EU Risk Management Plan (Version 0.9)

Global Patient Safety
Signatory information is available on request.

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EU Risk Management Plan for Donanemab (LY3002813)

RMP version to be assessed as part of the application: 0.9

Data lock point for this RMP: 28 April 2023 for clinical trial data; 02 April 2025 for post-marketing data

Date of final sign off: Refer to Page 1 for the approval date

Rationale for submitting an updated RMP:

Updated in line with the CHMP/PRAC request to amend the ARIA registry (category 1 PASS) to add an additional primary objective.

Summary of significant changes in this RMP:

This RMP has been updated to include an additional primary objective for the ARIA registry (category 1 PASS).

Other RMP versions under evaluation

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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List of abbreviations

Term	Definition
Aβ	β-amyloid
AD	Alzheimer's disease
ADA	antidrug antibody
All-Dona	Donanemab-Treated Integrated Analysis Set
aMCI	amnestic mild cognitive impairment
ApoE	apolipoprotein subtype E
ApoE ε4	apolipoprotein subtype E allele 4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–oedema/effusions
ARIA-H	amyloid-related imaging abnormality–haemorrhage/hemosiderin deposition (including brain microhaemorrhage and/or superficial siderosis)
aRMM	additional risk minimisation measures
CAA	cerebral amyloid angiopathy
CAP	controlled access programme
CHMP	committee for medicinal products for human use
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
CRF	case report form
Dona-PC	Placebo-Controlled Analysis Set
AACI-PC	AACI-Placebo-Controlled Analysis Set
EPAR	European Public Assessment Report
HCP	healthcare professionals
HR	hazard ratio
ICH	intracranial haemorrhage
InRAD	international practice-based registry for Alzheimer's disease and other dementias
Ig	humanised immunoglobulin
IRR	infusion-related reaction
MCI	mild cognitive impairment
mE8c	murine surrogate of donanemab
MRI	magnetic resonance imaging
PC	placebo controlled
PIL	patient information leaflet

Term	Definition
PRAC	pharmacovigilance risk assessment committee
PY	person-years
Q4W	every 4 weeks
RMP	risk management plan
SmPC	summary of product characteristics

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Donanemab
Pharmacotherapeutic group(s) (ATC Code)	N06DX05
Marketing authorisation Applicant	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	1 Donanemab
Invented name(s) in the European Economic Area (EEA)	Kisunla
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** IgG1 monoclonal antibody
	Summary of mode of action: Targeting and removal of deposited amyloid plaque
	Important information about its composition: Donanemab is an IgG1 monoclonal antibody composed of 2 identical immunoglobulin kappa light chains and 2 identical immunoglobulin gamma heavy chains. It is produced in Chinese hamster ovary cells.
Hyperlink to the product information	See eCTD Module 1.3.1
Indication(s) in the EEA	**Proposed:** Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.
Dosage in the EEA	**Proposed:** Donanemab is administered by IV infusion. The recommended dose of donanemab is 350 mg for the first infusion, 700 mg for the second infusion, and 1050 mg for the third infusion, once every 4 weeks, followed by 1400 mg every 4 weeks. Treatment should be maintained until amyloid plaques are cleared (for example, at 6 or 12 months), as confirmed using a validated method. The maximum treatment duration is 18 months, which should not be exceeded even if plaque clearance is not confirmed.
Pharmaceutical form(s) and strengths	**Proposed:** The medicinal product is a concentrate for solution for infusion. The solution formulation was developed and optimised based on pre-formulation studies and pharmaceutical development experience with the same inactive ingredients as the lyophilised formulation. The solution formulation was supplied as a 17.5-mg/mL solution drug product for IV administration in a 20-mL glass vial and is being used in Studies AACI and AACH. The solution formulation is the proposed commercial formulation.

Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: AACH = I5T-MC-AACH; AACI = I5T-MC-AACI; AD = Alzheimer's disease; ATC = anatomical therapeutic chemical; eCTD = electronic common technical document; EU = European Union; IgG1 = humanised immunoglobulin; IV = intravenous; INN = International Non-proprietary Names; RMP = risk management plan.

Part II: Safety Specification

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

SI.1 Alzheimer's Disease

Patients with early symptomatic AD include those with MCI due to AD and those with mild AD dementia. Among patients with MCI, about 15% develop dementia every year and about one third of people living with MCI develop dementia due to AD within 5 years (Alzheimer's Association 2022). Available epidemiological studies often provide the respective incidence or prevalence estimates for MCI and AD dementia, though studies focusing on AD dementia seldom differentiate between various stages of disease severity. Most of these studies use a term to refer to AD dementia in aggregate, which is likely to refer to all stages of the disease (mild, moderate, and severe). When it is available, information for mild AD dementia will be provided along with the epidemiological data for MCI.

SI.1.1 Incidence

Incidence of mild cognitive impairment

A systematic review and meta-analysis of population-based studies from the US, Europe, and Australia estimated the pooled MCI incidence per 1000 PYs to be 22.5 (95% CI: 5.1, 51.4) for ages 75 to 79 years, 40.9 (95% CI: 7.7, 97.5) for ages 80 to 84 years, and 60.1 (95% CI: 6.7, 159.0) for ages 85 years and older (Gillis et al. 2019). Studies of European older adults of different age ranges in various settings reported an incidence rate ranging from 12.2 to 168.0 per 1000 PYs for overall MCI (Roberts and Knopman 2013). For aMCI, which is considered the subtype most likely to progress to AD dementia, the estimated incidence rate among older adults ranged from 8.5 to more than 34.0 per 1000 PYs in European studies (Roberts and Knopman 2013). In Germany, a population-based study estimated an incidence of MCI of 0.15% per year among patients above 65 years of age and remained constant over time from 2015 to 2019 (Bohlken et al. 2021). In Spain, a population-based study estimated an overall MCI incidence rate of 33.19 per 1000 PYs with 95% CI: 26.02, 43.04 (Lara et al. 2017). In Hungary, a study conducted in the NEUROHUN database estimated an average age-standardised incidence of MCI of 70 per 100 000 PYs, using the 2013 European Standard Population (Balázs et al. 2021). In the Swedish Good Aging in Skane population-based study, incidence rates of overall MCI were 22.6 with 95% CI: 19.6, 25.9 and 8.67 with 95% CI: 7.0, 10.7 per 1000 PYs for lenient criterion (at least 1 impaired test for cognitive domain) and stricter criterion (at least 2 impaired tests per cognitive domain), respectively (Overton et al. 2019).

Incidence of AD dementia

A systematic review and meta-analysis estimated the incidence rate of AD dementia in community settings as 15.8 per 1000 PYs (95% CI: 12.9, 19.4) among individuals aged 60 years or older using data worldwide (Fiest et al. 2016). Another review and meta-analysis of epidemiological studies in European populations aged 55 years or older estimated that the overall incidence rate of AD was 11.1 (95% CI: 10.3, 11.9) per 1000 PYs with 9.0 (95% CI: 8.1, 9.9) per 1000 PYs in southern European countries (Greece, Italy, and Spain) and 15.9 (95% CI: 14.2, 17.7) per 1000 PYs in northern European countries (France, United Kingdom, Sweden, and Denmark) (Niu et al. 2017a). In Hungary, a study conducted in the NEUROHUN database

estimated an average age-standardised incidence of AD of 18 per 100 000 PYs, using the 2013 European Standard Population (Balázs et al. 2021).

SI.1.2 Prevalence

Prevalence of MCI

MCI, as the pre-clinical and transitional stage between healthy ageing and dementia, is viewed as a potential "target" for interventions designed to delay progression to dementia. A previous meta-analysis of 41 cohort studies found the cumulative proportion of MCI cases progressing to dementia was 39.2% (Bai et al. 2022). Bai et al. (2022) reported an overall MCI prevalence of 15.56% (95% CI: 13.24%, 18.03%), while Pessoa et al. (2019) reported an overall pooled prevalence of MCI of 17.3%, with 95% CI: 13.8%, 20.8%, involving 35 studies. A systematic review reported that the prevalence of MCI varied from 13.4% to 42.0% in studies with the age ranging from 55 years or older to 75 years or older across Europe, North America, Asia, and Australia (Petersen et al. 2018). A further meta-analysis of all studies among individuals aged 65 years or older estimated a pooled prevalence of 16.6% (95% CI: 11.6%, 26.9%; Petersen et al. 2018). Ultimately, a recent systematic review reported a prevalence of MCI from 1.2% to 87%, using 66 studies published worldwide. Authors reported a large heterogeneity among studies due to differences in the subjects' recruitment, diagnostic criteria, assessed cognitive domains, and other methodological aspects that account for a higher range of MCI prevalence (Casagrande et al. 2022). In European population-based studies, the estimated prevalence of MCI ranged from 5.1% among those aged 75 years or older in Germany to 35.3% in a recent Norway study of individuals aged 70 years or older (Roberts and Knopman 2013; Lara et al. 2016; Gjøra et al. 2021). In Europe, the reported prevalence of aMCI ranged from 0.5% in an Austrian study of all 75-year-old adults to 30.4% among those aged 70 years or older in Norway (Ward et al. 2012; Roberts and Knopman 2013; Gjøra et al. 2021). In Germany, a population-based study estimated a prevalence of MCI of 0.57% among patients above 65 years of age (Bohlken et al. 2021). In Hungary, a study conducted in the NEUROHUN database estimated an average age-standardised prevalence of MCI of 238 per 100,000 patients for 2011 to 2016 (Balázs et al. 2021). In the Swedish Good Aging in Skane population-based study, the prevalence of overall MCI using lenient criterion (at least 1 impaired test for cognitive domain) was 21.4% with 95% CI: 20.1, 22.8; while using the strict criterion (at least 2 impaired tests per cognitive domain) reduced the prevalence to 6.6% with 95% CI: 5.74, 7.42 (Overton et al. 2019).

Prevalence of AD dementia

According to the Alzheimer's Disease International, approximately 55 million people worldwide had AD or other dementia in 2020 and this number is expected to double every 20 years, reaching approximately 78 million in 2030 (Alzheimer's Disease International 2022; WHO 2023). The number of people living with dementia in the European Union (EU27) in 2019 was estimated to be 7,853,705 and in the European countries represented by Alzheimer Europe members, 9,780,678. It is expected that the numbers of people with dementia in Europe will almost double by 2050 increasing to 14,298,671 in the European Union and 18,846,286 in the wider European region (Alzheimer Europe 2019). A systematic review and meta-analysis estimated the global point prevalence of AD dementia among community-dwelling individuals

aged 60 years or older as 4.0% (95% CI: 2.9%, 5.6%; Fiest et al. 2016). Another systematic review and meta-analysis of population-based studies in Europe estimated the overall prevalence of AD to be 1.0%, 7.7%, and 22.5% for individuals aged 65 to 74 years, 75 to 84 years, and 85 years or older, respectively (Niu et al. 2017a). In Hungary, a study conducted in the NEUROHUN database estimated an average age-standardised prevalence of AD of 45 per 100,000 patients for 2011 to 2016 (Balázs et al. 2021). A limited number of population-based studies on the severity of AD dementia among prevalent cases reported that approximately 50% of all cases meeting the clinical criteria for AD dementia had a mild disease (Hebert et al. 2003; Yuan et al. 2021).

SI.1.3 Demographics of the Population in the Proposed Indication – Age, Gender, Racial, and/or Ethnic Origin and Risk Factors for the Disease

Demographics

Europe's general population is getting older. According to EuroStat figures, more than one fifth of the EU population was aged 65 or over in 2020, which represents an increase of 3% compared to 2010. As the primary risk factor for dementia is age, the continued increase in life expectancy and population ageing also increases the likelihood of people developing the condition. (Alzheimer Europe 2019). The available epidemiological studies with demographic information rely almost exclusively on the clinical diagnosis of MCI and AD dementia rather than diagnosis based on AD biomarkers such as abnormal levels of Aβ and/or tau protein as shown on positron emission tomography scans and in analysis of cerebrospinal fluid. Most AD cases are in persons aged 65 years or older (Gillis et al. 2019; Alzheimer's Association 2022; Alzheimer Europe 2019). The incidence and prevalence of MCI and AD dementia increase substantially with age, regardless of gender and geographic region (Sachdev et al. 2015; Fiest et al. 2016; Gillis et al. 2019; Alzheimer's Association 2021; Alzheimer Europe 2019). A review and meta-analysis of studies in European populations aged 55 years or older estimated a higher pooled incidence of AD in women than in men: 13.3 per 1000 PYs versus 7.0 per 1000 PYs (Niu et al. 2017a), though mixed findings have been reported for gender differences in AD dementia incidence in the US (Alzheimer's Association 2022; Alzheimer Europe 2019). No differences in the incidence or prevalence of overall MCI or the aMCI were found between women and men (Au et al. 2017). Nevertheless, across men and women and across most age groups, there has been a reduction in the prevalence of dementia over the past 10 years when compared to 2008 estimates. Women continue to be disproportionately affected by dementia with 6,650,228 women and 3,130,449 men living with dementia in Europe in 2019, as women have a higher life expectancy compared with men (Alzheimer Europe 2019). In Hungary, men were more frequently diagnosed with dementia between the ages of 35 and 65 years, while the proportion of women under the age of 35 and over 65 years was higher. Overall, more women were diagnosed with AD than men. The proportion of people diagnosed with AD increased in both genders with advancing age, with the peak occurring in the 80 to 84 years age group, followed by a decrease in the incidence from the age of 85 years, with male predominance (Balázs et al. 2021).

Risk factors

The greatest risk factors for AD include older age, genetics (especially the ε4 form of the ApoE gene), and a family history of AD (Alzheimer's Association 2022; Alzheimer Europe 2019). Less than 5% of all AD cases exhibit an autosomal dominant inheritance pattern (Wu et al. 2012). The remaining 95% are the non-dominantly inherited type known as sporadic AD, in which the ApoE ε4 acts as the strongest genetic risk factor (Alzheimer's Association 2022). Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of sporadic AD (Roberts and Knopman 2013; Alzheimer's Association 2022). These factors include active smoking and diabetes (Anstey et al. 2007; Durazzo et al. 2014; Lee et al. 2018). High serum cholesterol, hypertension, and obesity, particularly in midlife, have been shown to be associated with increased AD risk (Anstey et al. 2011; Meng et al. 2014; Anstey et al. 2017; Lennon et al. 2019). Other factors such as physical activity, healthy diet, more years of education, and being socially and mentally active are associated with a reduced AD risk (Chen et al. 2016; Rege et al. 2017; Alzheimer's Association 2021).

Individuals with Down Syndrome are at increased risk of AD and develop AD at a younger age than those without Down Syndrome. In Down Syndrome, having the triplicate APP gene on chromosome 21 is thought to lead to increased Aβ in the brain and subsequent neurofibrillary tangle formation and neurodegeneration, leading to early onset dementia (Ballard et al. 2016). As the average lifespan of people with Down Syndrome is increasing, AD is becoming an important health concern in this group (McCarron et al. 2017; Hithersay et al. 2019). About 30% of people with Down Syndrome who are in their 50s have AD dementia and approximately 50% of the people with Down Syndrome in their 60s have AD dementia (Alzheimer's Association 2022). Autopsy studies show that by the age 40 years, the brains of almost all individuals with Down Syndrome have significant levels of Aβ plaques and tau tangles, abnormal protein deposits considered AD's hallmarks (Alzheimer's Association 2022). Despite the presence of these brain changes, not everyone with Down Syndrome develops Alzheimer's symptoms. CAA has been reported to be more frequent in genetically determined AD, including Down Syndrome, than sporadic early onset AD (Carmona-Iragui et al. 2017).

SI.1.4 Main Existing Treatment Options

Symptomatic treatments, such as acetylcholinesterase inhibitors and memantine, exist to address the cognitive challenges experienced by those with AD. In the US, Eisai Inc.'s lecanemab received accelerated approval on 06 January 2023 and was submitted for approval on the same day. This accelerated approval was granted primarily based on the ability of this product to reduce amyloid plaque. It is expected that such plaque reduction in those with MCI or mild AD is reasonably likely to predict clinical benefits. On 06 July 2023, the US FDA converted lecanemab to traditional approval. Subsequently, Eisai Inc.'s lecanemab received approval in other major geographies, including Japan, China, and the UK. On 15 April 2025, lecanemab received approval in Europe. On 02 July 2024, Lilly's donanemab received approval in the US and subsequently in other major geographies including Japan, the UK, China, Mexico, Brazil, and Australia.

Donanemab has shown clinically meaningful slowing of AD decline measured by the integrated AD rating scale at 76 weeks in a Phase 2 study with results replicated in a larger Phase 3 study. The clinical meaningfulness of these results is supported by the magnitude of observed effects, disease stability at 12 months, and hazard ratio for no progression (data on file).

The most common adverse drug reactions of lecanemab include (Leqembi USPI, 2023 and Leqembi SmPC, 2025):

- ARIA
- ARIA-E
- ARIA-H
- headache, and
- infusion-related reactions.

The currently approved standard-of-care agents for symptomatic cognitive enhancement (acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine, and the N-methyl D-aspartate receptor antagonist memantine) improve cognition due to neurotransmitter changes, providing relatively limited changes in cognitive measures, and are not thought to change the underlying course of the disease. The most common adverse reactions for donepezil (Aricept SmPC), defined as those occurring at a frequency of ≥10% in patients receiving 10 mg/day, are largely predicted by donepezil's cholinomimetic effects. These include nausea, diarrhoea, and headache. Adverse events observed commonly (≥1% to <10%) include:

- anorexia
- vomiting
- muscle cramp
- insomnia
- fatigue
- hallucinations, and
- aggressive behaviour.

Based on the shared mechanism of action, similar side-effect profiles are reported for other acetylcholinesterase inhibitors (Exelon SmPC).

In the double-blind, placebo-controlled trials involving patients with AD dementia, the common adverse reactions (≥1% to <10%) in patients treated with memantine were (Ebixa SmPC):

- dizziness
- headache
- somnolence, and
- constipation.

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Natural history

AD is the most common cause of dementia. During the progression of AD from brain changes that are unnoticeable to the affected person to brain changes resulting in problems with memory and eventually physical disability, there are 3 broad phases: pre-clinical AD, MCI due to AD, and AD dementia (Alzheimer's Association 2021; Alzheimer Europe 2019). Depending on the degree to which symptoms interfere with one's ability to carry out daily tasks, the AD dementia phase is further broken down into mild, moderate, and severe stages (Alzheimer's Association 2021; Alzheimer Europe 2019). The indicated population with mild AD dementia may be able to function independently in many daily tasks but is likely to require assistance with some activities to maximise independence and remain safe (Alzheimer's Association 2021; Alzheimer Europe 2019).

MCI, which does not interfere with individuals' ability to carry out daily tasks (Alzheimer's Association 2021; Alzheimer Europe 2019), can be subdivided into aMCI (memory impaired) and non-aMCI (other domains affected, memory preserved; Roberts and Knopman 2013). Both types can be categorised further to single-domain and multi-domain subtypes according to the number of cognitive domains involved. aMCI is associated with a considerable risk to further conversion to AD dementia, while non-aMCI presentation may frequently progress to non-AD dementias (Roberts and Knopman 2013). Individuals diagnosed with MCI may remain stable, return to being neurologically intact, or progress to dementia (Petersen et al. 2018). In the Rotterdam study, MCI was associated with an increased risk of dementia (HR = 3.98, 95% CI: 2.97, 5.33) and AD (HR = 4.03, 95% CI: 2.92, 5.56) (de Bruijn et al. 2014). A systematic review and meta-analysis estimated that individuals with MCI were 3 times more likely to be diagnosed with AD dementia 2 to 5 years later as compared to the age-matched controls without MCI (Petersen et al. 2018). The annual conversion rate from aMCI to AD dementia was estimated between 5.6% and 16.5% per PY among community-based and clinic-based cohorts of patients (Ward et al. 2013).

Morbidity

Decline in memory has been considered the predominant and earliest symptom of AD, followed by impairments of other cognitive domains such as language, executive function, praxis, and complex visual processing, though heterogeneity in the presentation and course of cognitive impairments have been identified (Dubois et al. 2010). Behavioural and psychological symptoms have also been recognised as a key feature of AD dementia (Robert et al. 2005; Bature et al. 2017). A systematic review and meta-analysis of 48 studies across Europe, Asia, and the US showed that the most frequent behavioural or psychological symptom among individuals with AD was apathy with a pooled prevalence of 49%, followed by depression (42%), aggression (40%), anxiety (39%), and sleep disorder (39%) (Zhao et al. 2016). Another review found that the prevalence of any behavioural or psychological symptoms was between 35% and 85% among individuals with MCI who had a mean age ranging from 65.2 to 80.6 years across studies in different settings (Monastero et al. 2009). Patients who eventually progress to the severe stage

of AD dementia need help with daily tasks and are likely to require around-the-clock care. Therefore, dementia is a disease that impacts patients, their families, and ultimately the healthcare system. In 2018, the number of people with dementia in the EU, the European Free Trade Association, and the UK was estimated to be 9.1 million (Schmachtenberg et al. 2022). Severe dementia frequently causes complications, including immobility, swallowing disorders, and malnutrition, that significantly increase the risk of serious acute conditions such as pneumonia (Brucki et al. 2022).

Mortality

Individuals with MCI or AD dementia are at increased risk of mortality. Across studies, the HR of all-cause mortality among individuals with MCI ranged from 1.5 to 2.0 when compared to that among individuals without cognitive impairment (Guehne et al. 2007; Wilson et al. 2009; Vassilaki et al. 2015). The estimated HR relating AD dementia to all-cause mortality ranged from 1.4 to 3.1 in population-based studies (Ganguli et al. 2005; Wilson et al. 2009; Lönnroos et al. 2013; James et al. 2014). The median survival time was estimated as 8.3 years for individuals diagnosed as having AD at age 65 years and 3.4 years for individuals diagnosed as having AD at age 90 years (Brookmeyer et al. 2002). A European study of death data in 28 countries estimated that the overall age-standardised mortality rate of AD increased from 28.2 to 45.2 per 100,000 people during 1994 to 2013 (Niu et al. 2017b). It also found that the estimated AD mortality rate was highest in Finland (278.9 per 100,000) and lowest in Malta and Latvia (less than 5 per 100,000) in 2013 (Niu et al. 2017b). In a Dutch cross-sectional analysis of the population-based Rotterdam study, MCI was associated with an increased risk of mortality: HR = 1.54, 95% CI: 1.28, 1.85 (de Bruijn et al. 2014). In Europe, data from 1994 to 2003 Eurostat and WHO databases were analysed and mortality from AD has risen in the EU throughout the study period. Most of the countries showed upward trends, with the sharpest increases in Slovakia, Lithuania, and Romania. Statistically significant increases of 4.7% and 6.0% in mortality rates in men and women, respectively, in the whole EU were recorded (Niu et al. 2017b).

SI.1.6 Important Comorbidities

The most commonly observed co-existing medical conditions among patients with a diagnosis of AD and MCI are presented in Table Part II.1 and Table Part II.2.

Table Part II.1. Most Common Comorbidities in Patients with Alzheimer's Disease

Comorbidity	Incidence	Prevalence %	Age (Years)	Study
Anxiety		31.0 (mild AD)	50–100	Apostolova et al. 2014
Cardiovascular events				
Cardiac disorders				
Atrial fibrillation		5.9–7.3	≥65	Chi et al. 2013; Imfeld et al. 2013a, 2013b; Dugger et al. 2016
Coronary artery disease		10.8–46.3	65–100	Chi et al. 2013; Vogelgsang et al. 2018
Cardiac disease		8.1–10.3	46–108	Go et al. 2013; Laroche et al. 2013

Comorbidity	Incidence	Prevalence %	Age (Years)	Study
Heart failure[a]		6.3–17.4	≥65	Sicras et al. 2005; Wu et al. 2011; Chi et al. 2013; Imfeld et al. 2013a, 2013b; Cermakova et al. 2015
Ischaemic heart disease	15.6/1000 PYs; 19.7M, 13.9F			Tolppanen et al. 2013a
		4.4–17.7	42–101	Sicras et al. 2005; Imfeld et al. 2013a, 2013b; Tolppanen et al. 2013a; Cermakova et al. 2015
Myocardial infarction[a]		5.8	≥65	Wu et al. 2011
Peripheral artery disease		7.7–8.3	≥65	Sicras et al. 2005; Chi et al. 2013
Vascular events				
Microhaemorrhage	0.7 lesions per year[b]	18–48	≥42	Cordonnier et al. 2006; Uetani et al. 2013; Zonneveld et al. 2014; Shams et al. 2015; Yates et al. 2014
Cortical superficial siderosis		2.5–5.8	55–90	Kantarci et al. 2013; Zonneveld et al. 2014; Charidimou et al. 2016; Inoue et al. 2016; Shams et al. 2016
Venous thromboembolism		5.6	≥65	Dennis et al. 2017[c]
Pulmonary embolism		0.3	>70	Branagan 2022 (FDA)
Hypertension		59.3 (mild AD)	>65	Benoit et al. 2012
Hypertension (AD)		29.5–72.8	≥65	Sicras et al. 2005; Chi et al. 2013; Go et al. 2013; Imfeld et al. 2013a, 2013b; Dugger et al. 2016; Vogelgsang et al. 2018
		83.0%	≥55	De Bruijn et al. 2014
Stroke–all[a]	5.7%		42–101	Tolppanen et al. 2013b
	15.9 per 1000 PYs		≥50	Cook et al. 2015
		2.1–31.0	≥65	Sicras et al. 2005; Wu et al. 2011; Go et al. 2013
Stroke–ischaemic	4.5%		42–101	Tolppanen et al. 2013b
	4.7–37.8 per 1000 PYs		≥65	Chi et al. 2013; Imfeld et al. 2013b
		19.7	≥65	Wu et al. 2011
Stroke–haemorrhagic[a]	1.1%		42–101	Tolppanen et al. 2013b
		1.9	≥65	Wu et al. 2011
	2.7–5.2 per 1000 PYs		≥65	Chi et al. 2013; Imfeld et al. 2013b
Other				
Depression[a]		17.0–51.0 (mild AD)	50–100	Benoit et al. 2012; Apostolova et al. 2014; Siafarikas et al. 2018
		21.1–22.2	≥65	Sicras et al. 2005; Imfeld et al. 2013a, 2013b
		25.0%		van der Mussele et al. 2013

Comorbidity	Incidence	Prevalence %	Age (Years)	Study
	174.5 per 1000 PYs			Arbus et al. 2011
Diabetes mellitus[a]		7.6–39.3	42–101	Sicras et al. 2005; Bell et al. 2011; Wu et al. 2011; Chi et al. 2013; Go et al. 2013; Imfeld et al. 2013a, 2013b; Tolppanen et al. 2013c; Cermakova et al. 2015; Dugger et al. 2016; Vogelgsang et al. 2018
Lipid disorders		8.3–42.4	≥65	Sicras et al. 2005; Chi et al. 2013; Go et al. 2013; Imfeld et al. 2013a, 2013b; Vogelgsang et al. 2018
Gait disorders		18.9	≥65	Muñoz et al. 2010
Fall[a]		49.3 (mild AD)	>60	Allali et al. 2017
	2486 falls per 1000 Pys	51.4	>65	Allan et al. 2009
Hip fracture[a]	24 per 1000 Pys	4.7	42-101	Tolppanen et al. 2013
Osteoarthritis[a]		1.3–28.5	≥65	Wu et al. 2011; Heun et al. 2013[d]; Imfeld et al. 2013a
		1.4–12.9	65–84	Sicras et al. 2005; Chi et al. 2013; Vogelgsang et al. 2018
		15.6	46–108	Laroche et al. 2013[e]
Renal disease		6.8 (mild AD)	>65	Benoit et al. 2012

Abbreviations: AD = Alzheimer's disease; F = female; M = male; Pys = person-years.

[a] Comorbidities shown to be higher in patients with AD dementia compared to matched controls in at least 1 published study.

[b] The annual incidence for lobar microbleeds, including superficial siderosis, was calculated using the total number of incident lesions and maximum time interval between baseline and final scans among patients.

[c] Prevalence of venous thromboembolism was reported in the overall study patients with dementia, among whom 72% had AD.

[d] Prevalence is included here as 1 of the only sources of information on this comorbidity in the AD population. In Heun et al. (2013), the prevalence is based on hospitalised patients.

[e] Prevalence of renal disease was reported in the overall study patients with dementia, among whom 65.5% had AD.

Table Part II.2. Most Common Comorbidities in Patients with Mild Cognitive Impairment

Comorbidity	Prevalence % by MCI Type				Age (Years)	Study
	MCI	aMCI	aMCIs	aMCIm		
Anxiety	7.5–23.4	21.0			≥50	Moretti et al. 2013; Pink et al. 2015; Apostolova et al. 2014; Pankratz et al. 2015; Liew 2019
Cardiovascular events						
Cardiac disorders						
Atrial fibrillation	6.1–18.5	7.5–17.5	5.9	10.8	70–90	Forti et al. 2007; Sachdev et al. 2013; Sachdev et al. 2012; Pankratz et al. 2015; Viticchi et al. 2017
Coronary artery disease[a]	13.2–49.2	20.1	23.3	15.8	65–90	Sachdev et al. 2012; Singh et al. 2013; Solfrizzi et al. 2004; Pankratz et al. 2015
Cardiac disease[a]	28.3–34.3	18.7–34.9	35.5	34.2	≥65	Ganguli et al. 2013; Michaud et al. 2017; Viticchi et al. 2017
Congestive heart failure	1.8–13				≥65	Ganguli et al. 2013; Snowden et al. 2015; Pankratz et al. 2015; Montero-Odasso et al. 2017
Myocardial infarction	10.0–16.0				≥65	Pankratz et al. 2015; Montero-Odasso et al. 2017
Vascular events						
Hypertension	36.5–92.4	49.0–81.8	60.6	64.3	55–90	Sachdev et al. 2012; Li et al. 2013; Artero et al. 2008; Moretti et al. 2013; Solfrizzi et al. 2004; Park et al. 2014; de Bruijn et al. 2014; Ganguli et al. 2013; Singh et al. 2013; Roberts et al. 2014a; Lee et al. 2014; Limongi et al. 2017
	83.0%				≥55	De Bruijn et al. 2014
Stroke–all[a]	2.76–19.6	4.9–11.7	5.2	3.2	≥65	Sachdev et al. 2012; Artero et al. 2008; Moretti et al. 2013; Solfrizzi et al. 2004; Park et al. 2014; de Bruijn et al. 2014; Ganguli et al. 2013; Singh et al. 2013; Roberts et al. 2014a; Snowden et al. 2015; Dlugaj et al. 2015; Zuliani et al. 2020
Stroke–ischaemic TIA	8.73–9.1				≥65	Ganguli et al. 2013; Pieruccini-Faria et al. 2020
Microhaemorrhage	20-41				≥42	Cordonnier et al. 2006; Uetani et al. 2013; Zonneveld et al. 2014; Shams at al. 2015
Cortical superficial siderosis	1.1–3.9				55–90	Kantarci et al. 2013; Zonneveld et al. 2014; Charidimou et al. 2016; Inoue et al. 2016; Shams et al. 2016
Other						

Comorbidity	Prevalence % by MCI Type				Age (Years)	Study
	MCI	aMCI	aMCIs	aMCIm		
Depression[a]	8.5–29.4	17.7–19.5	13.0	25.3	≥50	Moretti et al. 2013; Apostolova et al. 2014; Pink et al. 2015; Sachdev et al. 2012; Van der Mussele et al. 2014; Singh et al. 2013; Snowden et al. 2015; Pankratz et al. 2015; Dlugaj et al. 2015; Liew 2019
	16%-22.2%	23.8%	20.1% naMCI		≥55	Van der Mussele et al. 2013; Lara et al. 2017
Diabetes mellitus[a]	11.0–25.1	8.0–23.4	14.0-22.1	12.6-24.7	≥55	Sachdev et al. 2012; Artero et al. 2008; de Bruijn et al. 2014; Li et al. 2013; Moretti et al. 2013; Park et al. 2014; Ganguli et al. 2013; Singh et al. 2013; Lee et al. 2014; Roberts et al. 2014b; Dlugaj et al. 2015; Snowden et al. 2015; Solfrizzi et al. 2004; Pankratz et al. 2015; Limongi et al. 2017; Viticchi et al. 2017
Lipid disorders	56.0–59.0	39.7–55.5	59.1	54.7	≥55	Artero et al. 2008; Sachdev et al. 2012; Ng et al. 2016; Viticchi et al. 2017
Gait disorders[a]		9.0–25.9			≥70	Verghese et al. 2008; Lee et al. 2014
Fall	31.0–31.8	20.4–30.0			>60	Verghese et al. 2008; Montero-Odasso et al. 2014; Allali et al. 2017; Pieruccini-Faria et al. 2020
Rheumatic disease (arthritis/ osteoarthritis)	14.555.7	53.1	59.3	48.9	≥55	Sachdev et al. 2012; Li et al. 2013; Pieruccini-Faria et al. 2020
Renal disease	3.1	3.7	2.6	3.2	70-90	Sachdev et al. 2012

Abbreviations: aMCI = amnestic mild cognitive impairment; aMCIm = amnestic multiple-domain mild cognitive impairment; aMCIs = amnestic single-domain mild cognitive impairment; MCI = mild cognitive impairment; naMCI = nonamnestic MCI; TIA = transient ischaemic attack.

[a] Comorbidities shown to be higher in patients with MCI compared to matched controls in at least 1 published study.

Module SII – Non-clinical Part of the Safety Specification

SII.1 Toxicity

The non-clinical safety of donanemab was evaluated in a 6-week repeat-dose toxicity study in cynomolgus monkeys, which included assessments of cardiovascular, respiratory, and CNS safety pharmacology. Expression of the donanemab target is limited to the CNS of aged animals and is not expressed in standard-age animals routinely used for toxicology testing; therefore, the toxicology study in monkeys with donanemab was conducted to characterise any potential off-target effects. No effects were observed with intravenous doses of donanemab up to 100 mg/kg per week for 6 weeks.

Additionally, an ex vivo tissue cross reactivity study was conducted with donanemab utilising a panel of human and monkey tissues, in which no relevant (that is, membranous) binding of donanemab occurred.

In vivo hazard evaluation studies of up to 6 months' duration were conducted in the target-relevant, aged PDAPP mouse using the murine surrogate molecule, mE8c. No mE8c-related effects were observed in repeat-dose studies of 6 weeks', 5 months' (approximately), and 6 months' duration. Separately, a 3-month, repeat-dose study in aged PDAPP mice specifically evaluating microhaemorrhage potential of mE8c revealed no exacerbation of microhaemorrhage compared to aged PDAPP mice receiving vehicle treatment.

Reproductive/developmental toxicity

No developmental and reproductive toxicity testing has been performed for donanemab. The sponsor considered,

- the intended patient population of donanemab (primarily elderly)
- the nature of the product (highly specific monoclonal antibody)
- the target (unique to amyloid plaque in brain)
- the biology and mechanism of action, and
- the data from non-clinical studies with donanemab and mE8c.

Based on these considerations as well as data from clinical studies with donanemab and other amyloid-targeting therapies, there is a low potential for reproductive risk resulting from donanemab exposure in humans.

In the toxicology studies, there were no effects on female or male reproductive organs, including spermatogenesis, in aged PDAPP mice treated with mE8c. Additionally, no effects on reproductive tissues occurred in donanemab-treated cynomolgus monkeys. Finally, consistent with International Council for Harmonisation S5(R3) (ICH 2020), further non-clinical studies are not considered meaningful or warranted since the target of donanemab is not present in standard or alternative models amenable to developmental and reproductive toxicity testing.

Genotoxicity

No studies were performed to test donanemab for potential genotoxicity. In general, assessment of genotoxicity for protein-based therapeutics is not warranted, as antibodies do not readily access intracellular compartments (that is, nuclei) and do not interact with genetic material (that is, DNA).

Carcinogenicity

No animal studies have been performed to test donanemab for potential carcinogenicity because the data do not support evidence of increased cancer risk associated with long-term treatment with amyloid-targeting therapy. There is no expectation that decreased levels of Aβ plaques in the CNS would play any role in carcinogenesis; rather, the preponderance of the literature relates to the cytotoxicity of Aβ.

The specificity of donanemab for the N-terminal pyroglutamate Aβ epitope specific to amyloid plaques makes it unlikely that donanemab would be involved in tumorigenesis via non-targeted pathways. Consistent with the pharmacology and highly specific mechanism of action of donanemab, the non-clinical studies demonstrated no evidence of toxicity or signals indicative of or associated with carcinogenic potential, for example, cytotoxicity or inflammation, evidence of hormonal perturbation, increased tumours, tissue hyperplasia or other preneoplastic lesions, or signs of immunomodulatory or immunosuppressive potential.

SII.2 Safety Pharmacology

Donanemab safety pharmacology assessments performed during the 6-week monkey toxicology study included the

- evaluation of body temperature
- assessment of cardiovascular safety
- observation for CNS signs with neurological examination, and
- qualitative assessment of respiratory depth with quantitative estimates of respiratory rate.

No drug-related changes occurred in any of these parameters.

SII.3 Other Toxicity-Related Information or Data

As described above, a weight-of-evidence analysis of numerous factors supports the low potential for reproductive risk resulting from donanemab exposure in humans. It is expected that the potential for pregnancy and lactation in the indicated population is negligible because AD is a condition that predominantly occurs in elderly patients. As a precautionary measure, it is preferable to avoid the use of donanemab during pregnancy.

Module SIII – Clinical Trial Exposure

Exposure data for donanemab (All LY3002813) are based on the following Phase 2 and 3 studies:

- Study AACG (data cut-off 26 October 2021)
- Study I5T-MC-AACI (AACI) main (AACI-PC and AACI-Long-term Extension) (data cut-off 14 April 2023)
- Study I5T-MC-AACN (AACN)-Dona Cohort (data cut-off 24 February 2023)
- Study I5T-MC-AACH (AACH)-Part B (data cut-off 16 March 2023)
- Study AACI-A9 Safety Addendum (data cut-off 02 March 2023)

Analysis for patients while on treatment is presented as follows:

- Dona-PC; placebo, N = 999; donanemab, N = 984,
- AACI-PC; placebo, N = 874; donanemab, N = 853, and
- All-Dona; N = 2727.

Patient-year is calculated as the sum of duration of exposure in month (1 injection = 1 month of exposure) for all patients in dosing regimen divided by 12.

Table SIII.1. Duration of Exposure, All-Dona

	All LY3002813 Treated	
Duration of Exposure	**Patients (n)**	**Patient-Years of Exposure**
≥1 m	2727	227.3
≥2 m	2552	439.9
≥3m	2358	636.4
≥4 m	2169	817.2
≥5 m	2051	988.1
≥6 m	1934	1149.3
≥7 m	1807	1299.8
≥8 m	1323	1410.1
≥9 m	1273	1516.2
≥10 m	1222	1618.0
≥11 m	1172	1715.7
≥12 m	1118	1808.8
≥13 m	1053	1896.6
≥14 m	935	1974.5
≥15 m	554	2020.7
≥16 m	468	2059.7
≥17 m	407	2093.6
≥18 m	343	2122.2
≥19 m	246	2142.7
≥20 m	115	2152.3
≥21 m	78	2158.8
≥22 m	56	2163.4

	All LY3002813 Treated	
Duration of Exposure	**Patients (n)**	**Patient-Years of Exposure**
≥23 m	43	2167.0
≥24 m	35	2169.9
≥25 m	21	2171.7
≥26 m	11	2172.6
≥27 m	5	2173.0
≥28 m	1	2173.1

Abbreviations: All-Dona = Donanemab-Treated Analysis Integrated Set; LY3002813 = donanemab; m = month; n = number of subjects within each specified category.

Table SIII.2. Age Group and Gender, All-Dona

	All LY3002813 Treated			
	Patients (n)		**Patient-Years of Exposure**	
Age Group	**M**	**F**	**M**	**F**
≥18 years and <65 years	96	96	93.3	95.1
≥ 65 years and <75 years	497	664	439.4	557.3
≥75 years and <85 years	593	698	469.8	472.4
≥85 years	37	46	22.8	23.0
Total	1223	1504	1025.3	1147.8

Abbreviations: All-Dona = Donanemab-Treated Integrated Analysis Set; F = females; LY3002813 = donanemab; M = males; n = number of subjects within each specified category.

Table SIII.3. Dose, All-Dona

	All LY3002813 Treated	
Dose of Exposure	**Patients (n)**	**Patient-Years of Exposure**
LY3002813 – 700 mg Q4W only	694	186.9
LY3002813 – Start with 700 mg and titration to 1400 mg Q4W	1990	1941.5
LY3002813 – Start with 1400 mg Q4W	43	44.7
Total	2727	2173.1

Abbreviations: All-Dona = Donanemab-Treated Integrated Analysis Set; LY3002813 = donanemab; n = number of subjects within each specified category; Q4W = every 4 weeks.

Table SIII.4. Ethnic Origin, All-Dona

	All LY3002813 Treated	
Ethnic Origin	**Patients (n)**	**Patient-Years of Exposure**
Asian	156	114.5
Black or African American	71	62.7
White	2481	1980.5
Multiple	6	4.1
Other[a]	7	6.2
Unknown	6	5.2
Total	2727	2173.1

Abbreviations: All-Dona = Donanemab-Treated Integrated Analysis Set; LY3002813 = donanemab; n = number of subjects within each specified category.

[a] Includes American Indian or Alaska Native as well as Native Hawaiian or Other Pacific Islander.

Module SIV – Populations Not Studied in Clinical Trials

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

Criterion: Exclusion of participants with AD stage other than early symptomatic AD.

Reason for exclusion: The clinical strategy for donanemab has focused on patients with early symptomatic AD. In the Dona-PC, the population of patients tested were those with early symptomatic AD with existing cerebral amyloid plaque as measured using the amyloid biomarker, florbetapir positron emission tomography imaging, and with intermediate (low to medium) cerebral tau burden. This strategy was based on the amyloid hypothesis of AD, which postulates that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical data supporting this hypothesis come from the observation that parenchymal Aβ levels are elevated prior to the manifestation of AD symptoms and further supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from MCI to AD dementia (Doraiswamy et al. 2012). These data suggest that removal of deposited amyloid and clearance of Aβ earlier in the disease process can result in the slowing of AD progression.

Participants with moderate AD have been treated but do not comprise a large population. Participants with high tau were included in Study AACI. Phase 1 studies and AACH study included participants with moderate AD. In addition, about 10% of subjects within Study AACG also progressed to moderate stages within the study period.

Is it considered to be included as missing information: No

Rationale (if not included as missing information): Labelling information will clearly indicate that donanemab is indicated for the treatment of patients with early symptomatic AD.

Criterion: Exclusion of patients less than 60 or greater than 85 years of age in most studies.

Reason for exclusion: This age range is appropriate for the target population of early symptomatic AD and minimises the likelihood of the presence of confounding neurological conditions.

Is it considered to be included as missing information: No

Rationale (if not included as missing information): The majority of sporadic AD cases occur in patients in the age range of 65 to 85 years. The safety profile is not expected to be significantly different in older or younger patients.

Criterion: Exclusion of women who are pregnant.

Reason for exclusion: Generally, it is not expected that women of childbearing potential will be significantly represented in the indicated population. Also, to date, use in pregnant women has

been a standard exclusion criterion in clinical development in general and specifically in AD studies.

Is it considered to be included as missing information: No

Rationale (if not included as missing information): Given that AD is a disease that occurs mainly in the elderly, donanemab is not expected to be administered to women of childbearing potential. Additionally, labelling will state that, as a precautionary measure, it is preferable to avoid the use of donanemab during pregnancy.

Criterion: Patients with Down Syndrome associated with AD.

Reason for exclusion: Although participants with Down Syndrome (with associated AD pathology) were not specifically excluded in clinical trials, given the following reasons, no participants with Down Syndrome were enrolled in clinical studies.

- protocol-specific requirement for age (versus the age of participants with Down Syndrome)
- requirement for AD neuropathology at baseline, and
- specific exclusion criteria related to comorbid neurological conditions (including significant neurological disease affecting the CNS that may affect cognition or ability to complete the study) often observed in Down Syndrome.

Is it considered to be included as missing information: No

Rationale (if not included as missing information): Despite a relatively earlier age of onset and having significant levels of Aβ neuropathology, the safety profile of donanemab is not expected to be different in participants with Down Syndrome associated with AD. As a precautionary measure, language included in labelling states that the safety and efficacy in patients with Down syndrome associated with AD have not been established.

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

The 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.

The size of the clinical development programme (N = 2727 in All-Dona) would have allowed detection of adverse reactions that were uncommon with a frequency of at least 1 in 900 (based on the rule of 3).

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment	No clinical studies focused on patients with hepatic and renal impairment have been conducted. Patients with these conditions were not specifically excluded from the Phase 2 study. However, in the Dona-PC, patients with a calculated creatine clearance <30 mL/min (Cockcroft-Gault formula; Cockcroft and Gault 1976), and those with active Hepatitis B or C at the screening visit were excluded.
Population with relevant different ethnic origin	Clinical trials enrolled patients of various racial and/or ethnic origins and there were no restrictions outlined in clinical protocols. No evidence of any ethnic differences in terms of safety was observed. **All LY3002813 (N = 2727)** Asian = 156 (114.5 patient-years of exposure) Black or African American = 71 (62.7 patient-years of exposure) White = 2481 (1980.5 patient-years of exposure) Multiple = 6 (4.1 patient-years of exposure) Other = 7 (6.2 patient-years of exposure) Unknown = 6 (5.2 patient-years of exposure)
Subpopulations carrying relevant genetic polymorphisms	ApoE ε4 carriers and non-carriers were included in clinical studies. In the Dona-PC, among participants who received donanemab monotherapy, 70.1% were ApoE ε4 carriers. In All-Dona, participants with known ApoE ε4 status, 67.1% were ApoE ε4 carriers.
Other	
Patients with Down Syndrome associated with AD	Although not specifically excluded, no patients with Down Syndrome were enrolled in the clinical development programme. Use of donanemab in this population to be studied in planned drug utilisation study.

Type of Special Population	Exposure
People with AD severity other than early symptomatic AD	Patients with moderate AD (at screening) were included in Phase 1 clinical trials of donanemab. In Phase 1 Studies AACC and AACD, 64 patients had moderate AD with a baseline MMSE <20 and were exposed to a range of doses (single doses) from 0.1 to 40 mg/kg in single doses IV or SC, including some patients given 10 mg/kg Q2W, 10 mg/kg Q4W, and 20 mg/kg Q4W. Additionally, in the Phase 2/3 integrated All-Dona exposure, there were 290 (10.6%) patients with moderate AD at screening[a]. A total of 271 participants with high tau were exposed to donanemab in Study AACI.

Abbreviations: AACH = I5T-MC-AACH; AACI = I5T-MC-AACI; AD = Alzheimer's disease; All-Dona = Donanemab-Treated Integrated Analysis Set; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; IV = intravenous; MMSE = Mini-Mental State Examination; N = number of subjects in the specified category: SC = subcutaneous; Q4W = every 4 weeks.

[a] If screening MMSE was unavailable, baseline MMSE was used. For patients in Study AACH Part B, and patients who were randomly assigned to placebo in the Study AACI placebo-controlled period, their last non-missing MMSE measurement prior to their first donanemab infusion was used.

Module SV – Post-authorisation Experience

Donanemab has been approved for marketing in a limited number of countries (including the US, the UK, Japan, China, Mexico, Brazil and Australia).

Worldwide sales of donanemab have been collected for the cumulative period ending 31 March 2025, since the sales data are only available in complete months.

As of 31 March 2025, a total of 52 224 vials (18 728 g) of donanemab had been sold worldwide.

The number of patients cannot be adequately estimated at this time due to small-volume sales and limited period of market availability. It should also be noted that early sales of a newly marketed product may often reflect stocking by wholesalers as opposed to actual patient exposure. Trending sales data across several periodic report periods will give an indication of the level of use of the product in the patient population.

Module SVI – Additional EU Requirements for the Safety Specification

SVI.1 – Potential for Misuse for Illegal Purposes

Donanemab has no known attributes that make it attractive for intentional overdose or illegal use. Donanemab will be available only through prescribing physicians and other healthcare professionals with prescriptive authority. In addition, it will be administered as an intravenous infusion under supervision at specific centres; therefore, there is negligible risk of the drug being available to patients or other individuals directly. Based on the non-clinical and clinical studies of donanemab to date, there have been no findings that donanemab causes physical or psychological dependency. Therefore, misuse for illegal purposes is not expected to occur with this medicinal product.

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

Not all adverse drug reactions for donanemab represent a risk per the guidelines on good pharmacovigilance practices Module V (Revision 2) based on their severity and clinical outcome. Therefore, this section focuses on those adverse drug reactions that are considered a risk, but not an important risk.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- None

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:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (for example, actions being part of standard clinical practice in each EU member state where the product is authorised):

- None

Known risks that do not impact the risk-benefit profile:

- Nausea
- Vomiting
- Headache

Other reasons for considering the risks not important:

- None

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

Important Identified Risk 1: ARIA-E (cerebral oedema/effusion)

Risk-benefit impact:

ARIA-E is an important identified risk because it has the potential to be life-threatening or fatal.

In the integrated Dona-PC, ARIA-E was reported in 240 patients (24.4%), symptomatic ARIA-E was reported in 57 patients (5.8%), and serious ARIA-E was reported in 15 patients (1.5%) treated with donanemab.

In the Study AACI-PC, ARIA-E was reported in 205 patients (24.0%), symptomatic ARIA-E was reported in 52 patients (6.1%), and serious ARIA-E was reported in 13 patients (1.5%) treated with donanemab.

In the All-Dona, ARIA-E was reported in 531 patients (19.5%), symptomatic ARIA-E was reported in 117 patients (4.3%), and serious ARIA-E was reported in 28 patients (1.0%) treated with donanemab.

In Dona-PC and AACI-PC, 2 donanemab-treated participants with serious ARIA-E subsequently died. The cause of death was related to ARIA-E for 1 participant, and the other participant had serious ARIA-E and ARIA-H prior to death. In All-Dona, an additional death due to ARIA-E was reported, for a total of 2 (0.1%) fatal ARIA-E events in donanemab-treated participants. All 3 donanemab-treated participants, who had serious ARIA-E and subsequently died, were ApoE ε4 heterozygous.

Based upon the frequency of ARIA-E events and the potential for some of them to be life threatening or fatal, the risk is likely to have an impact on the benefit-risk, hence considered as an important risk. Although this risk is considered impactful to the benefit-risk assessment, it can be monitored and managed and is considered acceptable in the context of the seriousness of the disease being treated.

Important Identified Risk 2: ARIA-H (cerebral microhaemorrhage and superficial siderosis)

Risk-benefit impact:

ARIA-H is an important identified risk because it has the potential to be life-threatening or fatal.

In the integrated Dona-PC, ARIA-H was reported in 308 patients (31.3%), symptomatic ARIA-H was reported in 10 patients (1.0%), and serious ARIA-H was reported in 4 patients (0.4%) treated with donanemab.

In the Study AACI-PC, ARIA-H was reported in 268 patients (31.4%), symptomatic ARIA-H was reported in 10 patients (1.2%), and serious ARIA-H was reported in 4 patients (0.5%) treated with donanemab.

In the All-Dona, ARIA-H was reported in 699 patients (25.6%) treated with donanemab. There were 14 patients (0.5%) with symptomatic ARIA-H, and 9 patients (0.3%) reporting serious ARIA-H (6 of which with concurrent serious ARIA-E).

In Dona-PC and AACI-PC, 2 donanemab-treated participants with serious ARIA-H subsequently died. The cause of death was related to ARIA-H for 1 participant, and the other participant had serious ARIA-E and ARIA-H prior to death. In All-Dona, no additional deaths due to ARIA-H were reported, for a total of 1 (0.04%) fatal ARIA-H event in donanemab-treated participants. The donanemab treated participant with fatal ARIA-H was an ApoE ε4 non-carrier with baseline superficial siderosis and the participant with serious ARIA-H, who subsequently died, was ApoE ε4 heterozygous.

ARIA-H is often associated with ARIA-E, and ARIA-H is believed to indicate higher risk for intracerebral haemorrhage greater than 1 cm as well as for the presence of significant CAA. Based upon the frequency of these events, the potential for them to be serious and their potential to have severe outcomes that can be life threatening or fatal is considered an important risk. Although this risk is considered impactful to the benefit-risk assessment, it can be monitored and managed and is considered acceptable in the context of the seriousness of the disease being treated.

Important Identified Risk 3: Hypersensitivity events (including IRR)

Risk-benefit impact:

Hypersensitivity events, including IRR, anaphylaxis, and immediate hypersensitivity reactions, may have an impact on the benefit-risk balance for donanemab because they have the potential to be life-threatening or fatal.

In the Dona-PC, hypersensitivity events, including IRRs, occurred in 147 donanemab-treated patients (14.9%).

- 100 patients (10.2%) had an immediate event (occurred within 1 day of the infusion) with a vast majority due to IRRs that were reported in 82 (8.3%) participants treated with donanemab
- 51 (5.2%) had a non- immediate event, and
- 6 donanemab-treated patients (0.6%) had a serious hypersensitivity event.

In the Study AACI-PC, hypersensitivity events, including IRRs, occurred in 132 donanemab-treated patients (15.5%).

- 89 patients (10.4%) had an immediate event with a vast majority due to IRRs that were reported in 72 (8.4%) participants treated with donanemab
- 47 (5.5%) had a non-immediate event, and
- 3 donanemab-treated patients (0.4%) had a serious hypersensitivity event.

In the All-Dona, hypersensitivity events, including IRRs, occurred in 348 donanemab-treated patients (12.8%).

- 246 patients (9.0%) had an immediate event with a vast majority due to IRRs that were reported in 216 (7.9%) participants treated with donanemab
- 111 donanemab-treated patients (4.1%) had a non-immediate event, and
- 13 donanemab-treated patients (0.5%) had a serious hypersensitivity event (12 immediate and 1 non-immediate), including,
    - 6 IRRs
    - 3 anaphylactic reactions
    - 1 anaphylactic shock
    - 1 infusion-related hypersensitivity reaction
    - 1 event of drug eruption, and
    - 1 of urticaria.

Analyses from Dona-PC and All-Dona analysis sets support that the primary hypersensitivity risk is related to immediate events, particularly IRRs. The majority of these events were mild to moderate in severity and occurred during the infusion or within 30 minutes of the end of the infusion, and most resolved on the same day. For non-immediate events, no pattern or consistency of presentation was noted.

Based on the immediate events of hypersensitivity or IRR observed after donanemab infusion, this is considered an important identified risk. The risk of hypersensitivity events appears manageable, given that overall, hypersensitivity or IRR events were primarily mild to moderate in severity, occurred during the infusion or within the post-infusion observation period recommended in labelling (30 minutes), most resolved on the same day, and many resolved without intervention. It is thus considered acceptable in the context of the seriousness of the disease being treated.

Important Potential Risk 1: Intracranial haemorrhage

Risk-benefit impact:

Intracranial haemorrhage events were identified using a modified approach to the Haemorrhagic CNS vascular conditions SMQ, excluding all microhaemorrhage related terms. Intracranial haemorrhage includes TEAE and/or MRI findings of subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macro-haemorrhage, and cerebrovascular accident.

Intracerebral haemorrhage greater than 1 cm (sometimes referred to as macro-haemorrhage) is a cerebral haemorrhage that measures greater than 10 mm in diameter and is sometimes included in the definition of ARIA-H. For donanemab, the frequency of intracerebral haemorrhage greater than 1 cm in diameter is reported separately.

Certain types of intracranial haemorrhages (cerebral haemorrhage and haemorrhagic stroke) have the potential to be life-threatening or fatal and thus have an impact on the risk-benefit profile of donanemab.

Serious (including fatal) cases of intracranial haemorrhage have been observed with other amyloid-targeting therapies.

In the donanemab clinical development programme, intracranial haemorrhage was observed at a higher frequency in donanemab-treated patients (1.3% in both Dona-PC and AACI-PC) than placebo (0.8% in both Dona-PC and AACI-PC). The largest difference between groups was observed for events of subdural haematoma, which were higher in the donanemab group (0.5% in both Dona-PC and AACI-PC) than placebo (0.2% in both Dona-PC and AACI-PC). Most of the subdural haematoma or subdural haemorrhage events were temporally associated with head trauma or falls. A similar frequency of events of intracerebral haemorrhage greater than 1cm (also referred to as macro-haemorrhage), including haemorrhagic stroke and cerebral haemorrhage, was observed in participants treated with either donanemab (0.3% in Dona-PC and 0.4% in AACI-PC) or placebo (0.2% in both Dona-PC and AACI-PC). In addition, events of

cerebrovascular accident, which were included in the intracranial haemorrhage cluster, did not present evidence of the stroke being haemorrhagic.

In All Dona, intracranial haemorrhage was observed in 1.3% of the participants, driven by subdural haematoma (0.4%), and subarachnoid haemorrhage (0.3%). Cerebral haemorrhage (0.1%) and haemorrhagic stroke (0.1%) were less frequent.

In All-Dona, 3 fatal intracranial haemorrhages were reported in donanemab-treated participants:

- one death (ApoE ε4 non-carrier) due to subarachnoid haemorrhage in a patient with no previous evidence of ARIA, which was assessed by the investigator as likely related to trauma following a fall
- one death (ApoE ε4 heterozygote) due to thalamus haemorrhage in a hypertensive patient with history of stroke, hyperlipidaemia, and no previous evidence of ARIA, which the investigator assessed as possibly related to donanemab, and
- one death (ApoE ε4 heterozygote) following administration of thrombolytic medication for acute ischaemic stroke with subsequent development of intracranial haemorrhage (later also found to have ARIA-E on MRI). In the opinion of the investigator, the haemorrhage could have been caused by the treatment with tissue plasminogen activator and made worse by CAA and amyloid removal by study treatment.

The SmPC includes a warning and precaution as noted below:

- ARIA can cause focal neurologic deficits similar to those observed in an ischaemic stroke. Clinicians treating ischaemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy to a patient being treated with donanemab. MRI or identification of vascular occlusion can help identify that ischaemic stroke, rather than ARIA, is the aetiology and inform the use of thrombolytics or thrombectomy when appropriate.

To date, there has been no clear evidence of an increased risk of intracranial haemorrhage in patients exposed to donanemab during clinical development. Therefore, intracranial haemorrhage is considered an important potential risk for donanemab and will be further characterised in ongoing clinical trials and planned post-marketing observational studies.

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

Not applicable, as this is the initial RMP.

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

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: ARIA-E (cerebral oedema/effusion)

Potential mechanisms:

ARIA-E is thought to be mechanistically linked to direct binding of Aβ and clearance from brain vasculature (Brashear et al. 2018). In a less probable conceptual model of ARIA-E, administration of anti-Aβ antibodies was postulated to result in increased Aβ trafficking and clearance with disruption of arteriolar smooth muscle and increased cerebrovascular permeability leading to fluid extravasation (Brashear et al. 2018).

Evidence source(s) and strength of evidence:

ARIA-E is a known class effect of amyloid-targeting therapies. Patients with ARIA-E are usually asymptomatic. If symptoms occur, these may include, but are not limited to (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021),

- headache
- vomiting
- unsteadiness
- dizziness
- tremor
- confusion
- visual disturbances
- speech disturbances
- worsening cognitive function
- alteration of consciousness, and
- seizures.

Intervention beyond withholding treatment may be required to address concomitant symptoms (for example, corticosteroids).

Events of ARIA-E were observed across the donanemab clinical development programme.

Characterisation of the risk:

Clinical trial data:

In Dona-PC, ARIA-E was reported in 240 patients (24.4%), symptomatic ARIA-E was reported in 57 patients (5.8%), and serious ARIA-E was reported in 15 patients (1.5%) treated with donanemab. Additional details of ARIA-E events from Dona-PC are presented in Table SVII.1 and Table SVII.2.

In Study AACI-PC, ARIA-E was reported in 205 patients (24.0%), symptomatic ARIA-E was reported in 52 patients (6.1%) of patients, and serious ARIA-E was reported in 13 patients (1.5%) treated with donanemab. Additional details of ARIA-E events from Study AACI-PC are presented in Table SVII.3 and Table SVII.4

In All-Dona, ARIA-E was reported in 531 patients (19.5%), symptomatic ARIA-E was reported in 117 patients (4.3%), and serious ARIA-E was reported in 28 patients (1.0%) treated with donanemab.

In Dona-PC and AACI-PC, 2 donanemab-treated participants with serious ARIA-E subsequently died. The cause of death was related to ARIA-E for 1 participant, and the other participant had serious ARIA-E and ARIA-H prior to death. In All-Dona, 1 additional death due to ARIA-E was reported, for a total of 2 (0.1%) fatal ARIA-E events in donanemab-treated participants. All 3 donanemab-treated participants, who had serious ARIA-E and subsequently died, were ApoE ε4 heterozygous.

Table SVII.1. Characterisation of ARIA-E Risk, Dona-PC

	Placebo (N = 999) n (%)	LY3002813 (N = 984) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with ARIA-E	19 (1.9)	240 (24.4)	12.8
Non-carrier (0 ApoE ε4 alleles)[a]	2 (0.2)	43 (4.4)	22
Carrier (≥1 ApoE ε4 alleles)[a]	16 (1.6)	196 (19.9)	12.4
Heterozygote (1 ApoE ε4 allele)	10 (1.0)	126 (12.8)	12.8
Homozygote (2 ApoE ε4 alleles)	6 (0.6)	70 (7.1)	11.8

Abbreviations: AE = adverse event; ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-E = amyloid-related imaging abnormality–oedema/effusions; CRF = case report form; Dona-PC = Placebo-Controlled Analysis Set; LTE = long-term extension; LY3002813 = donanemab; MRI = magnetic resonance imaging; N = total number of subjects; n = number of subjects in the specified category; TEAE = treatment-emergent adverse event.

[a] Subjects with missing ApoE ε4 Carrier Status were not included.

Note: ARIA-E on safety MRI or TEAE cluster. ARIA-E TEAE cluster preferred terms are 1) Amyloid-related imaging abnormality–oedema/effusions, 2) Brain oedema, and 3) Vasogenic cerebral oedema.

Table SVII.2. Summary of ARIA-E by ApoE ε4 Status, Dona-PC

	Placebo			LY3002813		
	Number of Participants with ARIA-E	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-E	Number of Participants with ARIA-E	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-E
Non-carrier (0 ApoE ε4 alleles)	2	282	0.7%	43	291	14.8%
Carrier (≥1 ApoE ε4 alleles)	16	712	2.2%	196	690	28.4%
Heterozygote (1 ApoE ε4 allele)	10	538	1.9%	126	522	24.1%
Homozygote (2 ApoE ε4 alleles)	6	174	3.4%	70	168	41.7%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-E = amyloid-related imaging abnormality–oedema/effusions; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; TEAE = treatment-emergent adverse event.

Note: ARIA-E on safety MRI or TEAE cluster. ARIA-E TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities–oedema/effusions, 2) Brain oedema, and 3) Vasogenic cerebral oedema.

Note: Subjects with missing ApoE ε4 carrier status were not included

Table SVII.3. Characterisation of ARIA-E Risk, AACI-PC

	Placebo (N = 874) n (%)	LY3002813 (N = 853) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with ARIA-E	18 (2.1)	205 (24.0)	11.4
Non-carrier (0 ApoE ε4 alleles) [a]	2 (0.2)	40 (4.7)	23.5
Carrier (≥1 ApoE ε4 alleles) [a]	15 (1.7)	164 (19.2)	11.3
Heterozygote (1 ApoE ε4 allele)	10 (1.1)	105 (12.3)	11.2
Homozygote (2 ApoE ε4 alleles)	5 (0.6)	59 (6.9)	11.5

Abbreviations: AE = adverse event; ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-E = amyloid-related imaging abnormality–oedema/effusions; CRF = case report form; AACI-PC = Placebo-Controlled Analysis Set; LTE = long-term extension; LY3002813 = donanemab; MRI = magnetic resonance imaging; N = total number of subjects; n = number of subjects in the specified category; TEAE = treatment-emergent adverse event.

[a] Subjects with missing ApoE ε4 carrier status were not included.

Note: ARIA-E on safety MRI or TEAE cluster. ARIA-E TEAE cluster preferred terms are 1) Amyloid-related imaging abnormality–oedema/effusions, 2) Brain oedema, and 3) Vasogenic cerebral oedema.

Table SVII.4. Summary of ARIA-E by ApoE ε4 Status, AACI-PC

	Placebo			LY3002813		
	Number of Participants with ARIA-E	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-E	Number of Participants with ARIA-E	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-E
Non-carrier (0 ApoE ε4 alleles)	2	250	0.8%	40	255	15.7%
Carrier (≥1 ApoE ε4 alleles)	15	620	2.4%	164	595	27.6%
Heterozygote (1 ApoE ε4 allele)	10	474	2.1%	105	452	23.2%
Homozygote (2 ApoE ε4 alleles)	5	146	3.4%	59	143	41.3%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-E = amyloid-related imaging abnormality–oedema/effusions; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; TEAE = treatment-emergent adverse event.

Note: ARIA-E on safety MRI or TEAE cluster. ARIA-E TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities–oedema/effusions, 2) Brain oedema, and 3) Vasogenic cerebral oedema.

Note: Subjects with missing ApoE ε4 carrier status were not included.

Post-marketing data:

As of 02 April 2025, 87 events of ARIA-E, including brain oedema were reported in the post-marketing setting. Of these, 27 events (31%) were symptomatic. The most common symptoms were headache and confusion, there were also instances of aphasia/dysphasia, and 1 case of seizure. Eleven events (13%) were received as serious reports; all serious due to hospitalisation and one was also reported as life-threatening. Among these 11 serious events, 9 were symptomatic.

The majority of the events with known radiographic severity were mild or moderate (26 out of 33 events [79%]).

Among the 17 patients with known ApoE ε4 genotype, ARIA-E occurred in 24% (4 patients) who were noncarriers, 47% (8 patients) heterozygotes, and 29% (5 patients) homozygotes. The majority of the symptomatic ARIA-E events reported were related to ApoE ε4 carriers (8 out of 9 events [89%]).

There has been one death with unknown cause in a patient with unknown ApoE ε4 status. The patient had concurrent serious events of brain oedema and cerebral haemorrhage, which was reported as a small brain bleed. Both events were reported as recovering at the time of death.

Additionally, 31 events of ARIA were reported without further information regarding the type of ARIA. Of these, 7 events (23%) were symptomatic, primarily characterised by headaches and brain fog. In one case, unspecified stroke-like symptoms were reported. None of these events were classified as serious reports.

Reversibility:

ARIA-E is generally reversible upon treatment discontinuation. In Dona-PC, the median time to radiographic resolution of ARIA-E was 59 days, with a range of 15 to 292 days. In Study AACI-PC, the median time to radiographic resolution of ARIA-E was 58 days, with a range of 15 to 292 days. From All-Dona, which is composed mostly of ongoing studies, of the donanemab-treated participants with ARIA-E as of the data cut-off, 90.7% had radiographic resolution of ARIA-E, with a median time to resolution of 58 days and a range from 13 to 294 days. Donanemab treatment should be permanently discontinued if serious ARIA-E or recurrent severe ARIA events occur.

Impact on quality of life:

Given the generally transient and asymptomatic course of ARIA-E and the low frequency of serious cases (1.5% in both Dona-PC and AACI-PC; 1.0% in All-Dona), it is expected that ARIA-E may have a significant impact on the quality of life for a small subset of patients.

Risk factors and risk groups:

In the donanemab clinical development programme, a higher frequency of ARIA-E was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis.

In Dona-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.7%, heterozygote 24.1%) compared to non-carriers (14.8%) (Table SVII.2). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 7.7%, heterozygote 6.1%) was increased compared with noncarriers (4.1%).

In Study AACI-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.3%, heterozygote 23.2%) compared to non-carriers (15.7%) (Table SVII.4). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 8.4%, heterozygote 6.6%) was increased compared with non-carriers (3.9%).

In All-Dona, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 33.9%, heterozygote 20.2%) compared with non-carriers (11.6%). A higher frequency of symptomatic ARIA-E was also noted for donanemab-treated patients ApoE ε4 carriers (homozygote 6.6%, heterozygote 4.3%) compared with non-carriers (3.2%).

Preventability:

A gradual titration schedule using 350 mg for the first dose, 700 mg for the second dose, and 1050 mg for the third dose once every 4 weeks before escalating to 1400 mg every 4 weeks was implemented to reduce the risk of serious ARIA-E. Measures for early diagnosis and prevention of progression of ARIA-E include an MRI at baseline, prior to the second dose, prior to the third dose, prior to the fourth dose, prior to the seventh dose, and if ARIA symptoms occur. An additional MRI prior to the 12th dose should be performed in patients with ARIA risk factors, such as ApoE ε4 heterozygotes. Most serious ARIA events occurred within 12 weeks of initiation of treatment.

Donanemab treatment is indicated in ApoE ε4 heterozygotes or non-carriers, and the treatment is contraindicated in patients with

- baseline MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), or other findings, which are suggestive of CAA
- bleeding disorders that are not under adequate control
- an ongoing anticoagulant therapy
- severe white matter disease
- poorly controlled hypertension, and
- conditions that do not allow MRI assessment, including claustrophobia or the presence of metal (ferromagnetic) implants/cardiac pacemaker.

Patients can be monitored for this condition and potentially long-term sequelae may be avoided by prompt diagnosis and appropriate management (See Part V).

Impact on the risk-benefit balance of the product:

At this time, cumulative data suggest that the risk-benefit impact of ARIA-E is acceptable in the context of the severity of the indication treated given that majority of the events are non-serious and asymptomatic and can be appropriately monitored and managed.

Public health impact:

Given the low frequency of serious cases (1.5% in both Dona-PC and AACI-PC; 1.0% in All-Dona), the public health impact of ARIA-E is expected to be low in the context of the overall serious, progressive, and terminal nature of AD and its public health burden for caregivers and society.

Important Identified Risk: ARIA-H (cerebral microhaemorrhage and superficial siderosis)

Potential mechanisms:

ARIA-H is often associated with ARIA-E and both are likely related to removal of pathological vascular Aβ followed by disruption of vascular wall integrity (Ketter et al. 2017).

ARIA-H includes

- cerebral microhaemorrhage (mH), which is a cerebral haemorrhage that measures less than or equal to 10 mm in diameter.
- superficial siderosis, which are deposits of iron in tissue in the form of hemosiderin and are felt to represent residua of a small leakage of blood from a vessel into the subpial or leptomeningeal layers of the brain.

Evidence source(s) and strength of evidence:

ARIA-H is a known class effect of amyloid-targeting therapies (Arrighi et al. 2016). Patients with ARIA-H are usually asymptomatic. ARIA-H may be related to vascular amyloid clearance with weakening and rupture of small blood vessels (Withington 2022). Whereas ARIA-E is usually radiographically visible over the course of weeks or months. ARIA-H can remain permanently visible on subsequent imaging (Salloway 2022). If symptoms occur, they may include,

- headache
- worsening confusion
- dizziness
- visual disturbances
- nausea, and
- seizures (Withington 2022).

Cases of ARIA-H were observed across the donanemab clinical development programme.

Characterisation of the risk:

Clinical trial data:

In Dona-PC, ARIA-H was reported in 308 patients (31.3%), symptomatic ARIA-H was reported in 10 patients (1.0%), and serious ARIA-H was reported in 4 patients (0.4%) treated with donanemab. Additional details of ARIA-H from Dona-PC are presented in Table SVII.5. and Table SVII.6.

In Study AACI-PC, ARIA-H was reported in 268 patients (31.4%), symptomatic ARIA-H was reported in 10 patients (1.2%), and serious ARIA-H was reported in 4 patients (0.5%) treated with donanemab. Additional details of ARIA-H from Study AACI-PC are presented in Table SVII.7 and Table SVII.8.

In All-Dona, ARIA-H was reported in 699 patients (25.6%) treated with donanemab. There were 14 patients (0.5%) with symptomatic ARIA-H, and 9 patients (0.3%) with serious ARIA-H (6 of which with concurrent serious ARIA-E).

In Dona-PC and AACI-PC, 2 donanemab-treated participants with serious ARIA-H subsequently died. The cause of death was related to ARIA-H for 1 participant, and the other participant had serious ARIA-E and ARIA-H prior to death. In All-Dona, no additional deaths due to ARIA-H were reported, for a total of 1 (0.04%) fatal ARIA-H event in donanemab-treated participants. The donanemab-treated participant with fatal ARIA-H was an ApoE ε4 non-carrier with baseline superficial siderosis, and the participant with serious ARIA-H, who subsequently died, was ApoE ε4 heterozygous.

Table SVII.5. Characterisation of ARIA-H Risk, Dona-PC

	Placebo (N = 999) n (%)	LY3002813 (N = 984) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with ARIA-H	130 (13.0)	308 (31.3)	2.4
Non-carrier (0 ApoE ε4 alleles)[a]	30 (3.0)	55 (5.6)	1.9
Carrier (≥1 ApoE ε4 alleles)[a]	100 (10.0)	252 (25.6)	2.6
Heterozygote (1 ApoE ε4 allele)	66 (6.6)	162 (16.5)	2.5
Homozygote (2 ApoE ε4 alleles)	34 (3.4)	90 (9.1)	2.7

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-H = amyloid-related imaging abnormality–haemorrhage/hemosiderin deposition; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; N = total number of subjects; n = number of subjects in the specified category; TEAE = treatment-emergent adverse event.

[a] Subjects with missing ApoE ε4 carrier status were not included.

Note: ARIA-H based on MRI or TEAE cluster. ARIA-H TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities–microhaemorrhage and hemosiderin deposits, 2) Brainstem microhaemorrhage, 3) Cerebellar microhaemorrhage, 4) Cerebral hemosiderin deposit, 5) Cerebral microhaemorrhage, and 6) Superficial siderosis of the central nervous system.

Table SVII.6. Summary of ARIA-H by ApoE ε4 Status, Dona-PC

	Placebo			LY3002813		
	Number of Participants with ARIA-H	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-H	Number of Participants with ARIA-H	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with ARIA-H
Non-carrier (0 ApoE ε4 alleles)	30	282	10.6%	55	291	18.9%
Carrier (≥1 ApoE ε4 alleles)	100	712	14.0%	252	690	36.5%
Heterozygote (1 ApoE ε4 allele)	66	538	12.3%	162	522	31.0%
Homozygote (2 ApoE ε4 alleles)	34	174	19.5%	90	168	53.6%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-H = amyloid-related imaging abnormality–haemorrhage/hemosiderin deposition; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; TEAE = treatment-emergent adverse event.

Note: ARIA-H based on MRI or TEAE cluster. ARIA-H TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities -microhaemorrhage and hemosiderin deposits, 2) Brainstem microhaemorrhage, 3) Cerebellar microhaemorrhage, 4) Cerebral hemosiderin deposit, 5) Cerebral microhaemorrhage**,** and 6) Superficial siderosis of the central nervous system.

Note: Subjects with missing ApoE ε4 carrier status were not included.

Table SVII.7. Characterisation of ARIA-H Risk, AACI-PC

	Placebo (N = 874) n (%)	LY3002813 (N = 853) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with ARIA-H	119 (13.6)	268 (31.4)	2.3
Non-carrier (0 ApoE ε4 alleles) [a]	28 (3.2)	48 (5.6)	1.7
Carrier (≥1 ApoE ε4 alleles) [a]	91 (10.4)	219 (25.7)	2.5
Heterozygote (1 ApoE ε4 allele)	61 (7.0)	147 (17.2)	2.5
Homozygote (2 ApoE ε4 alleles)	30 (3.4)	72 (8.4)	2.5

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-H = amyloid-related imaging abnormality–haemorrhage/hemosiderin deposition; AACI-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; N = total number of subjects; n = number of subjects in the specified category; TEAE = treatment-emergent adverse event.

[a] Subjects with missing ApoE ε4 carrier status were not included.

Note: ARIA-H based on MRI or TEAE cluster. ARIA-H TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities–microhaemorrhage and hemosiderin deposits, 2) Brainstem microhaemorrhage, 3) Cerebellar microhaemorrhage, 4) Cerebral hemosiderin deposit, 5) Cerebral microhaemorrhage, and 6) Superficial siderosis of the central nervous system.

Table SVII.8. Summary of ARIA-H by ApoE ε4 Status, AACI-PC

	Placebo			LY3002813		
	Number of Participants with ARIA-H	**Number of Participants in ApoE ε4 Category**	**Percentage of Participants in ApoE ε4 Category with ARIA-H**	**Number of Participants with ARIA-H**	**Number of Participants in ApoE ε4 Category**	**Percentage of Participants in ApoE ε4 Category with ARIA-H**
Non-carrier (0 ApoE ε4 alleles)	28	250	11.2%	48	255	18.8%
Carrier (≥1 ApoE ε4 alleles)	91	620	14.7%	219	595	36.8%
Heterozygote (1 ApoE ε4 allele)	61	474	12.9%	147	452	32.5%
Homozygote (2 ApoE ε4 alleles)	30	146	20.5%	72	143	50.3%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; ARIA-H = amyloid-related imaging abnormality–haemorrhage/hemosiderin deposition; AACI-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; TEAE = treatment-emergent adverse event.

Note: ARIA-H based on MRI or TEAE cluster. ARIA-H TEAE cluster preferred terms are 1) Amyloid-related imaging abnormalities -microhaemorrhage and hemosiderin deposits, 2) Brainstem microhaemorrhage, 3) Cerebellar microhaemorrhage, 4) Cerebral hemosiderin deposit, 5) Cerebral microhaemorrhage, and 6) Superficial siderosis of the central nervous system.

Note: Subjects with missing ApoE ε4 carrier status were not included.

Post-marketing data:

As of 02 April 2025, 84 events of ARIA-H including cerebral microhaemorrhage and superficial siderosis were reported in the post-marketing setting. Out of these, 33 events (39%) occurred concurrently with ARIA-E. Of the 84 events, 22 (26%) were symptomatic. The primary symptom reported was headaches, but there were also instances of aphasia/dysphasia, and 1 case of seizure. Additionally, 6 events (7%) were received as serious reports; all serious due to hospitalisation. Notably, all of these serious cases were symptomatic and occurred concurrently with serious ARIA-E.

The majority of the events with known radiographic severity were mild or moderate (25 out of 30 events [83%]). In 5 (6%) of the reports, patients were receiving a concomitant antiplatelet agent, all of which were aspirin. Additionally in 2 (2%) of the reports, patients were receiving concomitant anticoagulants, apixaban and warfarin. There were no reports of ARIA-H in any patients who had received a thrombolytic.

Among the 14 patients with known ApoE ε4 genotype, ARIA-H occurred in 21% (3 patients) who were noncarriers, 50% (7 patients) heterozygotes, and 29% (4 patients) homozygotes. The majority of the symptomatic ARIA-H events reported were related to ApoE ε4 carriers (6 out of 7 events [86%]).

There has been one death with unknown cause following a fall and head injury in a patient ApoE ε4 non-carrier who had a preceding event of non-serious, mild, and asymptomatic ARIA-H. At the time of death, donanemab therapy had been on hold for more than 6 weeks, and a repeat MRI had showed stable and unchanged mild ARIA-H.

As presented above in important identified risk of ARIA-E, additionally, 31 events of ARIA were reported without further information regarding the type of ARIA. Of these, 7 events (23%) were symptomatic, primarily characterised by headaches and brain fog. In one case, unspecified stroke-like symptoms were reported. None of these events were classified as serious reports.

Reversibility:

Generally, the radiographic findings of ARIA-H do not resolve but stabilise. Donanemab treatment discontinuation may or may not be required for stabilisation of ARIA-H. Donanemab treatment should be permanently discontinued if serious ARIA-H or recurrent severe ARIA events occur.

Impact on the quality of life:

Given the generally transient and asymptomatic course of ARIA-H and the low frequency of serious cases (0.4% in Dona-PC and 0.5% in AACI-PC; 0.3% in All-Dona), it is expected that ARIA-H may have significant impact on the quality of life for only a small subset of patients.

Risk factors and risk groups:

In the clinical development programme of donanemab, a higher frequency of ARIA-H was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis. In addition, risk factors that have been associated with ARIA-H also include the use of antithrombotic medication (Arrighi et al. 2016).

In Dona-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 53.6%, heterozygote 31.0%) compared to non-carriers (18.9%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.2%, heterozygote 1.3%) was increased compared to non-carriers (0.3%) (Table SVII.6).

In Study AACI-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 50.3%, heterozygote 32.5%) compared to non-carriers (18.8%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.4%, heterozygote 1.5%) was increased compared to non-carriers (0.4%) (Table SVII.8).

In All-Dona, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 43.2%, heterozygote 26.2%) compared with non-carriers (16.6%). The frequency of symptomatic ARIA-E was slightly higher in donanemab-treated participants ApoE ε4 carriers (homozygote 0.7%, heterozygote 0.6%) compared with non-carriers (0.3%).

Preventability:

Measures for early diagnosis and prevention of progression of ARIA-H include an MRI at baseline, prior to the second dose, prior to the third dose, prior to the fourth dose, prior to the seventh dose and if ARIA symptoms occur. An additional MRI prior to the 12th dose should be performed in patients with ARIA risk factors, such as ApoE ε4 heterozygotes. Most serious ARIA events occurred within 12 weeks of initiation of treatment.

Donanemab treatment is indicated in ApoE ε4 heterozygotes or non-carriers, and the treatment is contraindicated in patients with

- baseline MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), or other findings, which are suggestive of CAA
- bleeding disorders that are not under adequate control
- an ongoing anticoagulant therapy
- severe white matter disease
- poorly controlled hypertension, and
- conditions that do not allow MRI assessment, including claustrophobia or the presence of metal (ferromagnetic) implants/cardiac pacemaker.

Patients can be monitored for this condition and potentially long-term sequelae may be avoided by prompt diagnosis and appropriate management (See Part V).

Impact on the risk-benefit balance of the product:

At this time, cumulative data suggest that the risk-benefit impact of ARIA-H is acceptable in the context of severity of the indication treated and common background incidence rate, given that majority of the events are non-serious and asymptomatic and can be appropriately monitored and managed.

Public health impact:

Given the low frequency of serious cases (0.4% in Dona-PC and 0.5% in AACI-PC; 0.3% in All-Dona), the public health impact of ARIA-H is expected to be low in the context of the overall serious, progressive, and terminal nature of AD and its public health burden for caregivers and society.

Important identified risk: Hypersensitivity events (including IRR)

Potential mechanisms:

Biological drugs represent foreign protein and thereby can elicit hypersensitivity events, including IRRs. In some cases, these may be serious (Maggi et al. 2011).

Evidence source(s) and strength of evidence:

Biological drugs represent foreign protein and thereby can elicit immediate and non-immediate hypersensitivity events, including IRRs and anaphylaxis (Maggi et al. 2011).

Immediate hypersensitivity reactions, including IRRs, are associated with donanemab treatment and have been observed across the donanemab clinical development programme.

Characterisation of the risk:

Clinical trial data:

In Dona-PC, hypersensitivity events, including IRRs, occurred in 147 donanemab-treated patients (14.9%).

- 100 patients (10.2%) had an immediate event (occurred within 1 day of the infusion) with a vast majority due to IRRs that were reported in 82 (8.3%) participants treated with donanemab
- 51 (5.2%) had a non-immediate event, and
- 6 donanemab-treated patients (0.6%) had a serious hypersensitivity event.

Additional details of hypersensitivity events from Dona-PC are shown in Table SVII.9.

In Study AACI-PC, hypersensitivity events, including IRRs, occurred in 132 donanemab-treated patients (15.5%).

- 89 patients (10.4%) had an immediate event with a vast majority due to IRRs that were reported in 72 (8.4%) participants treated with donanemab
- 47 (5.5%) had a non-immediate event, and
- 3 donanemab-treated patients (0.4%) had a serious hypersensitivity event.

Additional details of hypersensitivity events from AACI-PC are shown in Table SVII.10.

In All-Dona, hypersensitivity events, including IRRs, occurred in 348 donanemab-treated patients (12.8%).

- 246 patients (9.0%) had an immediate event with a vast majority due to IRRs that were reported in 216 (7.9%) participants treated with donanemab
- 111 donanemab-treated patients (4.1%) had a non-immediate event, and
- 13 donanemab-treated patients (0.5%) had a serious hypersensitivity event (12 immediate and 1 non-immediate), including,
    - 6 IRRs
    - 3 anaphylactic reactions
    - 1 anaphylactic shock

- 1 infusion-related hypersensitivity reaction
- 1 event of drug eruption, and
- 1 of urticaria.

Analyses from the placebo controlled and All-Dona analysis sets support that the hypersensitivity risk is primarily related to immediate events, particularly IRRs. The majority of these events were mild to moderate in severity and occurred during the infusion or within 30 minutes of the end of the infusion, and most were resolved on the same day. For non-immediate events, no pattern or consistency of presentation was noted.

Table SVII.9. Characterisation of Hypersensitivity Risk, Dona-PC

	Placebo (N = 999) n (%)	LY3002813 (N = 984) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with any hypersensitivity events	60 (6.0)	147 (14.9)	2.5
Patients with any immediate hypersensitivity events	10 (1.0)	100 (10.2)	10.2
Patients with any non-immediate hypersensitivity events	52 (5.2)	51 (5.2)	1.0
Patients with serious hypersensitivity events	2 (0.2)	6 (0.6)	3
Patients with serious immediate hypersensitivity events	0	5 (0.5)	-
Patients with serious non-immediate hypersensitivity events	2 (0.2)	1 (0.1)	0.5
Hypersensitivity Event Outcomes[a]			
Fatal	0	0	-
Not recovered/not resolved	11	8	-
Recovering/resolving	7	7	-
Recovered with sequelae	0	0	-
Recovered/resolved	57	264	-
Unknown	0	1	-

Abbreviations: Dona-PC = Placebo-Controlled Analysis Set; N = total number of subjects; n = number of subjects with hypersensitivity events or number of hypersensitivity events; LY3002813 = donanemab.

[a] There might be more than 1 event reported in single patient.

Table SVII.10. Characterisation of Hypersensitivity Risk, AACI-PC

	Placebo (N = 874) n (%)	LY3002813 (N =853) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with any hypersensitivity events	46 (5.3)	132 (15.5)	2.9
Patients with any immediate hypersensitivity events	8 (0.9)	89 (10.4)	11.6
Patients with any non-immediate hypersensitivity events	39 (4.5)	47 (5.5)	1.2
Patients with serious hypersensitivity events	1 (0.1)	3 (0.4)	4
Patients with serious immediate hypersensitivity events	0	3 (0.4)	-
Patients with serious non-immediate hypersensitivity events	1 (0.1)	0	-
Hypersensitivity Event Outcomes			
Fatal	0	0	-
Not recovered/not resolved	6	8	-
Recovering/resolving	7	7	-
Recovered with sequelae	0	0	-
Recovered/resolved	42	223	-
Unknown	0	1	-

Abbreviations: AACI-PC = Placebo-Controlled Analysis Set; N = total number of subjects; n = number of subjects with hypersensitivity events or number of hypersensitivity events; LY3002813 = donanemab.

Post-marketing data:

As of 02 April 2025, 97 events of hypersensitivity were reported in the post-marketing setting. The most frequently reported preferred term was infusion related reaction (51 events [52.6%]). Anaphylactic reaction (6 events), anaphylactic shock (2 events), and anaphylactoid reaction (1 event) were reported among the total PTs. Except for one event where the outcome was not reported, all the other events were reported as recovered or recovering. In the reported hypersensitivity cases, some of the symptoms observed include nausea, chills, itching, blood pressure decrease, skin rash, flushing, and vomiting.

The majority of hypersensitivity events were non-serious (70, 72.2%), while 27 (27.8%) were serious due to the following reasons: being medically significant (22, 22.7%), causing initial or prolonged hospitalization (4, 4.1%), or being life threatening (1, 1%).

Outcome information was reported for 48 patients. Of these, 46 (95.8%) patients were recovered or recovering, and the remaining 2 (4.2%) patients were not recovered. No fatal events were reported.

Time to onset was reported for 11 events, while it remained unknown for other events. Of these 11 events, 9 events (81.8%) occurred within 24 hours of the last administered donanemab dose,

indicating immediate hypersensitivity. The remaining 2 events (18.2%) occurred after the 24 hours period, suggesting non-immediate hypersensitivity.

Reversibility:

Hypersensitivity reactions (including IRR) are generally reversible with monitoring, early recognition, and appropriate treatment. In Dona-PC, AACI-PC, and All-Dona, immediate hypersensitivity events were generally transient and fully resolved within less than a day.

Impact on the quality of life:

This risk does have the potential to have an effect on the quality of life, but this impact can be minimised and managed through appropriate monitoring and management.

Risk factors and risk groups:

No specific risk factors have been identified for hypersensitivity reactions. In clinical studies, 88.1% of donanemab-treated patients developed ADAs and all of the patients with ADA had neutralising antibodies. All patients reporting IRRs had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

Preventability:

Hypersensitivity reactions are preventable in patients with known hypersensitivity to the product by avoiding re-exposure. This is addressed in labelling by contraindicating donanemab in patients with known hypersensitivity to donanemab or to any of the excipients.

Impact on the risk-benefit balance of the product:

At this time, these data suggest that the benefit-risk impact is low in the context of the severity of the indication treated.

Public health impact:

Hypersensitivity reactions are not expected to have a significant public health impact in the context of the serious, progressive, and terminal nature of AD and its public health burden for caregivers and society.

Important potential risk: Intracranial haemorrhage

Potential mechanisms:

As ARIA-H is a known class effect of amyloid-targeting therapies, a potential increased risk of intracranial haemorrhage in patients treated with donanemab is plausible.

Evidence source(s) and strength of evidence:

Serious (including fatal) cases of intracranial haemorrhage have been observed with amyloid-targeting therapies including donanemab.

In the donanemab clinical development programme, intracranial haemorrhage was observed at a higher frequency in donanemab-treated patients (1.3% in both Dona-PC and AACI-PC) than

placebo (0.8% in both Dona-PC and AACI-PC). The largest difference between groups was observed for events of subdural haematoma, which were higher in the donanemab group (0.5% in both Dona-PC and AACI-PC) than placebo (0.2% in both Dona-PC and AACI-PC). Most of the subdural haematoma or subdural haemorrhage events were temporally associated with head trauma or falls. Events of intracerebral haemorrhage greater than 1cm (also referred to as macro-haemorrhage), including haemorrhagic stroke and cerebral haemorrhage, were observed at a similar frequency in participants treated with either donanemab (0.3% in Dona-PC and 0.4% in AACI-PC) or placebo (0.2% in both Dona-PC and AACI-PC).

In All Dona, intracranial haemorrhage was observed in 1.3% of the participants, driven by subdural haematoma (0.4%) and subarachnoid haemorrhage (0.3%). Cerebral haemorrhage (0.1%) and haemorrhagic stroke (0.1%) were less frequent.

In All-Dona, 3 (0.1%) fatal intracranial haemorrhages were reported in donanemab-treated participants. These 3 participants with fatal outcomes were at increased risk of intracranial haemorrhage due to history of hypertension, stroke, thrombolytic use, or the event being temporally associated with head trauma or fall.

To date, there has been no clear evidence of an increased risk of intracranial haemorrhage in patients exposed to donanemab during clinical development. Therefore, intracranial haemorrhage is considered an important potential risk for donanemab and will be further characterised in ongoing clinical trials and planned post-marketing observational studies.

Characterisation of the risk:

Clinical trial data:

In the Dona-PC, intracranial haemorrhage was reported in 13 (1.3%) donanemab-treated participants and 8 (0.8%) placebo-treated participants. The largest difference between groups was observed for subdural haematoma, observed in 5 donanemab-treated patients (0.5%) and in 2 (0.2%) participants in the placebo group. Intracerebral haemorrhage greater than 1cm, including haemorrhagic stroke and cerebral haemorrhage were observed in 3 (0.3%) donanemab-treated participants and 2 (0.2%) placebo-treated participants. Serious events of intracranial haemorrhage were reported in 9 (0.9%) participants in the donanemab group and 3 (0.3%) in the placebo group, and fatal outcomes were reported in 1 (0.1%) participant in the donanemab group and none in the placebo group. Additional details of intracranial haemorrhage from Dona-PC are presented in Table SVII.11 and Table SVII.12.

In AACI-PC, intracranial haemorrhage was observed in 11 (1.3%) donanemab-treated participants and 7 (0.8%) placebo-treated participants. The largest difference between groups was observed for subdural haematoma, observed in 4 (0.5%) donanemab-treated patients and in 2 (0.2%) participants in the placebo group. Intracerebral haemorrhage greater than 1cm, including haemorrhagic stroke and cerebral haemorrhage were observed in 3 (0.4%) donanemab-treated participants and 2 (0.2%) placebo-treated participants Serious events of intracranial haemorrhage were reported in 7 (0.8%) participants in the donanemab group and 3 (0.3%) in the placebo group, and fatal outcomes were reported in 1 (0.1%) participant in the donanemab group

and none in the placebo group. Additional details of intracranial haemorrhage from Study AACI-PC are presented in Table SVII.13 and Table SVII.14.

In All-Dona, intracranial haemorrhage was reported in 35 (1.3%) donanemab-treated participants, of which 9 patients (0.3%) reported intracerebral haemorrhage greater than 1 cm. Serious events of intracranial haemorrhage were reported in 18 (0.7%) patients treated with donanemab, of which 3 (0.1%) were intracerebral haemorrhage greater than 1 cm. The most frequently reported intracranial haemorrhage events during treatment with donanemab were:

- subdural haematoma (n=12; 0.4%)
- subarachnoid haemorrhage (n=7; 0.3%)
- cerebrovascular accident (n=7; 0.3%)
- cerebral haemorrhage (n=4; 0.1%)
- haemorrhagic stroke (n=3; 0.1%) and
- subdural haemorrhage (n=3; 0.1%).

Most of the subdural haematoma or subdural haemorrhage events were temporally associated with head trauma or falls. Among the 7 cerebrovascular accident events, 1 was later deemed to be ARIA-E and for the 6 remaining participants there was no evidence of the stroke being haemorrhagic.

In All-Dona, 3 (0.1%) fatal intracranial haemorrhages were reported in donanemab-treated participants:

- one participant (ApoE ε4 non-carrier) died due to subarachnoid haemorrhage, considered as likely trauma related following a fall with a possible contribution from the concomitant use of acetylsalicylic acid; this participant had no previous evidence of ARIA
- 1 participant (ApoE ε4 heterozygote) with history of hypertension, hyperlipidaemia, stroke, and no previous evidence of ARIA died due to thalamus haemorrhage, which the investigator assessed as possibly related to donanemab, and
- 1 participant (ApoE ε4 heterozygote) died following administration of thrombolytic medication for acute ischaemic stroke with subsequent development of intracranial haemorrhage (later also found to have ARIA-E on MRI). In the opinion of the investigator, the haemorrhage could have been caused by the treatment with tissue plasminogen activator and made worse by CAA and amyloid removal by study treatment.

Table SVII.11. Characterisation of Intracranial Haemorrhage Risk, Dona-PC

	Placebo (N = 999) n (%)	LY3002813 (N = 984) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with intracranial haemorrhage	7 (0.7)	13 (1.3)	1.9
Non-carrier (0 ApoE ε4 alleles)[a]	3 (0.3)	7 (0.7)	2.3
Carrier (≥1 ApoE ε4 alleles)[a]	4 (0.4)	6 (0.6)	1.5
Heterozygote (1 ApoE ε4 allele)	3 (0.3)	5 (0.5)	1.7
Homozygote (2 ApoE ε4 alleles)	1 (0.1)	1 (0.1)	1.0

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; CNS = central nervous system; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; MRI = magnetic resonance imaging; N = total number of subjects; n = number of subjects in the specified category; SMQ = Standardised MedDRA Queries.

[a] Subjects with missing ApoE ε4 carrier status were not included.

Note: Modification of Haemorrhage CNS Vascular Conditions SMQ (20000064), with terms including "microhaemorrhage" removed. Corresponding MRI events and macrohaemorrhage on MRI only are also counted.

Table SVII.12. Summary of Intracranial Haemorrhage by ApoE ε4 Status, Dona-PC

	Placebo			LY3002813		
	Number of Participants with Intracranial Haemorrhage	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with Intracranial Haemorrhage	Number of Participants with Intracranial Haemorrhage	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with Intracranial Haemorrhage
Non-carrier (0 ApoE ε4 alleles)	3	282	1.1%	7	291	2.4%
Carrier (≥1 ApoE ε4 alleles)	4	712	0.6%	6	690	0.9%
Heterozygote (1 ApoE ε4 allele)	3	538	0.6%	5	522	1.0%
Homozygote (2 ApoE ε4 alleles)	1	174	0.6%	1	168	0.6%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; CNS = central nervous system; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; N = total number of subjects; n = number of subjects in the specified category; SMQ = Standardised MedDRA Queries.

Note: Subjects with missing ApoE ε4 carrier status were not included.

Note: Modification of Haemorrhage CNS Vascular Conditions SMQ (20000064), with terms including "microhaemorrhage" removed. Corresponding MRI events and macrohaemorrhage on MRI only are also counted.

Table SVII.13. Characterisation of Intracranial Haemorrhage Risk, AACI-PC

	Placebo (N = 874) n (%)	LY3002813 (N = 853) n (%)	Relative Risk of LY3002813 vs Placebo
Patients with intracranial haemorrhage	6 (0.7)	11 (1.3)	1.9
Non-carrier (0 ApoE ε4 alleles)[a]	2 (0.2)	5 (0.6)	3.0
Carrier (≥1 ApoE ε4 alleles)[a]	4 (0.5)	6 (0.7)	1.4
Heterozygote (1 ApoE ε4 allele)	3 (0.3)	5 (0.6)	2.0
Homozygote (2 ApoE ε4 alleles)	1 (0.1)	1 (0.1)	1.0

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; CNS = central nervous system; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; N = total number of subjects; n = number of subjects in the specified category; SMQ = Standardised MedDRA Queries.

[a] Subjects with missing ApoE ε4 carrier status were not included.

Note: Modification of Haemorrhage CNS Vascular Conditions SMQ (20000064), with terms including "microhaemorrhage" removed. Corresponding MRI events and macrohaemorrhage on MRI only are also counted.

Table SVII.14. Summary of Intracranial Haemorrhage by ApoE ε4 Status, AACI-PC

	Placebo			LY3002813		
	Number of Participants with Intracranial Haemorrhage	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with Intracranial Haemorrhage	Number of Participants with Intracranial Haemorrhage	Number of Participants in ApoE ε4 Category	Percentage of Participants in ApoE ε4 Category with Intracranial Haemorrhage
Non-carrier (0 ApoE ε4 alleles)	2	250	0.8%	5	255	2.0%
Carrier (≥1 ApoE ε4 alleles)	4	620	0.6%	6	595	1.0%
Heterozygote (1 ApoE ε4 allele)	3	474	0.6%	5	452	1.1%
Homozygote (2 ApoE ε4 alleles)	1	146	0.7%	1	143	0.7%

Abbreviations: ApoE ε4 = apolipoprotein subtype E allele 4; CNS = central nervous system; Dona-PC = Placebo-Controlled Analysis Set; LY3002813 = donanemab; N = total number of subjects; n = number of subjects in the specified category; SMQ = Standardised MedDRA Queries.

Note: Subjects with missing ApoE ε4 carrier status were not included.

Note: Modification of Haemorrhage CNS Vascular Conditions SMQ (20000064), with terms including "microhaemorrhage" removed. Corresponding MRI events and macrohaemorrhage on MRI only are also counted.

Intracranial haemorrhage with antithrombotic use

Overall, intracranial haemorrhagic events in donanemab and placebo treated participants using antithrombotic medication was low (1 to 2%).

In Dona-PC, the frequency of intracranial haemorrhage was

- 1.9% in the donanemab group and 0.9% in the placebo group for those who used antithrombotic medications at any time
- 1.7% in the donanemab group and 0.9% in the placebo group for those who used antithrombotic medications within 30 days prior to the event, and
- 0.9 % in the donanemab group and 0.7% in the placebo group for those who did not use antithrombotic medications.

In Dona-PC, 6 SAEs of intracranial haemorrhage (1 fatal case with PT subarachnoid haemorrhage) were observed in the donanemab group, and 2 SAEs (no fatal case) were observed in placebo group, for participants who received at least 1 antithrombotic medication. Three SAEs (no fatal case) were observed in the donanemab group, and 1 SAE (no fatal case) was observed in placebo group, for participants who did not use antithrombotic medications.

In Study AACI-PC, the frequency of intracranial haemorrhage in donanemab-treated participants was

- 1.7% in the donanemab group and 0.8% in the placebo group for those who used antithrombotic medications at any time
- 1.4% in the donanemab group and 0.8% in the placebo group for those who used antithrombotic medications within 30 days prior to the event, and
- 1.0% in the donanemab group and 0.8% in the placebo group for those who did not use antithrombotic medications.

In AACI-PC, 4 SAEs of intracranial haemorrhage (1 fatal case with PT subarachnoid haemorrhage) were observed in the donanemab group, and 2 SAEs (no fatal case) were observed in placebo group, for participants who received at least 1 antithrombotic medication. Three SAEs (no fatal case) were observed in the donanemab group, and 1 SAE (no fatal case) was observed in placebo group, for participants who did not use antithrombotic medications.

In All-Dona, the frequency of intracranial haemorrhage in donanemab-treated participants was

- 1.7% for those who used antithrombotic medications at any time
- 1.6% for those who used antithrombotic medications within 30 days prior to the event, and
- 1.0% for those who did not use antithrombotic medications.

In All-Dona, 12 SAEs of intracranial haemorrhage (2 fatal cases with PTs subarachnoid haemorrhage and haemorrhage intracranial) were observed in participants who received at least 1 antithrombotic medication, and 6 SAEs (1 fatal case with PT thalamus haemorrhage) were observed in participants who did not use antithrombotic medications.

Post-marketing data:

As of 02 April 2025, 43 events of intracranial haemorrhage were reported in the post-marketing setting. This data was collected using a modified approach to the Haemorrhagic CNS Vascular Conditions Standardized Medical Queries (SMQ), excluding all terms related to microhaemorrhage. Of these 43 events, 8 events (19%) were received as serious reports. All these 8 events were reported serious due to hospitalisation; one was also reported as life-threatening, and another was reported as serious due to death.

These 43 events of intracranial haemorrhage included

- 24 events cerebral haemorrhage (56%)
- 13 events of cerebrovascular accident (30%)
- 4 events of subarachnoid haemorrhage (9%), and
- 2 events of subdural haematoma (5%).

Cerebral haemorrhage

The size of the cerebral haemorrhage was confirmed to be greater than 1 cm for one of the 24 events of cerebral haemorrhage, specifically reported as a 1.3 cm brain bleed. Another 2 events without confirmed size were reported as “two macrohaemorrhages” and “inoperable intracerebral haemorrhage”. This last event is described further in this section.

The majority (88%) of the cerebral haemorrhage events were received with a verbatim term of

- *brain bleeding*
- *small/minor/mild brain bleed*
- *spots of bleeding,* or
- *leakage from blood vessel.*

No information was provided about the size of the bleeding.

Cerebrovascular accident

Out of the 13 events of cerebrovascular accident, 2 (including one report of possible stroke) were concurrent with ARIA-H or both ARIA-E and ARIA-H. Additionally, there was 1 event of small stroke that was concurrent with a reported brain bleed. For the remaining 10 events, no evidence of the stroke being haemorrhagic was reported.

Subarachnoid haemorrhage

The 4 events subarachnoid haemorrhage were imaging findings, all concurrent with ARIA-H (in 1 case) or both ARIA-E and ARIA-H (in 3 cases).

Subdural haematoma

The 2 events of subdural haematoma lacked details to determine whether the events were traumatic or atraumatic in origin.

The frequency of intracranial haemorrhagic events in patients treated with donanemab while on antithrombotic medication was low. Only one patient (2%) was receiving a concomitant

antiplatelet medication (aspirin), and another patient (2%) reported concomitant use of anticoagulant (apixaban). However, the health care professional who reported this case could not confirm whether the anticoagulant was still being used at the time of the event. Additionally, there were no reports of intracranial haemorrhage in patients who had received a thrombolytic.

Among the 7 patients with known ApoE ε4 genotype, intracranial haemorrhage occurred in 29% (2 patients) who were noncarriers, 29% (2 patients) heterozygotes, and 43% (3 patients) homozygotes.

There have been 2 deaths reported in patients who had experienced cerebral haemorrhage events. The first death was associated with a fatal intracerebral haemorrhage in a patient who was a heterozygote for ApoE ε4 gene. This patient was found unconscious and hospitalised due to inoperable intracerebral haemorrhage and died 5 days later. The second death due to unknown cause occurred in a patient whose ApoE ε4 status was unknown. This patient experienced concurrent serious events of brain oedema and cerebral haemorrhage (reported as small brain bleed). Both events were reported as recovering at the time of death.

Reversibility:

Depending on the seriousness of the intracranial haemorrhage, reversibility may be limited. Donanemab treatment should be permanently discontinued if intracerebral haemorrhage greater than 1 cm occurs.

Impact on quality of life:

Given the low frequency of serious outcomes of intracranial haemorrhage related events, it may have significant impact on the quality of life for only a small subset of patients.

Risk factors and risk groups:

Overall, concomitant antithrombotic use did not impact the frequency, severity, or seriousness of intracranial haemorrhagic events. More than 40% of participants in both treatment groups used concomitant antithrombotics. Among those receiving any antithrombotic medication, the most frequently used was aspirin (approximately 80%), followed by anticoagulants (greater than 20%). Analysis of antithrombotic medication type (aspirin, non-aspirin antiplatelets, and anticoagulants) did not reveal any patterns different than that observed for antithrombotics overall. Given the limited number of exposures to thrombolytics, no conclusions can be made regarding the risk of intracranial haemorrhage with concomitant thrombolytic use.

Risk factors specifically associated with intracerebral haemorrhage in patients with AD include ApoE ε4 alleles, pre-existing cerebral microhaemorrhages, and CAA (Arrighi et al. 2016; Cummings et al. 2023). Given the small number of haemorrhagic events in the donanemab placebo-controlled studies, an association of intracranial haemorrhagic events with ApoE ε4 carrier state could not be established (Table SVII.13 and Table SVII.14). All the above-mentioned risk factors might further increase the risk for haemorrhagic complications during thrombolytic or antithrombotic therapies (Reisz et al. 2022; Cummings et al. 2023).

Preventability:

Measures for early diagnosis and prevention of progression of intracerebral haemorrhage include an MRI at baseline, prior to the second dose, prior to the third dose, prior to the fourth dose, prior to the seventh dose, and if symptoms of intracerebral haemorrhage occur. An additional MRI prior to the 12th dose should be performed in patients with ARIA risk factors, such as ApoE ε4 heterozygotes.

MRI or identification of vascular occlusion can help identify that ischaemic stroke rather than ARIA is the aetiology and inform use of thrombolytics or thrombectomy when appropriate.

Donanemab treatment is indicated in ApoE ε4 heterozygotes or non-carriers, and the treatment is contraindicated in patients with

- baseline MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), or other findings, which are suggestive of CAA
- bleeding disorders that are not under adequate control
- an ongoing anticoagulant therapy
- severe white matter disease
- poorly controlled hypertension, and
- conditions that do not allow MRI assessment, including claustrophobia or the presence of metal (ferromagnetic) implants/cardiac pacemaker.

Sections 4.2 and 4.4 of the SmPC provide guidance on discontinuing treatment permanently, should intracerebral haemorrhage greater than 1 cm occurs. In addition, a cautionary statement in Sections 4.4 and 4.5 is provided for prescribers emphasising the risk of intracerebral haemorrhage when using antithrombotic medication or thrombolytic agents in patients treated with donanemab.

Impact on the risk-benefit balance of the product:

At this time, cumulative data suggest that the risk-benefit impact is low given the low frequency of intracranial haemorrhage events in patients treated with donanemab.

Reported events of intracranial haemorrhage will be monitored through routine pharmacovigilance activities. Additional pharmacovigilance activities are proposed to further characterise this potential risk.

Public health impact:

Given the low frequency of serious cases of intracranial haemorrhage events, the public health impact of this potential risk is expected to be low in the context of the overall serious progressive nature of AD and its public health burden for society.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Module SVIII – Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracranial haemorrhage[a]
Missing information	None

Abbreviations: ARIA-E (cerebral oedema/effusion) = amyloid-related imaging abnormality–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; IRR = infusion-related reaction.

[a] Intracranial haemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macro-haemorrhage, and cerebrovascular accident.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

As part of routine pharmacovigilance activities, specific follow-up forms are used to collect additional scientific and medical data to facilitate evaluation of cases. The follow-up forms listed here only relate to the currently listed safety concerns: ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage.

Follow-up forms are as follows:

- To further characterise ARIA-E (cerebral oedema/effusion):
  - ARIA and intracranial haemorrhage follow-up form
- To further characterise ARIA-H (cerebral microhaemorrhage and superficial siderosis):
  - ARIA and intracranial haemorrhage follow-up form
- Intracranial haemorrhage:
  - ARIA and intracranial haemorrhage follow-up form

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Study short name and title: Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU.

Rationale and study objectives: This study includes 3 categories of objectives:

- Objective 1: safety events
- Objective 2: drug utilisation, and
- Objective 3: effectiveness of additional risk minimisation activities.

Serious hypersensitivity and intracranial haemorrhage events have been observed in the donanemab clinical development programme. This large secondary database study will provide the opportunity to describe the incidence of these infrequent events in patients in the EU treated with donanemab as part of real-world practice, including in real-world subgroups that may have been underrepresented or excluded from the clinical development programme. Understanding donanemab drug utilisation in the real-world patient populations in the EU, results in the following:

1. Accumulation of information regarding use of donanemab in populations not studied in clinical trials (for example, patients with Down syndrome), use of donanemab by patients with risk factors for safety outcomes and whether use is consistent with the donanemab label.

2. Insight into effectiveness of additional risk minimisation activities: the HCP educational materials.

The objectives of this study are as follows:

- Objective 1 (safety events): To describe the incidence of serious hypersensitivity events (as defined by hospitalisation, for example, due to anaphylaxis) and intracranial haemorrhage in patients with AD treated with donanemab. The incidence of intracranial haemorrhage will additionally be described within the subgroup of patients using concomitant antithrombotic or thrombolytic medications.
- Objective 2 (drug utilisation): To describe donanemab drug utilisation in terms of dose, length of treatment, and user demographics/characteristics overall and within the following subgroups: Patients with Down syndrome, and patients using concomitant antithrombotic or thrombolytic medications.
- Objective 3 (effectiveness of additional risk minimisation activities): To monitor the compliance to recommendations before donanemab treatment initiation and during donanemab treatment.

Study design: This observational cohort study will be conducted using secondary databases in EU cohorts of donanemab users. Selection of databases will be based on a feasibility assessment, which will include data quality and capability of the selected data sources. This study will target to include at least 3 countries within the EU.

Study population: All patients in the database(s) who initiate treatment with donanemab and have at least 12 months of baseline data prior to initiation of donanemab will be eligible for the cohort for all study objectives.

Milestones:

A study synopsis is included in Annex 3, Part C; the proposed milestones are as follows:

Milestone	Anticipated Due Date
Protocol submission	Within 6 months of EU regulatory approval
Start of data collection	Within 2 years of EU regulatory approval[a]
Study progress reports	To be provided with the PSUR/PBRER
End of data collection	31 December 2029
Final study report submission	31 December 2030

Abbreviations: EU = European Union; PBRER = periodic risk-benefit evaluation report; PSUR = periodic safety update report.

[a] Dependent on date of donanemab availability within EU countries.

Study short name and title: Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.

Rationale and study objectives: ARIA-E and ARIA-H were observed in clinical trials and are important identified risks for donanemab in the EU RMP.

The primary objective of this study is to describe the incidence and severity of symptomatic ARIA (ARIA-E and ARIA-H) within a cohort of donanemab-treated patients in real-world clinical practice in the EU. Symptomatic ARIA will be assessed in patients that receive donanemab based on MRI scans performed as part of routine care and the presence of ARIA-related symptoms. An additional primary objective is to characterise long-term cognitive outcomes and disease progression of patients with ARIA to assess whether these events are associated with accelerated cognitive decline or changes in the rate of disease progression. Secondary outcomes will include asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage. Intracranial haemorrhage will be described within the subgroup of patients receiving concomitant antithrombotic or thrombolytic medications. Patients with ARIA (symptomatic or asymptomatic) will be followed to document real-world interventions and radiographic resolution or stabilisation over time. All ARIA events will be described within the overall study population and within subgroups of ApoE ε4 genotype (heterozygote or non-carrier). Additional patient characterisation will include description of baseline demographics, comorbidities, and comedications (including the use of antithrombotic and thrombolytic medications).

Study design: This registry-based observational study will be conducted within EU cohorts of donanemab users enrolled within the international CorEvitas ALZ-710 Registry. The primary objective is to assess the incidence of symptomatic ARIA (ARIA-E and ARIA-H). The initial sample size estimate of 400 participants was based on the incidence of this outcome in the ApoE ε4 non-carrier population. Since symptomatic ARIA is more frequent in the larger target population that includes heterozygotes, the necessary sample size to achieve similar precision is smaller. However, the proposed registry sample size remains at 400 participants to account for potential limited real-world use in the heterozygote population. Sample size and countries included are subject to feasibility based on donanemab uptake in the EU. Patients will be followed post first donanemab administration using an as-treated design to the earliest of donanemab discontinuation or 12 months. Patients with an ARIA event during this follow-up period will be additionally followed for 6 months post-ARIA event to monitor for resolution (ARIA-E) or stabilisation (ARIA-H) of the event. This additional 6-month time period can extend beyond the initial follow-up period.

Study population: Patients who initiate treatment with donanemab at a study site as part of routine clinical practice and consent to involvement in the study will be included. In addition, the data in InRAD (The International practice-based Registry for Alzheimer's Disease and other dementias) will be utilised to supplement this study, as available, based on registry launch, data capture and completeness, and adoption by the community.

Milestones:

A study synopsis is included in Annex 3, Part C; the proposed milestones are as follows:

Milestone	Anticipated Due Date
Protocol submission	Within 6 months of EU regulatory approval
Start of data collection	Within 2 years of EU regulatory approval[a]
Study progress reports	To be provided with the PSUR/PBRER
End of data collection	31 December 2030
Final study report submission	31 December 2031

Abbreviations: EU = European Union; PBRER = periodic risk-benefit evaluation report; PSUR = periodic safety update report.

[a] Dependent on date of donanemab availability within EU countries.

Study short name and title: Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Rationale and study objectives: Additional risk minimisation activities will be implemented for donanemab. These activities include the following:

- To promote the safe and effective use of donanemab, initiation of treatment in all patients should be captured in the "EU CAP Registration System" implemented as part of the CAP. Use of donanemab treatment under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion-related reactions to ensure adequate management of patients treated with donanemab.
- Educational material for prescribers and radiologists on important safety risks related to the use of donanemab that is ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage. It will also inform HCPs about the indicated patient population, contraindications, information about the donanemab CAP, and the importance of the patient card, including carrying it at all times and to provide to HCPs in emergency situations. In addition, a prescriber checklist that includes guidance on initial and subsequent treatment, and recommendations for assessments before and during treatment with donanemab.
- A patient card designed to enhance the awareness and knowledge of patients and caregivers about the safety concerns with donanemab as well as inform physicians of ARIA differential diagnosis in an emergency setting.

The objectives of the survey are to assess the following:

1. Prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to: ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage.
2. Prescriber and radiologist self-reported adherence to the risk minimisation practices.

3. Prescriber knowledge of the prescriber checklist including guidance on initial and subsequent treatment and recommendation for assessments before and during treatment with donanemab.
4. Prescriber distribution of the patient card to patients prescribed donanemab for the first time.
5. Prescriber awareness and use of the CAP.

Study design: Observational, cross-sectional survey of prescribers of donanemab and radiologists in the EU. This study will aim to include 200 prescribers and 50 radiologists across at least 3 EU countries. The maximum contribution of completed surveys from any individual country will be set to 40% of total prescriber surveys and 40% of total radiologist's surveys. Sample size and countries included are subject to feasibility based on donanemab availability in the EU.

Study population: The survey will be administered to prescribers and radiologists in at least 3 EU countries, who have previously agreed to be contacted for such studies. The EU countries included will be based on product launch and anticipated market uptake.

Milestones:

A study synopsis is included in Annex 3, Part C; the proposed milestones are as follows:

Milestone	Planned Dates*
Protocol Submission	Within 6 months of EU regulatory approval
Start of data collection	Within 2 years of EU regulatory approval
End of data collection	When at least 250 surveys have been completed: anticipated 30 June 2030
Final study report submission	Anticipated 31 December 2030

Abbreviations: EU = European Union; PRAC = pharmacovigilance risk assessment committee.

*The planned timeline is contingent upon approval of the educational materials and the patient card by the National Competent Authority, protocol review and approval by the PRAC, and in addition, contingent on launch timing and market uptake.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

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				
Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. Planned	The objectives of this observational study, which will be conducted in donanemab-treated patients in routine clinical practice in the EU, are to describe • the incidence of serious hypersensitivity reactions and intracranial haemorrhage[a] • drug utilisation (including, use by patients with Down syndrome and users of antithrombotic or thrombolytic medications), and • the effectiveness of additional risk minimisation activities.	• Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports Final study report submission	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER 31 December 2030
Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU Planned	The objectives of this study are to describe • the incidence of symptomatic ARIA (ARIA-E and ARIA-H), asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage[a] within a cohort of donanemab-treated patients in routine clinical practice in the EU • long-term cognitive outcomes and disease progression of patients with ARIA to assess whether these events are associated with accelerated cognitive decline or changes in the	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports Final study report submission	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER 31 December 2031

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	rate of disease progression, and • intracranial haemorrhage within the subgroup of patients receiving concomitant anti-thrombotic or thrombolytic medications.			
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				
Category 3 – Required additional pharmacovigilance activities				
Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU Planned	The objectives of the survey are to assess • prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage, • prescriber and radiologist self-reported adherence to the risk minimisation practices. • prescriber knowledge of the prescriber checklist, including guidance on initial and subsequent treatment and recommendation for assessments before and during treatment with donanemab, • prescriber distribution of the patient card to patients prescribed donanemab for the first time, and	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Intracranial haemorrhage	Protocol Submission Final study report submission	Within 6 months of EU regulatory approval Anticipated 31 December 2030

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• prescriber awareness and use of the CAP.			

Abbreviations: AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusion) = ARIA– oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; CAP = controlled access programme; EU = European Union; IRRs = infusion-related reactions; PBRER = periodic risk-benefit evaluation report; PSUR = periodic safety update report.

[a] Intracranial haemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macrohaemorrhage, and cerebrovascular accident.

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
ARIA-E (cerebral oedema/effusion)	Routine risk communication: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8, and Section 2 and 4 of the PIL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-E, including symptomatic cases, are included in SmPC Sections 4.2 and 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-E, recurrent symptomatic or radiographically moderate, or severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. Other routine risk minimisation measures beyond the Product Information: • Legal Status: Restricted medical prescription
ARIA-H (cerebral microhaemorrhage and superficial siderosis)	Routine risk communication: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 and 4 of the PIL. Routine risk minimisation activities recommending specific clinical measures/monitoring to address the risk: • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-H, including symptomatic cases, are included in SmPC Sections 4.2 and 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-H, recurrent symptomatic or radiographically moderate or severe ARIA events is included in SmPC Sections 4.2 and 4.4.

	• Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, is included in SmPC Sections 4.4 and 4.5 and, Section 2 of the PIL. Other routine risk minimisation measures beyond the Product Information: • Legal Status: Restricted medical prescription
Hypersensitivity events (including IRR)	Routine risk communication: SmPC Sections 4.3, 4.4, 4.8, and Sections 2 and 4 of the PIL Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication for use in patients with prior history of hypersensitivity to donanemab is included in SmPC Section 4.3, and Section 2 of the PIL. • Recommendations for management of serious infusion-related reactions are included in SmPC Section 4.4, and Sections 2 and 4 of the PIL. Other routine risk minimisation measures beyond the Product Information: • Legal Status: Restricted medical prescription
Intracranial haemorrhage	Routine risk communication: SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8, and Section 2 of the PIL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Permanent discontinuation of donanemab on identification of intracerebral haemorrhage greater than 1 cm is included in SmPC Sections 4.2 and 4.4. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, is included in SmPC Section 4.4, 4.5, and Section 2 of the PIL. Other routine risk minimisation measures beyond the Product Information: • Legal Status: Restricted medical prescription

Abbreviations: AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormalities; ARIA-E (cerebral oedema/effusions) = amyloid-related imaging abnormalities–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = amyloid-related imaging abnormalities–microhaemorrhage/hemosiderin deposition; IRR = infusion-related reactions; PIL = patient information leaflet; SmPC = summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Activities:

1. **Controlled Access Programme (CAP)**

Objectives:

The objective of the donanemab CAP is to promote safe and effective use of donanemab. Initiation of treatment in all patients should be through the EU CAP Registration System implemented as part of the CAP.

The CAP will consist of locally run programmes within EU member states. The primary objective is to promote the safe and effective use of donanemab by confirming the correct selection of patients based on relevant indication or diagnosis, the genetic profile, and available MRI. HCPs from donanemab administration centres should register all patients in the CAP registration system prior to the initiation of donanemab. Registration will capture anonymised patient demographic and clinical characteristics such as patient age, gender, baseline MRI status, ApoE ε4 genotype status, and concomitant medication. The data collection elements will be customised to the requirements for each member state and a full list will be documented in a CAP protocol. HCPs will be instructed to report adverse events per local laws and procedures.

Donanemab treatment should be administered under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion-related reactions to ensure adequate management of patients treated with donanemab.

Donanemab administration centres should have the following characteristics:

- a multidisciplinary team able to assess eligibility for donanemab
- access to a validated method to assess brain amyloid pathology
- access to ApoE ε4 tests
- access to IV infusions
- access to MRI in a scheduled and non-scheduled way to monitor for ARIA, and
- access to educational materials.

Rationale for the additional risk minimisation activity:

- To promote the safe and effective use of donanemab by confirming the correct selection of patients based on relevant indication or diagnosis, the genetic profile, and available MRI. In addition, it will ensure that the donanemab treatment is administered in centres where a multidisciplinary team has access to educational materials, and which has all the capabilities for identification of eligible patients and safety management.

2. HCP Educational Material

Objectives:

The objective of the HCP educational material which includes a prescriber checklist is to provide an adequate tool designed to enhance awareness and knowledge of prescribers and radiologists about the safety concerns and ensure the optimal use of donanemab.

The HCP educational material will inform prescribers and radiologists about the risks of ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage. It will also inform HCPs about the indicated patient population, contraindications, information about the donanemab CAP, and the importance of the patient card, including carrying it at all times and to provide to HCPs in emergency situations. A prescriber checklist will include guidance on initial and subsequent treatment, and recommendations for assessments before and during treatment with donanemab.

Rationale for the additional risk minimisation activity:

- Additional awareness and knowledge of prescribers and radiologists about donanemab risks, patient population indicated and contraindications will help with patient eligibility as well as with management and mitigation of the risks.

Target audience and planned distribution path:

- Prior to launch and after the launch of donanemab in each member state, the HCP educational material will be provided to prescribers and radiologists in each member state as agreed upon with the National Competent Authority.

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

- Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU.
- Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

3. Patient Card

Objectives:

The objective of the patient card is to provide an appropriate tool designed to enhance the awareness and knowledge of patients/caregivers about the safety concerns with donanemab as well as inform physicians of ARIA differential diagnosis in an emergency setting.

The patient card will inform patients/caregivers on the signs and symptoms of ARIA-E and ARIA-H, recommendation when to contact their HCP, information for HCPs involved in the patient's care and alert emergency care physicians of a possible differential diagnosis of ARIA when presented with stroke-like symptoms.

Rationale for the additional risk minimisation activity:

- Awareness and knowledge for patients/caregivers as well as emergency care physicians pertaining to the risks associated with donanemab will help to mitigate/manage the risks.

Target audience and distribution path:

- The target audience is patients/caregivers via the prescribing physician. The patient card will be provided to prescribers in each member state as agreed upon with the National Competent Authority.

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

- Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
ARIA-E (cerebral oedema/effusion)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8, and Section 2 and 4 of the PIL. • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-E, including symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-E, recurrent symptomatic or radiographically moderate or severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3 and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	
ARIA-H (cerebral microhaemorrhage and superficial siderosis)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 and 4 of the PIL • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-H, including symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-H, recurrent symptomatic or radiographically moderate or severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	is included in SmPC sections 4.4 and 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	
Hypersensitivity events (including IRR)	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, 4.8 and, Sections 2 and 4 of the PIL • Contraindication for use in patients with prior history of hypersensitivity to donanemab is included in SmPC Section 4.3, and Section 2 of the PIL. • Recommendations for management of serious infusion-related reactions are included in SmPC Sections 4.3, 4.4, 4.8, and Sections 2 and 4 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • Controlled access programme	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.
Intracranial haemorrhage	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Permanent discontinuation of donanemab on identification of intracerebral haemorrhage greater than 1 cm is included in SmPC Sections 4.2 and 4.4. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, included in SmPC Sections 4.4, 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist. • Patient card • Controlled access programme	• Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusions) =ARIA–oedema/effusions; ARIA- H (cerebral microhaemorrhage and superficial siderosis) = ARIA–microhaemorrhage/hemosiderin deposition; EU = European Union; PIL = patient information leaflet; SmPC = summary of product characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Kisunla (Donanemab)

This is a summary of the risk management plan (RMP) for Kisunla. The RMP details important risks of Kisunla, how these risks can be minimised, and how more information will be obtained about Kisunla's risks and uncertainties (missing information).

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

This summary of the RMP for Kisunla should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Kisunla's RMP.

I – The Medicine and What It is Used for

Kisunla is authorised for the treatment of adults with early symptomatic AD who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers (see SmPC for the full indication). It contains donanemab as the active substance and it is given by IV infusion.

Further information about the evaluation of Kisunla's benefits can be found in Kisunla's EPAR, including in its plain-language summary, available on the 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 Kisunla, together with measures to minimise such risks and the proposed studies for learning more about Kisunla's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- 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 Kisunla, 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 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 Kisunla is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Kisunla are risks that need 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 proof of a link with the use of Kisunla. 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 needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracranial haemorrhage
Missing information	None

Abbreviations**:** ARIA-E (cerebral oedema/effusions) = amyloid-related imaging abnormalities–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = amyloid-related imaging abnormalities–haemorrhage/hemosiderin deposition; IRR = infusion-related reaction.

II.B Summary of Important Risks

Important Identified Risk: ARIA-E (cerebral oedema/effusion)	
Evidence for linking the risk to the medicine	ARIA-E is a known class effect of amyloid-targeting therapies. Patients with ARIA-E are usually asymptomatic. If symptoms occur, these may include, but are not limited to, headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021). Intervention beyond withholding treatment may be required to address concomitant symptoms (e.g., corticosteroids). Events of ARIA-E were observed across the donanemab clinical development programme.
Risk factors and risk groups	In the donanemab clinical development programme, a higher frequency of ARIA-E was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis.

	In the Dona-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.7%, heterozygote 24.1%) compared to non-carriers (14.8%). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 7.7%, heterozygote 6.1%) was increased compared to non-carriers (4.1%). In the Study AACI-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.3%, heterozygote 23.2%) compared to non-carriers (15.7%). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 8.4%, heterozygote 6.6%) was increased compared to non-carriers (3.9%). In the All-Dona, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 33.9%, heterozygote 20.2%) compared with non-carriers (11.6%). A higher frequency of symptomatic ARIA-E was also noted for donanemab-treated patients ApoE ε4 carriers (homozygote 6.6%, heterozygote 4.3%) compared with non-carriers (3.2%).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • HCP educational material, including prescriber checklist • Patient card • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: ARIA-H (cerebral microhaemorrhage and superficial siderosis)	
Evidence for linking the risk to the medicine	ARIA-H is a known class effect of amyloid-targeting therapies (Arrighi et al. 2016). Patients with ARIA-H are usually asymptomatic. ARIA-H may be related to vascular amyloid clearance with weakening and rupture of small blood vessels (Withington 2022). Whereas ARIA-E is usually radiographically visible over the course of weeks or months, ARIA-H can remain permanently visible on subsequent imaging (Salloway 2022). If symptoms occur, they may include headache, worsening confusion, dizziness, visual disturbances, nausea, and seizures (Withington 2022). Cases of ARIA-H were observed across the donanemab clinical development programme.
Risk factors and risk groups	In the clinical development programme of donanemab, a higher frequency of ARIA-H was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis. In addition, risk factors

	that have been associated with ARIA-H also include the use of antithrombotic medication (Arrighi et al. 2016). In the Dona-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 53.6%, heterozygote 31.0%) compared with non-carriers (18.9%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.2%, heterozygote 1.3%) was increased compared with non-carriers (0.3%). In the AACI-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 50.3%, heterozygote 32.5%) compared with non-carriers (18.8%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.4%, heterozygote 1.5%) was increased compared with non-carriers (0.4%). In All-Dona, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 43.2%, heterozygote 26.2%) compared to non-carriers (16.6%). The frequency of symptomatic ARIA-E was slightly higher in donanemab-treated participants ApoE ε4 carriers (homozygote 0.7%, heterozygote 0.6%) compared with non-carriers (0.3%).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • HCP educational material including prescriber checklist • Patient card • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Hypersensitivity events (including IRR)	
Evidence for linking the risk to the medicine	Biological drugs represent foreign protein and thereby can elicit immediate and non-immediate hypersensitivity events, including IRRs and anaphylaxis (Maggi et al. 2011). Immediate hypersensitivity reactions, including IRRs are associated with donanemab treatment and have been observed across the donanemab clinical development programme.
Risk factors and risk groups	No specific risk factors have been identified for hypersensitivity reactions. In clinical studies, 88.1% of donanemab-treated patients developed ADAs and all of the patients with ADA had neutralising antibodies. All patients reporting IRRs had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Intracranial haemorrhage	
Evidence for linking the risk to the medicine	Serious (including fatal) cases of intracranial haemorrhage have been observed with amyloid-targeting therapies including donanemab. In the donanemab clinical development programme, intracranial haemorrhage was observed at a higher frequency in donanemab-treated patients (1.3% in both Dona-PC and AACI-PC) than placebo (0.8% in both Dona-PC and AACI-PC). The largest difference between groups was observed for events of subdural haematoma, which were higher in the donanemab group (0.5% in both Dona-PC and AACI-PC) than placebo (0.2% in both Dona-PC and AACI-PC). Most of the subdural haematoma or subdural haemorrhage events were temporally associated with head trauma or fall. Events of intracerebral haemorrhage greater than 1cm (also referred to as macro-haemorrhage) including haemorrhagic stroke and cerebral haemorrhage were observed at a similar frequency in participants treated with either donanemab (0.3% in Dona-PC and 0.4% in AACI-PC) or placebo (0.2% in both Dona-PC and AACI-PC). In All Dona, intracranial haemorrhage was observed in 1.3% of the participants, driven by subdural haematoma (0.4%) and subarachnoid haemorrhage (0.3%). Cerebral haemorrhage (0.1%) and haemorrhagic stroke (0.1%) were less frequent. In All-Dona, 3 fatal intracranial haemorrhages were reported in donanemab-treated participants. These 3 participants with fatal outcomes were at increased risk of intracranial haemorrhage due to history of hypertension, stroke, thrombolytic use, or the event being temporally associated with head trauma or fall. To date, there has been no clear evidence of an increased risk of intracranial haemorrhage in patients exposed to donanemab during clinical development. Therefore, intracranial haemorrhage is considered an important potential risk for donanemab and will be further characterised in ongoing clinical trials and planned post-marketing observational studies.
Risk factors and risk groups	Overall, concomitant antithrombotic use did not impact the frequency, severity or seriousness of intracranial haemorrhagic events. The most frequently used antithrombotic was aspirin (approximately 80%), followed

	by anticoagulants (greater than 20%). Analysis of antithrombotic medication type, (aspirin, non-aspirin antiplatelets, and anticoagulants) did not reveal any patterns different than that observed for antithrombotics overall. Given the limited number of exposures to thrombolytics, no conclusions can be made regarding the risk of intracranial haemorrhage with concomitant thrombolytic use. Risk factors specifically associated with intracerebral haemorrhage in patients with AD include ApoE ε4 alleles, pre-existing cerebral microhaemorrhages, and CAA (Arrighi et al. 2016; Cummings et al. 2023). Given the small number of haemorrhagic events in the donanemab placebo-controlled studies, an association of intracranial haemorrhagic events with ApoE ε4 carrier state could not be established. All the above-mentioned risk factors might further increase the risk for haemorrhagic complications during thrombolytic or antithrombotic therapies (Reisz et al. 2022; Cummings et al. 2023).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8; legal status and Section 2 of the PIL **Additional risk minimisation measures:** • HCP education material, including prescriber checklist • Patient Card • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: ADA = antidrug antibody; AD = Alzheimer's disease; ApoE ε4 = apolipoprotein subtype E allele 4; ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusions) = ARIA–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; CAA = cerebral amyloid angiopathy; EU = European Union; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PIL = patient information leaflet; SmPC = summary of product characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

Following studies are a condition of the marketing authorisation or specific obligation of Kisunla.

Study short name and title: Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU.

Rationale and study objectives: This study includes 3 categories of objectives:

- Objective 1: Safety events
- Objective 2: Drug utilisation
- Objective 3: Effectiveness of additional risk minimisation activities

Serious hypersensitivity and intracranial haemorrhage events have been observed in the donanemab clinical development programme. This large secondary database study will provide the opportunity to describe the incidence of these infrequent events in EU patients treated with donanemab as part of real-world practice, including real-world subgroups that may have been underrepresented or excluded from the clinical development programme. Understanding donanemab drug utilisation in the real-world EU patient populations results in the following:

1. Accumulation of information regarding the use of donanemab in populations not studied in clinical trials (for example, patients with Down syndrome), use of donanemab by patients with risk factors for safety outcomes and whether the use is consistent with the donanemab label.
2. Insight into effectiveness of additional risk minimisation activities: the HCP educational materials.

The objectives of this study are as follows:

- Objective 1 (safety events): To describe the incidence of serious hypersensitivity events (as defined by hospitalisation, for example, due to anaphylaxis) and intracranial haemorrhage in patients with AD treated with donanemab. The incidence of intracranial haemorrhage will additionally be described within the subgroup of patients using concomitant antithrombotic or thrombolytic medications.
- Objective 2 (drug utilisation): To describe donanemab drug utilisation in terms of dose, length of treatment, and user demographics/characteristics overall and within the following subgroups: Patients with Down syndrome, and patients using concomitant antithrombotic or thrombolytic medications.
- Objective 3 (effectiveness of additional risk minimisation activities): To monitor the compliance to recommendations before donanemab treatment initiation and during donanemab treatment.

Study short name and title: Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.

Rationale and study objectives: ARIA-E and ARIA-H were observed in clinical trials and are important identified risks for donanemab in the EU RMP.

The primary objective of this study is to describe the incidence and severity of symptomatic ARIA (ARIA-E and ARIA-H) within a cohort of donanemab-treated patients in real-world clinical practice in the EU. Symptomatic ARIA will be assessed in patients that receive donanemab based on MRI scans performed as part of routine care and the presence of ARIA-related symptoms. An additional primary objective is to characterise long-term cognitive outcomes and disease progression of patients with ARIA to assess whether these events are

associated with accelerated cognitive decline or changes in the rate of disease progression. Secondary outcomes will include asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage. Intracranial haemorrhage will be described within the subgroup of patients receiving concomitant antithrombotic or thrombolytic medications. Patients with ARIA (symptomatic or asymptomatic) will be followed to document real-world interventions and radiographic resolution or stabilisation over time. All ARIA events will be described within the overall study population and within subgroups of ApoE ε4 genotype (heterozygote or non-carrier). Additional patient characterisation will include description of baseline demographics, comorbidities, and co-medications (including the use of antithrombotic and thrombolytic medications).

II.C.2 Other Studies in Post-authorisation Development Plan

Study short name and title: Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Rationale and study objectives: Additional risk minimisation activities will be implemented for donanemab. These activities include the following:

- To promote the safe and effective use of donanemab, initiation of treatment in all patients should be captured in the "EU CAP Registration System" implemented as part of the CAP. Use of donanemab treatment under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion-related reactions to ensure adequate management of patients treated with donanemab.
- Educational material for prescribers and radiologists on important safety risks related to the use of donanemab that is ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage. It will also inform HCPs about the indicated patient population, contraindications, information about the donanemab CAP, and the importance of the patient card, including carrying it at all times and to provide to HCPs in emergency situations. In addition, a prescriber checklist that includes guidance on initial and subsequent treatment, and recommendations for assessments before and during treatment with donanemab.
- A patient card designed to enhance the awareness and knowledge of patients and caregivers about the safety concerns with donanemab as well as inform physicians of ARIA differential diagnosis in an emergency setting.

The objectives of the survey are to assess the following:

1. Prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage.
2. Prescriber and radiologist self-reported adherence to the risk minimisation practices.

3. Prescriber knowledge of the prescriber checklist, including guidance on initial and subsequent treatment and recommendation for assessments, before and during treatment with donanemab.
4. Prescriber distribution of the patient card to patients prescribed donanemab for the first time.
5. Prescriber awareness and use of the CAP.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
ARIA and intracranial haemorrhage follow-up form	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Intracranial haemorrhage

Abbreviations: ARIA = amyloid-related imaging abnormalities; ARIA-E (cerebral oedema/effusions) = ARIA–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition.

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Reporter's profession: Patient's Birth Date or Age:

Patient's Name or Initials:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication (Complete the disease stage below):

Alzheimer's disease stage:

☐ Preclinical ☐ Mild cognitive impairment ☐ Mild dementia ☐ Moderate dementia ☐ Severe dementia

Dose:	Frequency:	Formulation:
Start Date:	Dose when event occurred:	Route:
Drug D/C? ☐ No ☐ Yes	Date D/C:	If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes	Date Restarted: Dose when restarted:	If Restarted, did the event occur? ☐ No ☐ Yes

List dates of all administered doses for Reported Drug:

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide the results or a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report

Lilly

Eli Lilly and Company - Global Patient Safety **Case Number:**

Possible Relatedness
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown
Please provide brief explanation:

ARIA[a] and intracranial hemorrhage

ARIA and intracranial hemorrhage greater than 1cm definitions:

- Amyloid-related imaging abnormality-edema/sulcal effusion (ARIA-E), also known as vasogenic edema. ARIA-E is thought to represent edema in the gray and white matter (due to increased permeability of brain capillary endothelial cells to serum proteins), or effusion or extravasated fluid in the sulcal space. Other concepts that could represent ARIA-E include brain edema and vasogenic cerebral edema.
- Amyloid-related imaging abnormality-haemorrhage/hemosiderin deposition (ARIA-H). ARIA-H is also known as
  - cerebral microhaemorrhage, which is a cerebral haemorrhage that measures less than or equal to 10 mm in diameter. Other concepts that could represent cerebral microhaemorrhage include brain stem microhaemorrhage, cerebellar microhaemorrhage, cerebral microhaemorrhage.
  - superficial siderosis, which are deposits of iron in tissue in the form of hemosiderin and are felt to represent residua of a small leakage of blood from a vessel into the subpial layers of the brain. Other concepts that could represent superficial siderosis include superficial siderosis of central nervous system and cerebral haemosiderin deposition.
- Intracranial hemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, cerebrovascular accident haemorrhagic, intraventricular haemorrhage.

[a]Sperling RA, Jack CR Jr, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367-385

ARIA-E MRI Classification Criteria[b]			
ARIA-E extent	**ARIA-E focality**	**3-point scale**	**5-point scale**
No ARIA-E	NA	0	0
<5cm	Monofocal	Mild (1)	Mild (1)
	Multifocal	Moderate (2)	Mild + (2)
5 – 10 cm	Monofocal		Moderate (3)
	Multifocal		Moderate + (4)
>10 cm	Monofocal	Severe (3)	Severe (5)
	Multifocal		

[b] ARIA-E, amyloid-related imaging abnormalities – edema. Reproduced with permission from Bracoud L, et al. Alz Dement 2017;13(Supple): P253-P254.

ARIA-H MRI Classification Criteria			
ARIA type	**Radiographic Severity**		
	Mild	**Moderate**	**Severe**
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5-9 new incident microhemorrhages	10 or more new incident microhemorrhages

Eli Lilly and Company - Global Patient Safety **Case Number:**

ARIA-H superficial siderosis	1 new incident focal area of superficial siderosis	2 new incident focal areas of superficial siderosis	>2 new incident focal areas of superficial siderosis

What was the final diagnosis on MRI? (Refer to MRI classification criteria above for severity assessment)					
☐ ARIA-E			Date of MRI:		
Severity of ARIA-E	☐ Mild	☐ Mild +	☐ Moderate	☐ Moderate +	☐ Severe
Scale used for ARIA-E assessment: ☐ 3-point scale ☐ 5-point scale.					
☐ ARIA-H microhaemorrhage			Date of MRI:		
Severity of Microhaemorrhage	☐ Mild		☐ Moderate		☐ Severe

☐ ARIA-H superficial siderosis		Date of MRI:	
Severity of superficial siderosis	☐ Mild	☐ Moderate	☐ Severe

☐ Both ARIA-E and ARIA-H microhaemorrhage and/or superficial siderosis			Date of MRI:		
Severity of ARIA-E	☐ Mild	☐ Mild +	☐ Moderate	☐ Moderate +	☐ Severe
Severity of microhaemorrhage	☐ Mild		☐ Moderate		☐ Severe
Severity of superficial siderosis	☐ Mild		☐ Moderate		☐ Severe
Scale used for ARIA-E assessment: ☐ 3-point scale ☐ 5-point scale					

☐ Intracranial hemorrhage	Date of MRI:
Type of hemorrhage (example subdural, subarachnoid, intracerebral):	

Hospitalization for this event? ☐ No ☐ Yes

Provide number, area(s) and/or location(s) as applicable
ARIA-E:
ARIA-H microhaemorrhage:
ARIA-H superficial siderosis:
Intracranial hemorrhage:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Any other MRI findings:

Any other imaging findings: for example, Computed Tomography (CT), Computed Tomography Angiography (CTA), and Magnetic Resonance Angiography (MRA)

Were any clinical symptoms experienced with the ARIA event? ☐ Yes ☐ No
Were these associated with ☐ ARIA-E ☐ ARIA-H ☐ both ARIA-E and ARIA-H or ☐ Intracranial hemorrhage
If yes, please provide details below:

ARIA symptom	Present? (If yes check box)	Severity of the symptom	Start date of symptom	Symptom stop date	Symptom outcome
Headache	☐	☐ mild			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
		☐ moderate			
		☐ severe			
Vomiting	☐	☐ mild			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
		☐ moderate			
		☐ severe			
Dizziness	☐	☐ mild			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
		☐ moderate			
		☐ severe			
Confusion	☐	☐ mild			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
		☐ moderate			
		☐ severe			

Eli Lilly and Company - Global Patient Safety **Case Number:**

ARIA symptom	Present? (If yes check box)	Severity of the symptom	Start date of symptom	Symptom stop date	Symptom outcome
Visual disturbances	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Speech disturbances	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Unsteadiness	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Tremor	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Seizures	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Alteration of consciousness	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Other:	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown
Other:	☐	☐ mild ☐ moderate ☐ severe			☐ Recovered ☐ Recovering ☐ Not recovered ☐ Worsened ☐ Unknown

Eli Lilly and Company - Global Patient Safety **Case Number:**

Is ARIA-E/ARIA-H/Intracranial hemorrhage still ongoing? ☐ Yes ☐ No
Provide a clinical update in neurological/cognitive and health status:
Provide outcome of radiographic abnormality: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown. ☐ Recovered with Sequalae (Please provide details):
Provide date of radiographic resolution of ARIA-E Date:
Provide date of radiographic stabilization for ARIA-H Date:
Provide date of radiographic recovery of intracranial hemorrhage, Date:

Provide information on presence, extension, and possible progression of cortical and subcortical atrophy, if feasible or if serial MRI are available:

Has there been any treatment given for ARIA-E, ARIA-H and/or intracranial hemorrhage?
☐ Yes ☐ No
If yes, describe:

Please provide any prior MRI/other imaging findings below.		
Test	Result	Date of imaging
Brain MRI		
Other imaging (please specify):		
Other imaging (please specify):		
Report(s) attached? ☐ Yes ☐ No		

Was there any repeat/follow-up MRI/other imaging done after diagnosis of ARIA/Intracranial hemorrhage? ☐ Yes ☐ No		
Test	Result	Date of imaging
Brain MRI		
Other imaging (please specify):		
Other imaging (please specify):		
Report(s) attached? ☐ Yes ☐ No		

Eli Lilly and Company - Global Patient Safety **Case Number:**

Relevant Laboratory Tests (for ARIA-H/Intracranial hemorrhage)				
	Normal range for your institution	**Baseline value for patient**	**Abnormal value**	**Improvement value**
		Date:	Date:	Date:
Hemoglobin				
Hematocrit				
WBC				
Platelets				
INR/Prothrombin time				
aPTT				
d-Dimer				
Creatinine				
Other:				

Relevant medical history	
☐ Hypertension	☐ Cerebral amyloid angiopathy
☐ Alcohol use	☐ Illicit drug use
☐ Any recent head injury or fall (specify)	
☐ Cardiovascular disease (specify)	
☐ Cerebrovascular disease (specify)	
☐ Other	
ApoE4 genotype status (if known): ☐ non-carrier ☐ homozygous carrier ☐ heterozygous carrier	
ApoE2 genotype status (if known): ☐ non-carrier ☐ homozygous carrier ☐ heterozygous carrier	

Has the patient received any prior therapy with anti-amyloid drugs? ☐ Yes ☐ No
If yes, provide details of treatment (including dates of therapy):

Any history of ARIA-E, ARIA-H, both ARIA-E and ARIA-H or intracranial hemorrhage? ☐ Yes ☐ No
If yes, provide details:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Concomitant medications (dose/dates, if known)	
☐ Aspirin	☐ Non-aspirin antiplatelet(s)
☐ Anticoagulant(s)	☐ Thrombolytic(s)
☐ Other	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequalae (please provide details):	

Please provide rationale for relatedness assessment:

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

Prior to the launch of Kisunla 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, with the National Competent Authority. The MAH shall also agree the details of the controlled access programme (CAP).

The CAP is aimed at promoting the safe and effective use of donanemab by confirming the correct selection of patients based on relevant indication or diagnosis, the genetic profile, and available magnetic resonance imaging (MRI). All patients will be registered in the CAP registration system prior to the initiation of donanemab treatment.

The educational materials are aimed at educating healthcare professionals and patients/caregivers of the potential risk factors for the development of ARIA (-E/-H) including signs, symptoms, and management.

The MAH shall ensure that in each Member State where Kisunla is marketed, prior to launch and after launch, all healthcare professionals and patients/caregivers who are expected to prescribe/receive Kisunla have access to/are provided with the following educational materials:

- HCP educational materials
- Patient Card

Proposed key messages of the additional risk minimisation measures:

HCP educational materials:

The educational material for prescribers and radiologists shall contain a guide for HCPs and a prescriber checklist, including the following key elements:

HCP Guide:

- Information about the conditions of the donanemab CAP. Donanemab treatment should be administered under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion-related reactions to ensure adequate management of patients treated with donanemab.
- Donanemab use may cause ARIA (-E or -H), and patients should be instructed to seek medical advice immediately if signs or symptoms suggesting ARIA appear.
- Symptoms of ARIA may include, but are not limited to, headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures, and may mimic stroke or stroke-like symptoms.
- ARIA -E and -H can both be classified as mild, moderate, or severe based on MRI, and as symptomatic or asymptomatic based upon the clinical symptoms. Most serious ARIA

reactions occurred within 12 weeks of initiation of treatment. Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E.

- Risk factors for ARIA -E or -H include pre-treatment cerebral microhaemorrhage, superficial siderosis, and ApoE ε4 carrier status (homozygotes greater than heterozygotes) compared to non-carriers. Donanemab is indicated in ApoE ε4 heterozygotes or non-carrier patients.
- Testing for ApoE ε4 carrier status is mandatory prior to initiating donanemab treatment to inform the risk of developing ARIA.
- Donanemab treatment should be initiated or continued as per the indication and contraindications described in sections 4.1 and 4.3 of the SmPC, respectively.
- Dosing recommendations and treatment discontinuation for patients with ARIA-E and ARIA-H should be followed as described in Section 4.2 of the SmPC.
- Events of ARIA-H and intracerebral haemorrhage greater than 1 cm have been reported in patients on donanemab treatment. Caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent to a patient on donanemab treatment as this may increase the risk of bleeding in the brain as described in section 4.4 of the SmPC.
- ARIA should be considered in the differential diagnosis of patients presenting with stroke-like symptoms.
- ARIA can cause focal neurologic deficits similar to those observed in an ischaemic stroke. Clinicians treating ischaemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy to a patient being treated with donanemab. MRI or identification of vascular occlusion can help identify that ischaemic stroke rather than ARIA is the aetiology, and inform the use of thrombolytics or thrombectomy when appropriate.
- The purpose and use of the patient card including the importance of carrying the card at all times and to provide to HCPs in emergency situations.

Prescriber checklist will include:

***Prior to treatment initiation*:**

- Initiation of donanemab treatment in all patients should be captured in the "EU CAP Registration System" implemented as part of the CAP.
- ApoE ε4 carrier status testing is mandatory to inform the risk of developing ARIA. The use of donanemab in ApoE ε4 homozygous carrier patients is not indicated (see section 4.1 of the SmPC).
- Patients treated with donanemab must be given the patient card and be informed about the risks of this medicinal product.
- The presence of amyloid beta pathology and a clinical diagnosis of either mild cognitive impairment due to AD or mild AD dementia should be confirmed prior to initiating donanemab treatment.
- MRI should be performed at baseline (within 6 months prior to initiating treatment) for risk factors of ARIA including presence of cerebral microhaemorrhage and superficial

siderosis. The use of donanemab in patients with more than 4 microhaemorrhages or superficial siderosis is contraindicated.
- Donanemab treatment should not be initiated as per the contraindications described in section 4.3 of the SmPC.

Monitoring during treatment:

- Treatment should be maintained until amyloid plaques are cleared (e.g. at 6 or 12 months, see section 5.1 of the SmPC) as confirmed using a validated method. The maximum treatment duration is 18 months which should not be exceeded even if plaque clearance is not confirmed.
- MRIs should be performed prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose. An additional MRI at one year of treatment (prior to the 12th dose) in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and patients with previous ARIA events earlier in treatment, should be performed.
- In case of ARIA, please follow the recommendations for dosing interruptions described in section 4.2 of the SmPC. Additional MRI is indicated if ARIA symptoms occur. A follow-up MRI to assess for resolution (ARIA-E) or stabilisation (ARIA-H) should be performed 2 to 4 months after initial identification.
- Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E.
- Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilisation should be guided by clinical judgment, including re-evaluation of risk factors.
- Donanemab should be permanently discontinued after serious ARIA-E, serious ARIA-H, intracerebral haemorrhage greater than 1 cm, or recurrent symptomatic or radiographically moderate or severe ARIA events.

Patient Card:

The donanemab patient educational material will consist of a patient card which will be provided to the patient and/or caregiver as part of the initial discussion by the prescriber.

The following key elements are directed towards the patient/caregiver:

- The patient card should be kept with the patient/caregiver at all times, and it should be shared with other healthcare providers involved in their treatment including emergency situations.
- Treatment with donanemab may cause amyloid related imaging abnormalities (ARIA).
- Symptoms of ARIA may include headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure.
- Patients should seek medical attention or advice if symptoms of ARIA occur.
- Emergency contact details of family member or caregiver.
- Contact details of the prescriber.

The following key elements are directed toward HCPs involved in the patient's treatment:

ARIA (detected by MRI) can cause focal neurologic deficits similar to those observed in an ischaemic stroke. Because ARIA occurs more commonly in the first 6 months of treatment with donanemab, clinicians treating ischaemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy in a patient being treated with donanemab (for additional details, see Kisunla SmPC section 4.4 ARIA and Concomitant antithrombotic treatment).

Controlled Access Programme

The proposed CAP in EU member states aims to act as a risk minimization measure in 2 ways:

(1) restricting access of donanemab to preselected centres and
(2) implementing a registration system to assist HCPs in
    i. assessing patient eligibility,
    ii. providing quick reference to educational materials, and
    iii. confirming adherence to the materials.

The CAP allows for pre-selection of centres with required criteria, (prescribers able to assess eligibility for donanemab, access to a validated method to assess brain amyloid pathology, access to IV infusions, access to MRI [scheduled and non-scheduled] to monitor for ARIA, and access ApoE ε4 tests. This will be followed by drug distribution to pharmacies of these selected centres with affiliated prescribers, who have received HCP educational materials on donanemab treatment. Prescribers within these centres will, prior to a patient receiving donanemab, use the registration system to

- attest to receiving and understanding the required HCP education guide,
- confirm that the (anonymised) patient meets required eligibility criteria per label,
- and verify that the patient has been counselled regarding the risks of donanemab and provided the patient card.