrhage: 64 [7.1%] and 3 [0.3%], respectively; ARIA-H superficial siderosis: 25 [2.8%] and 8 [0.9%], respectively), most cases occurred within the first 3 months of treatment. **Indicated Population** The incidence of concurrent ARIA-H and ARIA-E was higher in LEC10-BW compared with PBO (ARIA-H microhaemorrhage: 28 [3.7%] and 2 [0.3%], respectively; ARIA-H superficial siderosis: 14 [1.8%] and 5 [0.7%], respectively), most cases occurred within the first 3 months of treatment. Most treatment-emergent ARIA-H microhaemorrhage and superficial siderosis were asymptomatic and were radiographically mild to moderate in severity. A low number of ARIA-H microhaemorrhage and superficial siderosis events resulted in discontinuation of lecanemab treatment. There were no deaths due to ARIA-H microhaemorrhage and superficial siderosis.

Table 19 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact
	ARIA-H microhaemorrhage and ARIA-H superficial siderosis represent hemosiderin staining observed on MRI which are differentiated by morphology and size. The management and monitoring of these categories are the same, thus both are captured as a single important identified risk. ARIA-H microhaemorrhage and superficial siderosis management includes follow up MRI assessment, potentially with dose suspension depending on radiographic and clinical severity. Dose suspension and follow-up MRI assessments should occur in patients with mild or moderate symptomatic or asymptomatic, radiographically moderate ARIA-H until stabilisation of the ARIA-H episode. Dosing can be resumed following stabilisation and resolution of symptoms, if present, of the ARIA-H episode. In the event of radiographically or symptomatic severe ARIA-H, treatment with lecanemab should be permanently discontinued. Dosing can be continued uninterrupted for asymptomatic, radiographically mild ARIA-H, with spontaneous stabilisation.
Important Identified Risks	

Table 19 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact
ARIA (intracerebral haemorrhage >1 cm in diameter)	The biological mechanism of ARIA intracerebral haemorrhage >1 cm in diameter is poorly understood but may be related to increased cerebrovascular permeability. Published hypotheses suggest that increased cerebrovascular permeability could be caused either by increased Aβ clearance from the parenchyma, leading to saturation of the perivascular drainage system, and/or by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls (Greenberg, et al., 2020; Zago, et al., 2013, Sperling, et al., 2012). Background rates of ARIA intracerebral haemorrhage >1 cm in placebo arms of prior AD clinical trials are 0.4% - 1% and a meta-analysis study found rates of ARIA intracerebral haemorrhage in AD of 2.7 - 5.2 per 1000 person-years (Waziry, et al., 2020). ARIA intracerebral haemorrhage >1 cm in diameter both on PBO and LEC10-BW occurred randomly throughout the course of treatment. **Overall Population** In Study 301 Core, ARIA intracerebral haemorrhage >1 cm in diameter occurred in 2/897 (0.2%; exposure-adjusted rate 1.6 per 1000 person-years) PBO and 6/898 (0.7%; exposure-adjusted rate 5.1 per 1000 person-years) LEC10-BW similar to that in Study 201 Core 0/245 (0%) PBO and 1/161 (0.6%) LEC10-BW. **Indicated Population** ARIA intracerebral haemorrhage >1 cm in diameter occurred in 2/764 (0.3%) subjects on PBO (1.9 per 1000 person-years and 4/757 (0.5%) subjects on LEC10-BW (4.0 per 1000 person-years). The rates of ARIA intracerebral haemorrhage >1 cm in diameter observed in lecanemab is within the expected range for patients with AD. Events of ARIA intracerebral haemorrhage >1 cm in diameter, including fatal events, in patients taking lecanemab have been observed. The risk of ARIA intracerebral haemorrhage >1 cm in diameter is greater for subjects on both LEC10BW and anticoagulation, but the relative contribution from LEC10-BW to this risk is unclear as anticoagulants alone confer a higher risk of ARIA intracerebral haemorrhage >1 cm in diameter in non-AD populations. The risk in AD populations with CAA is not known but is expected to be higher; therefore, any incremental risk cannot be judged.
Important Potential Risks	
Acceleration of disease progression due to ARIA induced brain atrophy	Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed.
Missing Information	
None	None

Table 19 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-Benefit Impact

Aβ = amyloid beta, AD = Alzheimer's disease, *APOE4* = apolipoprotein E4 variant, ARIA--E = amyloid-related- imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit, CAA = cerebral amyloid angiopathy, IgG = immunoglobulin G, LEC10-BW = lecanemab 10 mg/kg biweekly (every 2 weeks), mAb = monoclonal antibody, MRI = magnetic resonance imaging, PBO = placebo, RMP = Risk Management Plan.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not Applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks

Table 20 Important Identified Risk: ARIA-E/Vasogenic Cerebral Oedema

Potential mechanisms	The biological mechanism of ARIA-E is poorly understood but may be related to increased cerebrovascular permeability. Published hypotheses suggest that increased cerebrovascular permeability could be caused either by increased Aβ clearance from the parenchyma, leading to saturation of the perivascular drainage system, and/or by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls (Greenberg, et al., 2020; Zago, et al., 2013, Sperling, et al., 2012). In epidemiologic studies and AD clinical studies, the background rates of ARIA-E rate in PBO arms of clinical trials ranges from 1.7% – 2.7% over 18 months (Honig, et al., 2024).
Evidence source(s) and strength of evidence	ARIA-E was prospectively identified as a potential effect of mAb based therapies that target Aβ and was considered an important identified risk following a thorough review of the data from Study 301 and Study 201.
Characterization of the Risk	
Frequency	**Overall Population** Data from Study 301 Core for subjects treated with LEC10-BW (n=898) or PBO (n=897) showed the following: • The incidence of ARIA-E was lower in PBO (15/897 [1.7%]) than LEC10-BW (113/898 [12.6%]) • In Study 301 Core, subjects with asymptomatic radiographically mild ARIA-E (n=54) were permitted to continue dosing (per investigators' decision). Of those 54 subjects with mild ARIA-E, 44 continued dosing, with most (32/44 [72.7%] subjects) resolved spontaneously without dose interruption. In Study 201 Core, per protocol, all subjects with ARIA-E were discontinued, therefore a comparison cannot be made. **Indicated Population**

Table 20 Important Identified Risk: ARIA-E/Vasogenic Cerebral Oedema

	Data from Study 301 Core for subjects treated with LEC10-BW (n=757) or PBO (n=764) showed the following: • The incidence of ARIA-E was lower in PBO (10/764 [1.3%]) than LEC10-BW (67/757 [8.9%])
Severity	**Overall Population** *Radiological Severity* In Study 301 Core, of those subjects with ARIA-E, most treatment emergent ARIA–E were radiographically mild (PBO 9/15 [60.0%]; LEC10BW 37/113 [32.7%]) or moderate (PBO 6/15 [40.0%]; LEC10-BW 66/113 [58.4%]) in severity; with no subjects in PBO and 9/113 (7.96%) subjects in LEC10-BW categorized as having radiographically severe ARIA–E. *Clinical Severity* In Study 301 Core, the incidence of symptomatic ARIA-E was low, with no subjects in PBO and 25/898 (2.8%) subjects in LEC10-BW. In LEC10-BW, the moderate and severe symptomatic rates were lower in *APOE4* noncarriers or heterozygous *APOE4* carriers than homozygous *APOE4* carriers: • *APOE4* noncarriers, moderate clinical severity: 3/278 (1.1%); severe clinical severity: 0/278. • Heterozygous *APOE4* carriers, moderate clinical severity: 2/479 (0.4%); severe clinical severity: 2/479 (0.4%). • Homozygous *APOE4* carriers, moderate clinical severity: 7/141 (5.0%); severe clinical severity: 1/141 (0.7%). **Indicated Population** *Radiological Severity* In Study 301 Core, of those subjects with ARIA-E, most treatment emergent ARIA–E were radiographically mild (PBO 7/10 [70.0%]; LEC10BW 31/67 [46.3%]) or moderate (PBO 3/10 [30.0%]; LEC10-BW 33/67 [49.3%]) in severity; with no subjects in PBO and 2/67 (3.0%) subjects in LEC10-BW categorized as having radiographically severe ARIA–E. *Clinical Severity* In Study 301 Core, the incidence of symptomatic ARIA-E was low, with no subjects in PBO and 12/757 (1.6%) subjects in LEC10-BW: • *APOE4* noncarriers, moderate clinical severity: 3/278 (1.1%); severe clinical severity: 0/278. Heterozygous *APOE4* carriers, moderate clinical severity: 2/479 (0.4%); severe clinical severity: 2/479 (0.4%).
Reversibility	Most events of ARIA-E in lecanemab clinical studies resolved within 4 months of detection.
Long-term outcomes	In Study 301 Core, most episodes of ARIA-E (81%) resolved within 4 months. All cases of first episode of ARIA-E in LEC10-BW in Study 301 Core resolved. Of the subjects with second ARIA-E episodes, most

Table 20 Important Identified Risk: ARIA-E/Vasogenic Cerebral Oedema

	(96.4%) recovered. Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed.
Impact on quality of life	**Overall Population** Symptomatic ARIA-E occurred in 2.8% of subjects in Study 301. Most symptoms were mild or moderate in severity and transient in nature, their impact is expected to be manageable. **Indicated Population** Symptomatic ARIA-E occurred in 1.6% of subjects in Study 301. Most symptoms were mild or moderate in severity and transient in nature, their impact is expected to be manageable.
Risk groups and risk factors	Data from lecanemab studies and from trials of other anti-Aβ mAbs have shown that the incidence of ARIA-E is dose dependent, occurs early in treatment, with a greater incidence of ARIA-E reported at higher doses. ARIA-E has also been reported more frequently in *APOE4* carriers than in noncarriers and more frequently in homozygous *APOE4* carriers than heterozygous *APOE4* carriers, a finding that was also observed in lecanemab studies. Pre-treatment MRI findings of more than 4 microhemorrhages or an area of superficial siderosis, which are suggestive of severe CAA is a risk factor for ARIA-E.
Preventability	Routine MRI monitoring of all patients who initiate treatment will enable detection and dosing management during ARIA-E episodes. Dose suspension for any symptomatic or radiographically moderate or severe ARIA-E is a potential risk minimisation measure and might prevent a higher incidence of adverse events (AEs) potentially associated with ARIA-E. Because lecanemab does not require titration, most ARIA-E occurs early in treatment (within the first 7 doses) compared with other mAbs with a titration where the period of heightened vigilance needs to be longer.
Impact on the risk benefit balance of the product	AD is a progressive, fatal, neurodegenerative disorder of unknown aetiology and the most common form of dementia among older people. There is a high unmet need for effective treatments that will modify the underlying AD neuropathology to slow clinical progression of the disease, and delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of AD. The lecanemab clinical studies enrolled subjects with early AD (MCI due to AD and mild AD). The clinical data for both efficacy and safety demonstrate a favourable benefit-risk profile. The events of ARIA-E were monitorable and clinically manageable, and in cases of mild radiographic severity, dosing could be continued. Severe events of ARIA-E were infrequently reported. The proposed SmPC includes language on monitoring for ARIA-E and dosing recommendations for patients with ARIA-E. The totality of available data demonstrates that LEC10-BW has a positive benefit-risk profile.
Public health impact	**Overall Population**

Table 20 Important Identified Risk: ARIA-E/Vasogenic Cerebral Oedema

	The risk of serious adverse events (SAEs) resulting from ARIA-E was low (7/898 [0.8%]). Overall, 1.0% of LEC10-BW subjects had severe maximum radiographic severity ARIA-E events in Study 301 Core. **Indicated Population** The risk of SAEs resulting from ARIA-E was low (4/757 [0.5%]). Overall, 0.3% of LEC10BW subjects had severe maximum radiographic severity ARIA-E events in Study 301 Core. Considering the rarity of any significant clinical consequences, the development of ARIA-E in lecanemab--treated patients is not anticipated to impact public health.

Aβ = amyloid beta, AD = Alzheimer's disease, AE = adverse event, *APOE4* = apolipoprotein E4 variant, ARIA-E = amyloid related- imaging abnormalities – oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly (every 2 weeks), mAb = monoclonal antibody, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, PBO = placebo, SAE = serious adverse event, SmPC = Summary of Product Characteristics.

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

Potential mechanisms	The biological mechanism of ARIA-H is poorly understood but may be related to increased cerebrovascular permeability. Published hypotheses suggest that increased cerebrovascular permeability could be caused either by increased Aβ clearance from the parenchyma, leading to saturation of the perivascular drainage system, and/or by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls (Greenberg, et al., 2020; Zago, et al., 2013, Sperling, et al., 2012). In epidemiologic studies and AD clinical studies, the background rates of ARIA-H in PBO arms of clinical trials ranges from 8.6% – 13.6% over 18 months (Honig, et al., 2024).
Evidence source(s) and strength of evidence	ARIA-H (cerebral microhaemorrhage and superficial siderosis) was prospectively identified as a potential effect of mAb based therapies that target Aβ.
Characterization of the Risk	
Frequency	**Overall Population** Data from the PBO controlled Study 301 Core for subjects treated with LEC10-BW (n=898) or PBO (n=897) showed the following (note that incidences given are at event level, some subjects may have both ARIA-H microhaemorrhage and superficial siderosis): *Isolated ARIA-H (microhaemorrhage and superficial siderosis)* • The overall incidence of isolated ARIA-H was similar in LEC10-BW and PBO (ARIA-H microhaemorrhage: 60 [6.7%] and 63 [7.0%], respectively; ARIA-H superficial siderosis: 23 [2.6%] and 13 [1.4%], respectively) • PBO rates increased from noncarriers (ARIA-H microhaemorrhage: 9/286 [3.1%]; ARIA-H superficial siderosis: 1/286 [0.3%]), to heterozygous *APOE4* carriers ARIA-H microhaemorrhage: 31/478 [6.5%]; ARIA-H superficial siderosis: 9/478 [1.9%]), to homozygous *APOE4* carriers (ARIA-H microhaemorrhage: 23/133 [17.3%]; ARIA-H superficial siderosis: 3/133 [2.3%]). LEC10-BW showed a similar pattern of increasing frequency based on increasing number of *E4* alleles. • Isolated ARIA-H microhaemorrhage and superficial siderosis events occurred throughout the course of PBO treated and LEC10-BW-treated subjects. *Concurrent ARIA-E and ARIA-H (*microhaemorrhage and superficial siderosis) • The overall incidence of concurrent ARIA-E and ARIA-H was lower in PBO than LEC10-BW (ARIA-H microhaemorrhage: 3 [0.3%] and 64 [7.1%], respectively; ARIA-H superficial siderosis: 8 [0.9%] and 25 [2.8%], respectively), • PBO rates increase from noncarriers (ARIA-H microhaemorrhage: 0/286 [0%]; ARIA-H superficial siderosis: 1/286 [0.3%], to heterozygous *APOE4* carriers (ARIA-H microhaemorrhage: 2/478 [0.4%]; ARIA-H superficial siderosis: 4/478 [0.8%], to

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

	homozygous *APOE4* carriers (ARIA-H microhaemorrhage: 1/133 [0.8%]; ARIA-H superficial siderosis: 3/133 [2.3%]. LEC10-BW showed a similar pattern of increasing frequency based on increasing number of *E4* alleles. *Overall ARIA-H* *Cerebral microhaemorrhage:* • PBO, 68/897 (7.6%); LEC10-BW, 126/898 (14.0%) o For PBO, 9/286 (3.1%) were noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers, and 25/133 (18.8%) were homozygous *APOE4* carriers. o For LEC10-BW, 20/278 (7.2%) were noncarriers, 58/479 (12.1%) were heterozygous *APOE4* carriers, and 48/141 (34.0%) were homozygous *APOE4* carriers. *Cerebral microhaemorrhage >10* • PBO 1/897 (0.1%); LEC10-BW 27/898 (3.0%) o For PBO, 0/286 were noncarriers, 1/478 (0.2%) were heterozygous *APOE4* carriers, and 0/133 were homozygous *APOE4* carriers. o For LEC10-BW, 0/278 were noncarriers, 8/479 (1.7%) were heterozygous *APOE4* carriers, and 19/141 (13.5%) were homozygous *APOE4* carriers. *Cerebral microhaemorrhage ≤10* • PBO 68/897 (7.6%); LEC10-BW 119/898 (13.3%) o For PBO, 9/286 (3.1%) were noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers, and 25/133 (18.8%) were homozygous *APOE4* carriers. o For LEC10-BW, 20/278 (7.2%) were noncarriers, 57/479 (11.9%) were heterozygous *APOE4* carriers, and 42/141 (29.8%) were homozygous *APOE4* carriers. *Superficial siderosis* • PBO, 21/897 (2.3%); LEC10-BW, 50/898 (5.6%) o For PBO, 2/286 (0.7%) were noncarriers, 13/478 (2.7%) were heterozygous *APOE4* carriers, and 6/133 (4.5%) were homozygous *APOE4* carriers. o For LEC10-BW, 13/278 (4.7%) were noncarriers, 19/479 (4.0%) were heterozygous *APOE4* carriers, and 18/141 (12.8%) were homozygous *APOE4* carriers. **Indicated Population** Data from Study 301 Core for subjects treated with LEC10-BW (n=757) or PBO (n=764) showed the following (note that incidences

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

	given are at event level, some subjects may have both ARIA-H microhaemorrhage and superficial siderosis): *Isolated ARIA-H (microhaemorrhage and superficial siderosis)* • The overall incidence of isolated ARIA-H was similar in LEC10-BW and PBO (ARIA-H microhaemorrhage: 48 [6.3%] and 40 [5.2%], respectively; ARIA-H superficial siderosis: 17 [2.2%] and 10 [1.3%], respectively). • PBO rates increased from noncarriers (ARIA-H microhaemorrhage: 9/286 [3.1%]; ARIA-H superficial siderosis: 1/286 [0.3%]), to heterozygous *APOE4* carriers ARIA-H microhaemorrhage: 31/478 [6.5%]; ARIA-H superficial siderosis: 9/478 [1.9%]). LEC10-BW showed a similar pattern. • Isolated ARIA-H microhaemorrhage and superficial siderosis events occurred throughout the course of PBO treated and LEC10-BW-treated subjects. *Concurrent ARIA-E and ARIA-H (*microhaemorrhage and superficial siderosis) • The overall incidence of concurrent ARIA-E and ARIA-H was lower in PBO than LEC10-BW (ARIA-H microhaemorrhage: 2 [0.3%] and 28 [3.7%], respectively; ARIA-H superficial siderosis: 5 [0.7%] and 14 [1.8%], respectively). • PBO rates increase from noncarriers (ARIA-H microhaemorrhage: 0/286 [0%]; ARIA-H superficial siderosis: 1/286 [0.3%], to heterozygous *APOE4* carriers (ARIA-H microhaemorrhage: 2/478 [0.4%]; ARIA-H superficial siderosis: 4/478 [0.8%]. LEC10-BW showed a similar pattern. *Overall ARIA-H* *Cerebral microhaemorrhage:* • PBO, 43/764 (5.6%); LEC10-BW, 78/757 (10.3%) o For PBO, 9/286 (3.1%) were noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers o For LEC10-BW, 20/278 (7.2%) were noncarriers, 58/479 (12.1%) were heterozygous *APOE4* carriers *Cerebral microhaemorrhage >10* • PBO 1/764 (0.1%); LEC10-BW 8/757 (1.1%) o For PBO, 0/286 were noncarriers, 1/478 (0.2%) were heterozygous *APOE4* carriers. o For LEC10-BW, 0/278 were noncarriers, 8/479 (1.7%) were heterozygous *APOE4* carriers *Cerebral microhaemorrhage ≤10* • PBO 42/764 (5.5%); LEC10-BW 70/757 (9.2%)

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

	○ For PBO, 9/286 (3.1%) were noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers. ○ For LEC10-BW, 20/278 (7.2%) were noncarriers, 57/479 (11.9%) were heterozygous *APOE4* carriers. *Superficial siderosis* • PBO, 15/764 (2.0%); LEC10-BW, 32/757 (4.2%) ○ For PBO, 2/286 (0.7%) were noncarriers, 13/478 (2.7%) were heterozygous *APOE4* carriers. ○ For LEC10-BW, 13/278 (4.7%) were noncarriers, 19/479 (4.0%) were heterozygous *APOE4* carriers.
Severity	**Overall Population** Most events of isolated ARIA-H microhaemorrhage and superficial siderosis in Study 301 Core were mild or moderate in severity. • Most treatment emergent ARIA–H were radiographically mild (ARIA-H microhaemorrhage: PBO 61/897 [6.8%]; LEC10-BW 52/898 [5.8%]; ARIA-H superficial siderosis: PBO 12/897 [1.3%]; LEC10-BW 20/898 [2.2%]) to moderate (ARIA-H microhaemorrhage PBO 2/897 [0.2%]; LEC10-BW 7/898 [0.8%] ARIA-H superficial siderosis: PBO 1/897 [0.1%]; LEC10-BW 2/898 [0.2%])) in severity; with few reporting severe ARIA–H (ARIA-H microhaemorrhage: PBO 0; LEC10-BW 1/898 [0.1%]; ARIA-H superficial siderosis: PBO 0; LEC10-BW 1/898 [0.1%]). • Symptomatic ARIA-H microhaemorrhage was reported in 2/897 (0.2%) PBO and in 1/898 (0.1%) LEC10-BW. Symptomatic superficial siderosis was reported in 0/897 (0%) PBO and in 1/898 (0.1%) **Indicated Population** Most events of isolated ARIA-H microhaemorrhage and superficial siderosis in the indicated population were mild or moderate in severity. • Most treatment emergent ARIA–H were radiographically mild (ARIA-H microhaemorrhage: PBO 40/764 [5.2%]; LEC10-BW 43/757 [5.7%]; ARIA-H superficial siderosis: PBO 9/764 [1.2%]; LEC10-BW 15/757 [2.0%]) to moderate (ARIA-H microhaemorrhage PBO 0/764 [0%]; LEC10-BW 4/757 [0.5%] ARIA-H superficial siderosis: PBO 1/764 [0.1%]; LEC10-BW 1/757 [0.1%]) in severity; with few reporting severe ARIA–H (ARIA-H microhaemorrhage: PBO 0/764; LEC10-BW 1/757 [0.1%]; ARIA-H superficial siderosis: PBO 0/764; LEC10-BW 1/757 [0.1%]). • Symptomatic ARIA-H microhaemorrhage was reported in 1/764 (0.1%) PBO and in 1/757 (0.1%) LEC10-BW. Symptomatic superficial siderosis was reported in 0/764 (0%) PBO and in 1/757 (0.1%)
Reversibility	Most cases of ARIA-H microhaemorrhage and superficial siderosis with PBO and LEC10-BW were ongoing at the end of the Study 301 Core.

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

	MRI findings for ARIA-H microhaemorrhage and superficial siderosis are typically persistent because hemosiderin deposits are generally stable and long-lived.
Long-term outcomes	In Study 301 Core, of the cases of first episode of cerebral microhaemorrhage or superficial siderosis, the first episode events had resolved radiographically in 14/112 and 2/48 of LEC10-BW treated subjects, respectively. Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed.
Impact on quality of life	Symptoms can occur in the setting of ARIA-H microhaemorrhage and superficial siderosis including headache, confusional state, and dizziness. Most symptoms were mild or moderate and a minority of subjects experienced severe symptoms.
Risk groups and risk factors	ARIA-H microhaemorrhage and superficial siderosis has been reported more frequently in *APOE4* carriers than in noncarriers, a finding that was also observed in lecanemab studies. Patients with cerebral small vessel disease (lacunar infarct, diffuse white matter disease) and patients taking anticoagulant treatments may be at increased risk of ARIA. Pre-treatment MRI findings of more than 4 microhaemorrhages or an area of superficial siderosis, which are suggestive of severe CAA is an independent risk factor for ARIA-H.
Preventability	Routine MRI monitoring of all patients who initiate treatment will enable detection and dosing management during ARIA-H microhaemorrhage and superficial siderosis episodes. Dose suspension and follow-up MRI assessments should occur in patients with mild or moderate symptomatic or asymptomatic, radiographically moderate ARIA-H until stabilisation of the ARIA-H episode. Dosing can be resumed following stabilisation of the ARIA-H episode. In the event of radiographically or symptomatic severe ARIA-H, treatment with lecanemab should be permanently discontinued. Dosing can be continued uninterrupted for asymptomatic, radiographically mild ARIA-H, with spontaneous stabilisation. These risk minimisation measures for ARIA-H microhaemorrhage and superficial siderosis might prevent a higher incidence of AEs potentially associated with ARIA-H.

Table 21 Important Identified Risk: ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

Impact on the risk benefit balance of the product	AD is a progressive, fatal, neurodegenerative disorder of unknown aetiology and the most common form of dementia among older people. There is a high unmet need for effective treatments that will modify the underlying AD neuropathology to slow clinical progression of the disease, and delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of AD. The lecanemab clinical studies enrolled subjects with early AD (MCI due to AD and mild AD). The clinical data for both efficacy and safety demonstrate a favourable benefit-risk profile. The events of ARIA-H microhaemorrhage and superficial siderosis were monitorable and clinically manageable. The proposed SmPC includes language on monitoring for ARIA and dosing recommendations for patients with ARIA-H. The totality of available data demonstrates LEC10-BW has a positive benefit-risk profile.
Public health impact of safety concern	The risk of SAEs (and the requirement for hospitalisation) resulting from ARIA--H microhaemorrhage and superficial siderosis was low. **Overall Population** Overall, 3.1% and 0.4% of LEC10-BW treated subjects had severe maximum radiographic severity ARIA-H events of microhaemorrhage and superficial siderosis, respectively, in Study 301 Core. **Indicated Population** Overall, 1.3% and 0.3% of LEC10-BW treated subjects had radiographically severe ARIA-H events of microhemorrhage and superficial siderosis respectively as their maximum observed severity in Study 301 Core. Considering the rarity of any significant clinical consequences, the development of ARIA-H in lecanemab-treated patients is not anticipated to impact- public health.

Aβ = amyloid beta, AD = Alzheimer's disease, AE = adverse event, *APOE4* = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit, LEC10-BW = lecanemab 10 mg/kg biweekly (every 2 weeks), mAb = monoclonal antibody, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, PBO = placebo, SAE = serious adverse event, SmPC = Summary of Product Characteristics.

Table 22 Important Identified Risk: ARIA Intracerebral haemorrhage >1 cm in diameter

Potential mechanisms	The biological mechanism of ARIA intracerebral haemorrhage >1 cm in diameter is poorly understood but may be related to increased cerebrovascular permeability. Published hypotheses suggest that increased cerebrovascular permeability could be caused either by increased Aβ clearance from the parenchyma, leading to saturation of the perivascular drainage system, and/or by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls (Greenberg, et al., 2020; Zago, et al., 2013, Sperling, et al., 2012).

	Low rates of ARIA intracerebral haemorrhage >1 cm in diameter with LEC10-BW are consistent with what has been reported in the literature for patients with AD; background rates of ARIA intracerebral haemorrhage >1 cm in diameter in PBO arms of prior AD clinical trials being 0.4% - 1% and a meta-analysis study found rates of ARIA intracerebral haemorrhage >1 cm in AD of 2.7 - 5.2 per 1000 person-years (Waziry, et al., 2020).
Evidence source(s) and strength of evidence	ARIA intracerebral haemorrhage > 1 cm in diameter) was prospectively identified as a potential effect of mAb based therapies that target Aβ and was considered an important identified risk following a thorough review of the data from Study 301 and Study 201.
Characterization of the Risk	
Frequency	**Overall Population** Data from the PBO controlled Study 301 Core for subjects treated with LEC10-BW (n=898) or PBO (n=897) showed the following: • The overall incidence of ARIA intracerebral haemorrhage >1 cm in diameter was lower in PBO 2/897 (0.2%; exposure-adjusted rate 0.0016); LEC10-BW 6/898 (0.7%; exposure-adjusted rate 0.0051) o For PBO 1/286 (0.3%) was a noncarrier, 1/478 (0.2%) was a heterozygous *APOE4* carrier o For LEC10-BW 1/278 (0.4%) was a noncarrier and 3/479 (0.6%) were heterozygous *APOE4* carriers **Indicated Population** Data from the PBO controlled Study 301 Core for subjects treated with LEC10-BW (n=757) or PBO (n=764) showed the following: • The overall incidence of ARIA intracerebral haemorrhage >1 cm in diameter was lower in PBO 2/764 (0.3%; exposure-adjusted rate 0.0019); LEC10-BW 4/757 (0.5%; exposure-adjusted rate 0.0040)
Severity	**Overall Population** Events of ARIA intracerebral haemorrhage >1 cm in diameter in Study 301 Core were mild (2/898 [0.2%]) or moderate in severity (2/898 [0.2%]). Severe events occurred in 1/897 (0.1%) PBO and 2/898 (0.2%) LEC10-BW). • Symptomatic ARIA intracerebral haemorrhage >1 cm in diameter was reported in 1/897 (0.1%) in PBO and 3/898 (0.3%) in LEC10-BW **Indicated Population** Events of ARIA intracerebral haemorrhage >1 cm in diameter in the indicated population were mild (1/757 [0.1%]) or moderate in severity (2/757 [0.3%]). Severe events occurred in 1/764 (0.1%) PBO and 2/757 (0.3%) LEC10-BW • Symptomatic ARIA intracerebral haemorrhage >1 cm in diameter was reported in 1/764 (0.1%) in PBO and 3/757 (0.4%) in LEC10-BW
Reversibility	All cases of ARIA intracerebral haemorrhage >1 cm in diameter (Table 22) with PBO and LEC10-BW were ongoing, which was expected.

Long term outcomes	In Study 301 Core, for events of ARIA intracerebral haemorrhage >1 cm in diameter, the events had not resolved radiographically (0/6 of LEC10-BW treated subjects). Of these subjects, 3/6 were symptomatic. Of the 3 symptomatic subjects, symptoms resolved in 2 subjects and one had residual symptoms (dysarthria, asthenia) at the time of discontinuation. The one ICH > 1 cm on placebo was fatal.
Impact on quality of life	Symptoms can occur in the setting of intracerebral haemorrhage including headache, vision changes as well as more severe symptoms such as focal neurologic deficits and altered levels of consciousness. These events can be severe, including life threatening and fatal events.
Risk groups and risk factors	*APOE4* carriers may be at increased risk of ARIA intracerebral haemorrhage >1 cm in diameter. Patients taking anticoagulant treatments may be at increased risk of ARIA intracerebral haemorrhage >1 cm in diameter.
Preventability	Routine MRI monitoring of all patients who initiate treatment will enable detection and dosing management during ARIA episodes. Lecanemab dose suspension is recommended for new incident symptomatic or asymptomatic ARIA intracerebral haemorrhage >1 cm in diameter. Lecanemab should be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs. Additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with lecanemab.
Impact on the risk benefit balance of the product	AD is a progressive, fatal, neurodegenerative disorder of unknown aetiology and the most common form of dementia among older people. There is a high unmet need for effective treatments that will modify the underlying AD neuropathology to slow clinical progression of the disease, and delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of AD.
Public health impact of safety concern	The risk of SAEs resulting from ARIA intracerebral haemorrhage >1 cm in diameter was low (cerebral haemorrhage in LEC10-BW. **Overall Population** Severe events occurred in 1/897 (0.1%) PBO and 2/898 (0.2%) LEC10-BW.In each PBO and LEC10-BW, there was 1 event of severe ARIA intracerebral haemorrhage >1 cm in diameter in each treatment group (0.1% each). **Indicated Population** Severe events occurred in 1/764 (0.1%) PBO and 2/757 (0.3%) LEC10-BW. Considering the low incidence of ARIA intracerebral haemorrhage >1 cm in diameter, the development of intracerebral haemorrhage >1 cm in diameter in lecanemab treated patients is not anticipated to impact public health.

Aβ = amyloid beta, AD = Alzheimer's disease, AE = adverse event, *APOE4* = apolipoprotein E4 variant, ARIA = amyloid related imaging abnormalities, CAA = cerebral amyloid angiopathy, LEC10-BW = lecanemab 10 mg/kg biweekly (every 2 weeks), mAb = monoclonal antibody, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, PBO = placebo, SAE = serious adverse event, SmPC = Summary of Product Characteristics.

SVII.3.2 Presentation of Important Potential Risks

Table 23 Important Potential Risks: Acceleration of disease progression due to ARIA induced brain atrophy

Potential mechanisms	The biological mechanism of ARIA is poorly understood but may be related to increased cerebrovascular permeability. Published hypotheses suggest that increased cerebrovascular permeability could be caused either by increased Aβ clearance from the parenchyma, leading to saturation of the perivascular drainage system, and/or by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls (Greenberg, et al., 2020; Zago, et al., 2013, Sperling, et al., 2012, Belder et al., 2024).
Evidence source(s) and strength of evidence	Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed. Across 36 months of treatment, for any threshold of cognitive decline over time in CDR-SB, there was no acceleration of long-term progression for patients with ARIA compared to those without ARIA. Evaluation of subjects through 36 months treatment has not identified long term negative outcomes
Characterization of the Risk	
Frequency	ARIA-E: See Table 20, Frequency ARIA-H (cerebral microhaemorrhage and superficial siderosis): See Table 21, Frequency ARIA intracerebral haemorrhage >1 cm in diameter: See Table 22, Frequency
Severity	ARIA-E: See Table 20, Severity ARIA-H (cerebral microhaemorrhage and superficial siderosis): See Table 21, Severity ARIA intracerebral haemorrhage >1 cm in diameter: See Table 22, Severity
Reversibility	ARIA-E: See Table 20, Reversibility ARIA-H (cerebral microhaemorrhage and superficial siderosis): See Table 21, Reversibility ARIA intracerebral haemorrhage >1 cm in diameter: See Table 22, Reversibility
Long term outcomes	Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed. The important identified risk of ARIA, namely, ARIA-E/vasogenic cerebral oedema, ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis) and ARIA intracerebral haemorrhage >1 cm in diameter are outlined above. The long-term safety in patients with ARIA is supported by clinical data through 36 months total treatment across Study 301 Core and OLE. ARIA-E occurs early in treatment; in Study 301 Core, 92% of ARIA-E occurs within the 1st 6 months of treatment and typically resolves within 4 months. This early onset and resolution allow for long-term follow-up during the remaining Core treatment period and OLE Phase.

Table 23 Important Potential Risks: Acceleration of disease progression due to ARIA induced brain atrophy

	Isolated ARIA-H (cerebral microhaemorrhage and superficial siderosis) occurs at the same rate as PBO, is randomly distributed throughout the treatment period, is almost always asymptomatic, and does not require alterations in dosing. Isolated ARIA-H is part of the natural history of AD and cerebral amyloid angiopathy (CAA), and does not require specific monitoring. In Study 301 Core there was a low discontinuation rate due to ARIA, with most subjects continuing in the study (PBO: 84/85 [99%], LEC10- BW: 173/193 [90%]). The majority of patients who experienced ARIA had subsequent post-ARIA CDR-SB assessment(s) after occurrence of the last treatment-emergent ARIA (PBO: 85/85 [100%], LEC10-BW: 184/193 [95%]), which are included in the primary and sensitivity analyses. Across 36 months of treatment, for any threshold of cognitive decline over time in CDR-SB, there was no acceleration of long-term progression for patients with ARIA compared to those without ARIA.
Impact on quality of life	Evaluation of subjects through 36 months treatment has not identified any impact on quality of life post-ARIA event
Risk groups and risk factors	ARIA has been reported more frequently in *APOE4* carriers than in noncarriers, a finding that was also observed in lecanemab studies. Thus, the *APOE4* homozygotes are not included in the approved indication. However the clinical course of ARIA is the same, irrespective of genotype.
Preventability	Routine MRI monitoring of all patients who initiate treatment will enable detection and dosing management during an ARIA event. Recommendations for dose suspension or discontinuation of treatment depending on the type of ARIA event are outlined in: ARIA-E: See Table 20, Preventability ARIA-H (cerebral microhaemorrhage and superficial siderosis): See Table 21, Preventability ARIA intracerebral haemorrhage >1 cm in diameter: See Table 22, Preventability
Impact on the risk benefit balance of the product	AD is a progressive, fatal, neurodegenerative disorder of unknown aetiology and the most common form of dementia among older people. There is a high unmet need for effective treatments that will modify the underlying AD neuropathology to slow clinical progression of the disease, and delay, halt, or reverse the pathophysiological processes that ultimately lead to the clinical deficits of AD.
Public health impact of safety concern	The risk of serious adverse events (SAEs) (and the requirement for hospitalisation) resulting from ARIA-E, ARIA-H (cerebral microhaemorrhage and superficial siderosis) and ARIA intracerebral haemorrhage >1 cm in diameter was low. **Overall Population** • ARIA-E: Overall, 1.0% of LEC10-BW subjects had severe maximum radiographic severity ARIA-E events in Study 301 Core. • ARIA-H (cerebral microhaemorrhage and superficial siderosis): Overall, 3.1% and 0.4% of LEC10-BW treated subjects had severe maximum radiographic severity ARIA-H events of

Table 23 Important Potential Risks: Acceleration of disease progression due to ARIA induced brain atrophy

	microhaemorrhage and superficial siderosis, respectively, in Study 301 Core. • ARIA intracerebral haemorrhage >1 cm in diameter: Severe events occurred in 1/897 (0.1%) PBO and 2/898 (0.2%) LEC10-BW. • Considering the rarity of any significant clinical consequences, the development of ARIA E, ARIA-H (cerebral microhaemorrhage and superficial siderosis) and ARIA intracerebral haemorrhage >1 cm in diameter in lecanemab-treated patients is not anticipated to impact public health. **Indicated Population** • ARIA-E: Overall, 0.3% of LEC10-BW subjects had severe maximum radiographic severity ARIA-E events in Study 301 Core. • ARIA-H (cerebral microhaemorrhage and superficial siderosis): Overall, 1.3% and 0.3% of LEC10-BW treated subjects had severe maximum radiographic severity ARIA-H events of microhemorrhage and superficial siderosis respectively in Study 301 Core. • ARIA intracerebral haemorrhage >1 cm in diameter: Severe events occurred in 1/764 (0.1%) PBO and 2/757 (0.3%) LEC10-BW. • Considering the rarity of any significant clinical consequences, the development of ARIA E, ARIA-H (cerebral microhaemorrhage and superficial siderosis) and ARIA intracerebral haemorrhage >1 cm in diameter in lecanemab-treated patients is not anticipated to impact public health.

SVII.3.3 Presentation of the Missing Information

None.

Part II Module SVIII - Summary of the Safety Concerns

Table 24 Summary of Safety Concerns

Important identified risks	• ARIA-E/vasogenic cerebral oedema • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • ARIA intracerebral haemorrhage >1 cm in diameter
Important potential risks	• Acceleration of disease progression due to ARIA induced brain atrophy
Missing information	None

ARIA-E = -amyloid related imaging abnormalities – oedema/effusion, ARIA--H = amyloid-related imaging abnormalities microhaemorrhage- and hemosiderin deposit.

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

For all safety concerns, routine pharmacovigilance is conducted. Appropriate patient selection, dose adjustment in case of ARIA-E and ARIA-H is specified in the SmPC. Recognition of ARIA-E, ARIA-H (microhaemorrhage and superficial siderosis), and ARIA intracerebral haemorrhage > 1 cm in diameter, with a description of events and symptoms, need for medical advice, and need for diagnostics; as well as dose adjustments, are described in the SmPC and PI. Activities beyond adverse reactions reporting and signal detection are presented in Table 25.

Table 25 Specific Adverse Reaction Follow-Up Questionnaires

Follow-Up Questionnaire (Annex 4)	Safety Concerns	Purpose
Eisai lecanemab questionnaire for reports of suspected ARIA	• ARIA--E/vasogenic cerebral oedema • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • ARIA intracerebral haemorrhage >1 cm in diameter	To monitor the nature of ARIA in postmarketing to further characterise the risk

ARIA-E = amyloid-related imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit.

III.2 Additional Pharmacovigilance Activities

1. Acceleration of Disease Progression Due to ARIA Induced Brain Atrophy

Data from Study BAN2401-G000-301 OLE and BAN2401-G000-303 and patient registry will further characterise the important potential of "Acceleration of disease progression due to ARIA induced brain atrophy":

Study name and title: BAN2401-G000-301 OLE

A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease

Rationale and study objectives:

To evaluate the long-term safety and tolerability of LEC10-BW in subjects with early Alzheimer's disease in the Extension Phase.

Milestones:

Study is ongoing. Subjects will receive 10 mg/kg IV, biweekly treatment with BAN2401 (or if participating in the optional subcutaneous (vial) substudy, weekly subcutaneous injections of 720 mg, administered as 2 consecutive injections of 360mg (2x1.8mL of 400 mg/2 mL SC formulation) for up to 2 years, or until BAN2401 is commercially available, or until a positive risk-benefit assessment in this indication is not demonstrated.

[redacted] [redacted]

Study name and title: BAN2401-G000-303

Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study with an Extension Phase to Evaluate Efficacy and Safety of Treatment With BAN2401 in Subjects With Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)

Rationale and study objectives:

To evaluate efficacy and safety of lecanemab in the preclinical AD population.

Milestones:

Study is ongoing. Subjects will receive lecanemab for up to 216 weeks.

Interim Report	Not applicable
Final Report Submission:	[redacted]

EU Lecanemab All-Patient Registry (Imposed Category I study)

Study name and title: *Pending. Will be amended, when the protocol is approved.*

Pending - Registry

Rationale and study objectives:

[redacted]

Milestones:

[redacted]

III.3 Summary Table of Additional Pharmacovigilance Activities

A summary of the studies included in the pharmacovigilance plan is summarised in Table 26.

Table 26 Ongoing and planned additional pharmacovigilance activities

Study name and description Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
[redacted]				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities				
BAN2401-G000-301 OLE	Evaluate the long-term safety and tolerability of LEC10-BW in subjects with early Alzheimer's disease in the Extension Phase.	Acceleration of disease progression due to ARIA induced brain atrophy	[redacted]	
BAN2401-G000-303	To evaluate efficacy and safety of lecanemab in the preclinical AD population.			

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 27 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
ARIA--E/vasogenic cerebral oedema	Routine risk communication: • SmPC Section 4.2, Section 4.3, Section 4.4, and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine MRI monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA-E is provided in Section 4.2 and Section 4.4 of the SmPC (PL Section 3). Other routine risk minimisation measures beyond the PI: Legal status: Restricted medicinal prescription
ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)	Routine risk communication: • SmPC Section 4.2, Section 4.3, Section 4.4, and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine MRI monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA-H microhaemorrhage and superficial siderosis is provided in Section 4.2 and Section 4.4 of the SmPC (PL Section 3). Other routine risk minimisation measures beyond the PI: Legal status: Restricted medicinal prescription
ARIA intracerebral haemorrhage >1 cm in diameter	Routine risk communication: • SmPC Section 4.2, Section 4.4 and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine MRI monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA intracerebral haemorrhage >1 cm in diameter is provided in Section 4.2 and Section 4.4 of the SmPC (PL Section 3).

Table 27 Description of Routine Risk Minimisation Measures by Safety Concern

	Other routine risk minimisation measures beyond the PI: Legal status: Restricted medicinal prescription
Important Potential Risks	
Acceleration of disease progression due to ARIA induced brain atrophy	Routine risk minimisation measures N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the PI: • Legal status: Restricted medicinal prescription
Missing Information	
None	

ARIAE = amyloid related- imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities microhaemorrhage- and hemosiderin deposit, MRI = magnetic resonance imaging, PI = Product Information, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

1. Controlled Access Program (CAP)

To ensure appropriate use in clinical practice and prevent off-label use, to provide HCPs with the appropriate information on the safe use of lecanemab and the need for special monitoring of patients before and during treatment a controlled access program will be in place prior to initiation of treatment.

Rationale and objectives:

A controlled access programme is required to promote the safe and effective use of lecanemab and prevent off-label use. Treatment in all patients will be initiated through an imposed central registration system implemented as part of a controlled access programme. The central registration system will ensure appropriate and relevant information on the specified data fields prior to the first infusion of lecanemab, for all patients.

Each HCP will be registered separately before they are able to enroll patients in the CAP. Part of the HCP registration process will require an attestation from the HCP that they have been provided with, and understand, the Guide for Healthcare Professionals and the SmPC and that they meet requirements to comply with the restricted medicinal prescription status (section 4.2 of the SmPC).

Milestones:

Agreement on CAP design (including data parameters and implementation approach):	Post MAA approval

CAP Initiation	Prior to when commercial product is made available
Progress Reports	Annually
Final Report	Not applicable

2. Educational Materials

Additional risk minimisation measures (in the form of an ARIA Guide for Healthcare Professionals) will be implemented for the important identified risks for lecanemab. These are described in detail below.

Additional risk minimisation: Guide for Healthcare Professionals

Physicians who prescribe lecanemab will be educated on the important identified risks to aid prescribers in appropriate patient selection and ensure routine follow-up is arranged.

Objectives:

The objective of the HCP Guide is to provide prescribing physicians and radiologists with educational information on the risks of ARIA and intracerebral haemorrhage >1cm. The HCP Guide is intended to assist physicians in managing the risks of ARIA and ARIA intracerebral haemorrhage >1cm.

Rationale for the additional risk minimisation activity:

Prescribers may not be familiar with ARIA, and it is important that they are provided with material on the management of ARIA and ARIA intracerebral haemorrhage >1cm through MRI monitoring, radiographic severity criteria and treatment recommendations in clinical practice.

Target audience and planned distribution path:

The ARIA materials have been developed for prescribing physicians initiating and supervising treatment with lecanemab and radiologists.

The educational materials will be available in printed and/or electronic copy and will be distributed in EU countries according to local laws and requirements.

Additional risk minimisation: Patient Card

Objectives:

- To inform healthcare professionals that the patient is being treated with lecanemab
- To inform patients and/or caregivers about the clinical symptoms of ARIA that should prompt them to seek medical attention

Rationale for the additional risk minimisation activity:

The lecanemab Patient Card focuses on providing targeted information on the potential clinical symptoms in the setting of ARIA and to reinforce the importance of seeking medical advice in a timely manner, thus promoting patient safety. The Patient Card is to be used by patients to inform healthcare professionals that the patient is being treated with lecanemab.

Target audience and planned distribution path:

The Patient Card is intended for use by patients. It will be available in printed and/or electronic format and will be distributed to the patient at the time of treatment initiation or upon request.

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the HCP Guide and Patient Card will be assessed using ARIA/ICH reporting rates from the registry when they are available.
  - The estimated serious ARIA/ICH reporting rates will be compared to data from the clinical programme and the MAH will propose its own quantitative criteria for success (see Section III.2 - EU Lecanemab All-Patient Registry)
  - To evaluate compliance and effectiveness of the risk minimisation measures described in SmPC and the HCP educational material (such as indication, posology, monitoring and management of ARIA).

V.3 Summary of Risk Minimisation Measures

Table 28 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
ARIA--E/vasogenic cerebral oedema	Routine risk communication: • SmPC Section 4.8 and PL Section 4 where ARIA-E is listed as an ADR • SmPC Sections 4.3, 4.4 and 4.8 where relevant clinical information from clinical studies on the incidence, nature, and risk factors of ARIA-E is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Program	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • [redacted]
ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)	Routine risk communication: • SmPC Section 4.8 and PL Section 4 where ARIA-H is listed as an ADR • SmPC Sections 4.3, 4.4 and 4.8 where relevant clinical information from clinical studies on the incidence, nature, and risk factors of ARIA-H is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Program	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • [redacted]
ARIA Intracerebral Haemorrhage >1 cm in diameter	Routine risk communication: • SmPC Section 4.3, 4.4 and PL Section 4 where ARIA intracerebral haemorrhage >1 cm is listed as an AE that has occurred in patients treated with lecanemab and also	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction

Table 28 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	occurring spontaneously in patients with AD. • SmPC Sections 4.4 and 4.8 where relevant clinical information from clinical studies on the incidence, nature, and risk factors of ARIA is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Program	Additional pharmacovigilance activities: • [redacted]
Important Potential Risk		
Acceleration of disease progression due to ARIA induced brain atrophy	Routine risk minimisation measures • N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Data from ongoing studies BAN2401-G000-301 OLE and BAN2401-G000-303 will be used to further characterise the important potential risks of "Acceleration of disease progression due to ARIA induced brain atrophy". • [redacted]
Missing Information		
None		

ADR = adverse drug reaction, AE = adverse event, ARIAE = amyloid related- imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities microhaemorrhage- and hemosiderin deposit, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for LEQEMBI® (lecanemab)

This is a summary of the risk management plan (RMP) for LEQEMBI. The RMP details important risks of LEQEMBI, how these risks can be minimized, and how additional information will be obtained about LEQEMBI's risks.

LEQEMBI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LEQEMBI should be used.

This summary of the RMP for LEQEMBI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LEQEMBI's RMP.

I The Medicine and What it is Used for

LEQEMBI is indicated for the treatment of mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (AD) in adult patients with no (non-carriers) or one copies (heterozygotes) of the apolipoprotein E ε4 (ApoE ε4) gene. It contains lecanemab as the active substance and it is given intravenously by a qualified healthcare professional (HCP) upon prescription.

Further information about the evaluation of LEQEMBI's benefits can be found in LEQEMBI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of LEQEMBI, together with measures to minimise such risks and the proposed studies for learning more about LEQEMBI 's risks, are outlined below.

Measures to minimise the risks identified for this medicinal product include:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCP
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of LEQEMBI, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken, as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of LEQEMBI is not yet available, it will be listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of LEQEMBI are risks that require special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient evidence of a likely link with the use of LEQEMBI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and requires further evaluation. Missing information refers to information on the safety of the medicinal product that has not yet been collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• ARIA-E/vasogenic cerebral oedema • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • ARIA intracerebral haemorrhage > 1 cm in diameter
Important potential risks	• Acceleration of disease progression due to ARIA induced brain atrophy
Missing information	None

ARIA-E = amyloid-related imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit.

II.B Summary of Important Risks

Important Identified Risks	
ARIA-E/Vasogenic Cerebral Oedema	
Evidence for linking the risk to the medicine	ARIA-E was prospectively identified as a potential effect of monoclonal antibody (mAb)-based therapies that target amyloid beta (Aβ) and was considered an important identified risk following a thorough review of the data from Study 301 and Study 201.
Risk groups and risk factors	Data from lecanemab studies and from trials of other anti-Aβ mAbs have shown that the incidence of ARIA-E is dose dependent, occurs early in treatment, with a greater incidence of ARIA-E reported at higher doses. ARIA-E has also been reported more frequently in

Important Identified Risks	
	apolipoprotein E4 variant (*APOE4)* carriers than in noncarriers and more frequently in homozygous *APOE4* carriers than heterozygous carriers, a finding that was also observed in lecanemab studies.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.2, Section 4.3, Section 4.4, and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine magnetic resonance imaging (MRI) monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA-E is provided in Section 4.2 and Section 4.4 of the SmPC. Additional risk minimisation measures • Patient Card • Guide for healthcare professionals • Controlled Access Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: [redacted] See section II.C of this summary for an overview of the post-authorisation development plan.

Aβ = amyloid beta, APOE4 = apolipoprotein E4 variant, ARIAE = amyloid related imaging abnormalities – oedema/effusion, mAb = monoclonal antibody, MRI = magnetic resonance imaging, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

Important Identified Risks

ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)

Evidence for linking the risk to the medicine	ARIA-H (cerebral microhaemorrhage and superficial siderosis) was prospectively identified as a potential effect of mAb based therapies that target Aβ and was considered an important identified risk following a thorough review of the data from Study 301 and Study 201.
Risk groups and risk factors	ARIA-H has been reported more frequently in *APOE4* carriers than in noncarriers, a finding that was also observed in lecanemab studies. Patients with cerebral small vessel disease (lacunar infarct, diffuse white matter disease) and patients taking anticoagulant treatments may be at increased risk of ARIA.

Important Identified Risks	
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.2, Section 4.3, Section 4.4, and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine MRI monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA-H is provided in Section 4.2 and Section 4.4 of the SmPC. Additional risk minimisation measures • Patient Card • Guide for healthcare professionals • Controlled Access Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: [redacted] See section II.C of this summary for an overview of the post-authorisation development plan.

Aβ = amyloid beta, *APOE4* = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit, mAb = monoclonal antibody, MRI = magnetic resonance imaging, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

ARIA Intracerebral Haemorrhage > 1 cm in diameter	
Evidence for linking the risk to the medicine	ARIA intracerebral haemorrhage >1 cm in diameter was prospectively identified as a potential effect of mAb based therapies that target Aβ and was considered an important identified risk following a thorough review of the data from Study 301 and Study 201.
Risk groups and risk factors	*APOE4* carriers may be at increased risk of ARIA intracerebral haemorrhage >1 cm in diameter. Patients taking anticoagulant treatments may be at increased risk of ARIA intracerebral haemorrhage >1 cm in diameter.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.3, Section 4.4 and Section 4.8 • PL Section 2, Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the required routine MRI monitoring for all patients who initiate treatment and ARIA management guidelines, including follow-up MRI assessments, for patients who experience ARIA is provided in Section 4.2 and Section 4.4 of the SmPC. Additional risk minimisation measures • Patient Card • Guide for healthcare professionals • Controlled Access Program

Important Identified Risks	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: [redacted] See section II.C of this summary for an overview of the post-authorisation development plan.

Aβ = amyloid beta, *APOE4* = apolipoprotein E4 variant, ARIA = amyloid-related imaging abnormalities, mAb = monoclonal antibody, MRI = magnetic resonance imaging, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

Important Potential Risks	
Acceleration of disease progression due to ARIA induced brain atrophy	
Evidence for linking the risk to the medicine	Data from the Study 301 indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety profile in long-term progression differs from that characterised so far, thus the further evaluation is needed.
Risk minimisation measures	Routine risk minimisation measures N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: BAN2401-G000-301 OLE BAN2041-G000-303 [redacted] See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Postauthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

[redacted]

II.C.2 Other Studies in Postauthorisation Development Plan

Study title: BAN2401-G000-301 OLE

Purpose of the study: To evaluate the long-term safety and tolerability of LEC10-BW in subjects with early Alzheimer's disease in the Extension Phase.

Study title: BAN2401-G000-303

Purpose of the study: To evaluate efficacy and safety of lecanemab in the preclinical AD population.

PART VII ANNEXES

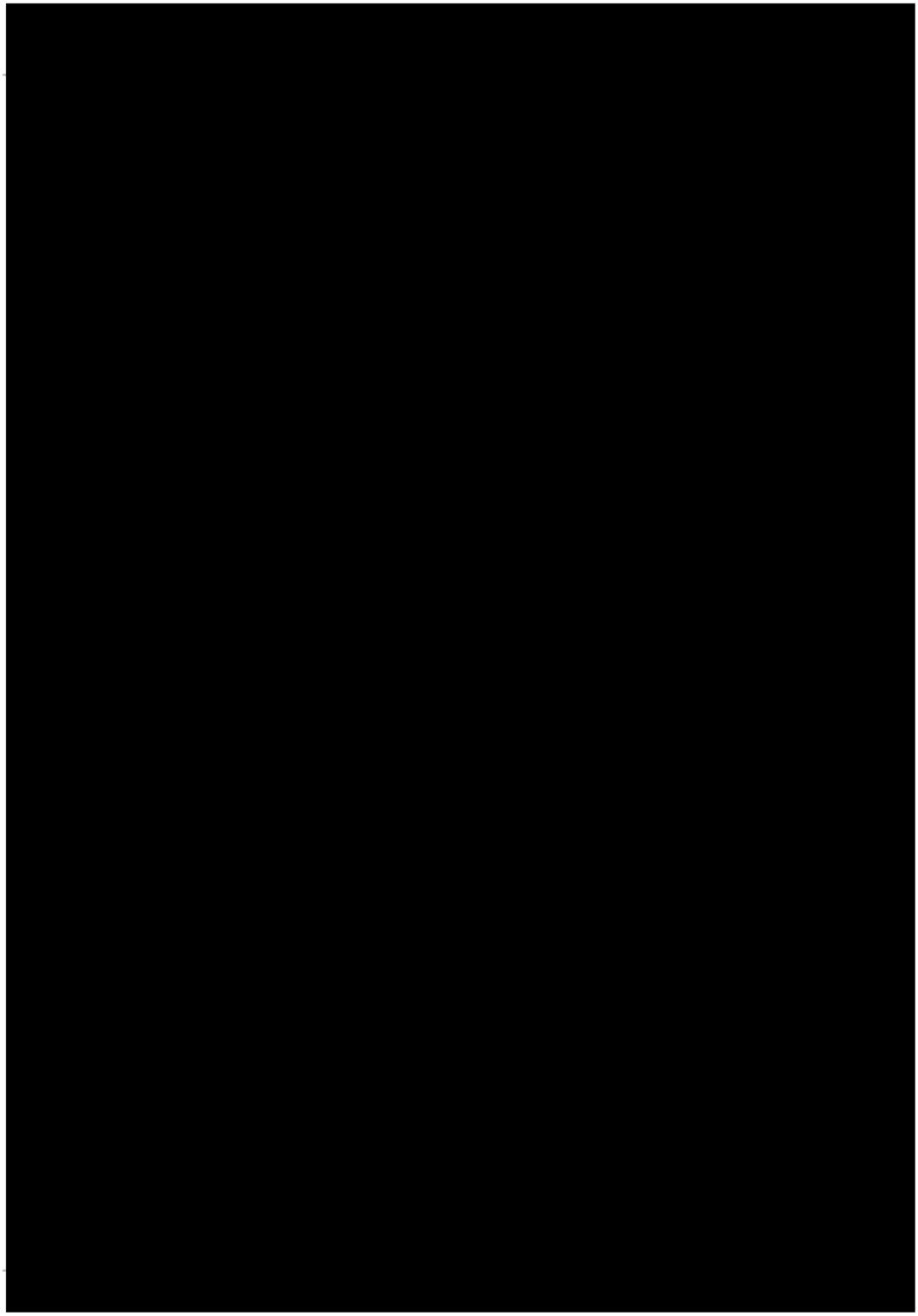
Annex 4 Specific Adverse Drug Reaction Follow-Up Forms

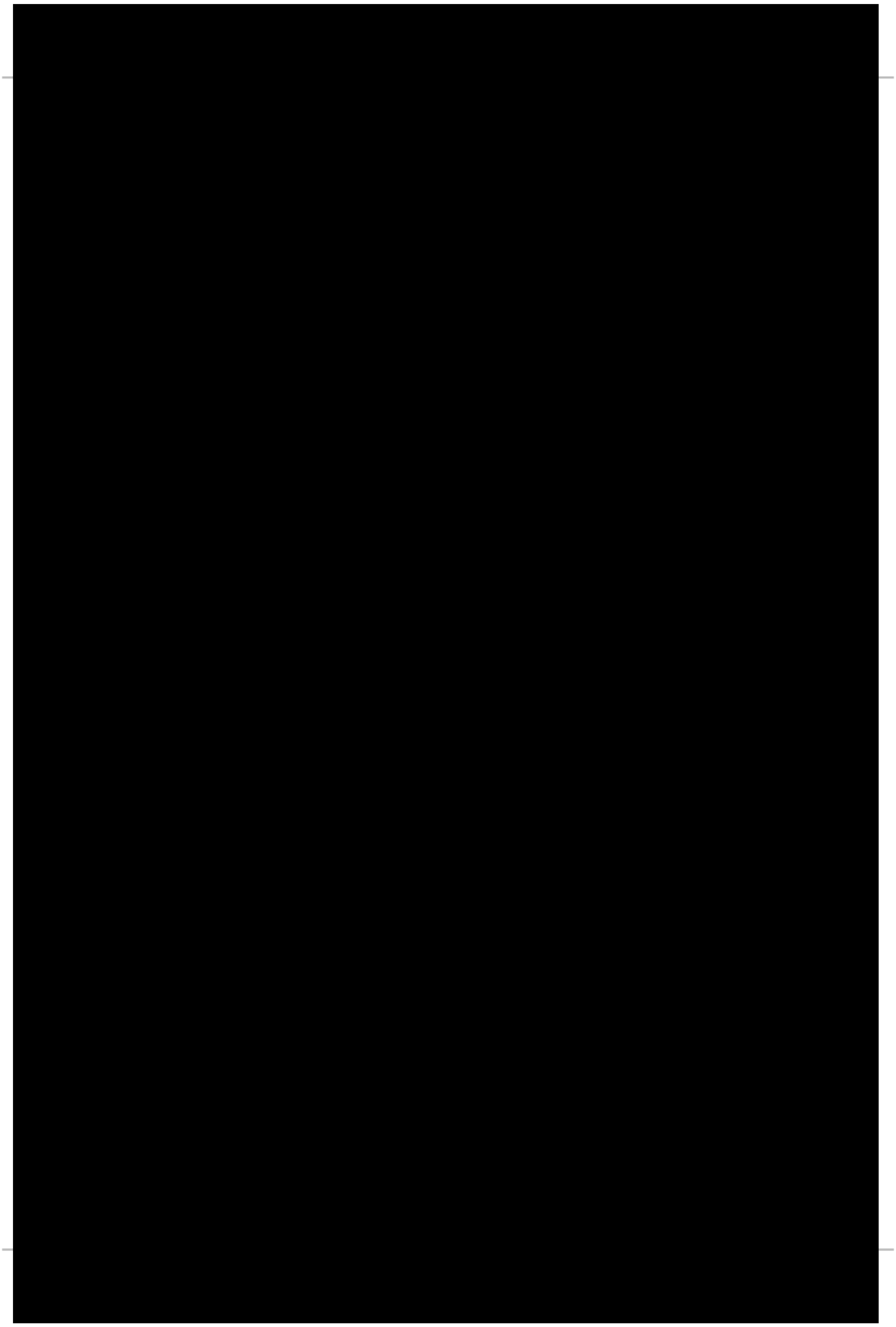
Table of Contents

Follow-up forms.

Follow-Up Form Title	Version Number	Date of Follow-Up Version
Eisai lecanemab questionnaire for reports of suspected ARIA	3.0	January 2024
Eisai lecanemab questionnaire for reports of suspected ARIA-E or ARIA-H	1.0	December 2022
Eisai lecanemab questionnaire for reports of suspected ARIA	0.2	August 2023

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit.





Annex 6 Details of Proposed Additional Risk Minimisation Activities (if applicable)

Prior to the launch of Leqembi (lecanemab) in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at all physicians who are expected to prescribe Leqembi.

The MAH shall ensure that in each Member State where Leqembi is marketed, all healthcare professionals who are expected to prescribe Leqembi have access to/are provided with the following educational package:

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (Checklist as a subsection in the Guide)

Guide for Healthcare Professionals

- Statement outlining there is a controlled access program.
- Statement that all EU lecanemab patients must be registered in the registry and brief information on how to enrol patients
- Contraindications.
- Information on ARIA, including what it is, incidence and symptoms (ARIA-E and ARIA-H (microhaemorrhages and superficial siderosis).
- ARIA Intracerebral haemorrhage >1 cm in diameter including what it is, incidence, and use of concomitant antithrombotic medication.
- Activities to be undertaken prior to treatment including in particular baseline MRI and *APOE4* testing.
- How to identify and manage ARIA through MRI monitoring, radiographic severity criteria, and the treatment recommendations (can be adjusted based on the national clinical practice).
- Patients who are homozygous *APOE4* carriers have a higher incidence of ARIA when treated with monoclonal antibodies directed against aggregated forms of Aβ, including lecanemab, compared to heterozygous *APOE4* carriers and noncarriers. Lecanemab is not indicated for use in homozygous *APOE4* carriers.
- Statement that ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke.
- PIL and Patient Card must be given to the patient/caregiver.

- Reminder of how and where to report side effects.

Checklist (as a subsection in the Guide)

- Lists of tests to be conducted for the initial screening of the patient:
  - The patient has a clinical diagnosis of MCI due to Alzheimer's disease or Mild Alzheimer's disease, including the presence of amyloid beta pathology. A recent (within 6 months) baseline brain MRI has been obtained prior to initiating treatment with Leqembi.
  - *APOE* ε4 (gene) (understanding *APOE* ε4 genotype is important to identify appropriate patients to treat).
  - No findings suggestive of CAA on pre-treatment MRI.
- Booking of follow up MRI scans.

Patient Card:

- Request to read the PIL.
- Summary of what Leqembi is used for.
- Information that treatment with Leqembi should not be initiated in patients receiving ongoing anticoagulant therapy.
- Information on how Leqembi is administered, time management of administration and information about the need and number of MRI scans.
- A warning message for physicians treating the patient at any time, including in conditions of emergency, that the patient is using lecanemab.
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional.

Controlled Access Program

The MAH shall agree the details of a controlled access program with each National Competent Authorities and must implement such programme nationally to ensure that a controlled access program promotes the safe and effective use of lecanemab and prevents off-label use.

The controlled access program includes the following key principles that will be incorporated within each system in all Member States. These are:

- Each HCP will be registered separately before they are able to enroll patients in the CAP. As part of the HCP registration process, HCPs will be required to confirm that they have been provided with and understand the Guide for Healthcare Professionals and the SmPC and that they meet requirements to comply with the resticted medicinal prescription status (described in the section 4.2 of the SmPC).

- Treatment in all patients should be initiated through an imposed central registration system. The system will ensure appropriate and relevant information on the specified data fields (such as amyloid pathology, MCI or mild AD, *APOE4* genotype, MRI, history of cerebral haemorrhage, anticoagulant therapy, patient card and PIL, acknowledgment of risks) prior to the first infusion of lecanemab, for all patients.
- The program will allow HCP to prescribe lecanemab only to the patient who meets the given criteria.