swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Kisunla

International non-proprietary name:	donanemab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	350 mg (17.5 mg/mL)
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Eli Lilly (Suisse) SA
Marketing authorisation no.:	69523
Decision and decision date:	approved on 22 January 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADA	Anti-drug antibody
ADAS-Cog13	Alzheimer's Disease Assessment Scale - Cognitive subscale (13 Items)
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living scale
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
API	Active pharmaceutical ingredient
ApoEε4	Apolipoprotein Eε4
AR	Assessment report
ARIA	Amyloid-related imaging abnormality
ARIA-E	Amyloid-related imaging abnormality-oedema/effusions
ARIA-H	Amyloid-related Imaging abnormality-haemorrhage/haemosiderin deposition
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CAP	Controlled Access Programme
Cavg	Average plasma/serum concentration of drug
CDR-G	Clinical Dementia Rating - Global score
CDR-SB	Clinical Dementia Rating - Sum of Boxes
CHO	Chinese Hamster Ovary
CI	Confidence interval
CL	Centiloid
C_{max}	Maximum observed plasma/serum concentration of drug
CSF	Cerebrospinal fluid
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESRD	End-stage renal disease
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HSA	Singapore's Health Sciences Authority (HSA)
iADRS	Integrated Alzheimer's Disease Rating Scale
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IRR	Infusion-related reaction
ITT	Intention-to-treat
LoQ	List of Questions
LTE	Long-term extension
MAA	Marketing Authorisation Application

mAB	Monoclonal antibody
MAH	Marketing authorisation holder
Max	Maximum
MCI	Mild cognitive impairment
MCID	Minimally clinical important difference
Min	Minimum
MMSE	Mini-Mental State Examination
MRHD	Maximum recommended human dose
MRI	Magnetic Resonance Imaging
N3pG Aβ	N-terminal truncated form of amyloid beta
N/A	Not applicable
NAB	Neutralising antibodies
NAS	New active substance
NCS	Natural cubic spline
NO(A)EL	No observed (adverse) effect level
PASS	Post-authorisation safety study
PBO	Placebo
PBPK	Physiology-based pharmacokinetics
PC	Placebo-controlled
PD	Pharmacodynamics
PE	Primary endpoint
PET	Positron emission tomography
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
Q2W	Every 2 weeks
Q4W	Every 4 weeks
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
SE	Secondary endpoint
SOC	System Organ Class
ss	steady state
SUVr	Standardised uptake value ratio
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TGA	Australia’s Therapeutic Goods Administration (TGA)
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
RMP	Risk management plan
SAE	Serious adverse event
vMRI	Volumetric Magnetic Resonance Imaging

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for donanemab in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia (TGA) and Singapore (HSA).

The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Kisunla is indicated to slow disease progression in adult patients with Alzheimer's disease (AD). Treatment with Kisunla should be initiated in patients with evidence of amyloid beta pathology and either mild cognitive impairment or mild dementia.

2.2.2 Approved indication

Kisunla is indicated for slowing the progression of symptomatic Alzheimer's disease (AD) in adult patients with proven Alzheimer's-type amyloid-beta pathology and a clinical diagnosis of mild cognitive impairment or mild dementia, who are heterozygotes or non-carriers of the apolipoprotein E ε4 (ApoE ε4) allele (see "Contraindications" and "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose of donanemab is 700 mg every 4 weeks for the first 3 doses, followed by 1400 mg every 4 weeks. Treatment should be maintained until amyloid plaques are cleared. Continue treatment for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible (see "Clinical efficacy").

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 August 2023
Formal control completed	2 October 2023
List of Questions (LoQ)	20 February 2024
Response to LoQ	22 April 2024
Second List of Questions (LoQ)	14 June 2024
Response to 2nd LoQ	15 July 2024
Preliminary decision	3 March 2025
Response to preliminary decision	6 July 2025
Labelling corrections and/or other aspects	17 October 2025
Response to labelling corrections and/or other aspects	16 November 2025
Labelling corrections	10 December 2025
Response to labelling corrections	19 December 2025
Labelling corrections	7 January 2026
Response to labelling corrections	13 January 2026
Final decision	22 January 2026
Decision	approval

3 Medical context

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive impairments in memory, language, and thinking, with the eventual loss of the ability to perform social and functional activities in daily life. It is characterized by amyloid and tau protein pathology, neuronal loss and brain atrophy.
Pathological changes usually start more than 20 years prior to first clinical manifestations. The syndrome usually starts as mild cognitive impairment (MCI) mainly affecting memory with subsequent progression to full-blown dementia that is characterised by general cognitive impairment in various functional domains.

In Switzerland, the incidence of dementia is expected to be 34`800 persons per year and the prevalence is estimated at 161`000 patients. AD is the most common cause of dementia. Age represents the main risk factor of AD.

Current treatment strategies for patients with AD are usually addressing cognitive deficits, behavioural and psychological symptoms and signs of dementia. Medicinal products authorised in Switzerland for the symptomatic treatment of cognitive symptoms of AD include cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine.

Kisunla contains the new active substance donanemab, a recombinant immunoglobulin gamma 1 monoclonal humanised antibody - produced in Chinese Hamster Ovary (CHO) cells - directed against the insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present in brain amyloid plaques. Donanemab binds to deposited amyloid plaque and aids plaque removal through microglia mediated phagocytosis.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, Australia's Therapeutic Goods Administration (TGA) (see section 2.1 Applicant's request / Work-sharing procedure).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, Australia's Therapeutic Goods Administration (TGA) (see section 2.1 Applicant's request / Work-sharing procedure).

6 Clinical aspects

The applicant has applied for a three-way work-sharing assessment as a standard evaluation within the Access Consortium with the regulatory agencies HSA, TGA, and Swissmedic.
For the clinical module, HSA acted as the Lead Agency in the ACCESS Work Sharing Procedure with peer-review by TGA and Swissmedic. From the start of the assessment of the clinical dossier, PK/PD data were assessed independently by Swissmedic. Early during the assessment procedure, it became evident that the final decision on the Marketing Authorisation Application (MAA) might differ across the three contributing regulatory authorities. Therefore, Swissmedic set up a separate written assessment report based on the HSA AR and the company's responses to Rounds 1-4 List of Questions.

At the time of the initial submission of the MAA, the clinical study programme of donanemab included the following scientific data:

Completed studies:
Phase 1 studies
- Study Phase 1 I5T-MC-AACC (**AACC**) – safety, tolerability, and PK profile of single and multiple IV doses of donanemab
- Study Phase 1b I5T-MC-AACD (**AACD**) – safety, tolerability, PK and PD profiles of single and multiple IV doses of donanemab

Phase 2 study
- Study I5T-MC-AACG (**AACG**, **TRAILBLAZER-ALZ**) – safety and efficacy of donanemab, assessment whether removal of existing amyloid plaque can slow the progression of AD in up to 72 weeks of treatment

Phase 3 study
- Study I5T-MC-AACI (**AACI**, **TRAILBLAZER-ALZ2, Cohort AACI-PC**) – assessment of the effect of donanemab in a 76-week study period on the clinical progression of AD, brain amyloid deposition, brain tau deposition, and brain region volumes, to evaluate the safety and tolerability of donanemab, and evaluation of peripheral PK and the presence of anti-donanemab antibodies.

Ongoing studies:
Phase 2 study
- Study I5T-MC-AACH (**AACH**, **TRAILBLAZER-EXT**) - in patients from AACG or AACC, Part B with patients who received placebo in AACG: safety and tolerability of donanemab, assessment of the effect of donanemab on clinical progression, brain amyloid deposition, and brain region volume

Phase 3 studies
- Study I5T-MC-AACN (**AACN**, **TRAILBLAZER-ALZ4**) - comparing amyloid plaque clearance with donanemab and with aducanumab
- Study I5T-MC-AACI (**AACI, TRAILBLAZER-ALZ2, Cohort AACI-LTE**) - following the main study period a 76-week long-term extension (LTE) period is added to further evaluate efficacy and safety of donanemab over time. Re-accumulation of amyloid plaque will be monitored in patients previously dosed with donanemab.

6.1 Clinical pharmacology

Absorption and Biopharmaceutical Development
Four formulations, 3 lyophilised and one solution were employed in the clinical development of donanemab. The proposed commercial presentation of donanemab is a concentrate for the preparation of a solution for intravenous infusion, which was administered in the pivotal Phase 3 study AACI. In most other studies, the lyophilised formulations were administered.

Dose Proportionality
The donanemab exposures increased proportionally to the administered dose. The following dose ranges were investigated:

- single dosing: 0.1 mg/kg to 10 mg/kg and from 10 mg/kg to 40 mg/kg
- multiple dosing: 10 mg/kg Q2W and Q4W and 20 mg/kg Q2W and Q4W

Pharmacokinetics after multiple dosing
There was a 1.06-fold to 1.26-fold accumulation after Q4W dosing. Steady state after the proposed dosing regimen of 700 mg Q4W (3 applications) followed by 1400 mg Q4W is attained after the first dose of 1400 mg.

Distribution
The donanemab CSF to serum concentration ratio was approximately 0.208%. The estimated donanemab central volume of distribution was 3.36 L.

Metabolism
No *in vitro* or clinical metabolism studies were done for donanemab due to the biological nature of the molecule.

Elimination
The estimated donanemab clearance and half-life in a typical patient were 0.0255 L/h and 12.1 days, respectively.

Special populations / Intrinsic factors
Donanemab exposures in healthy subjects were approximately 15% higher than in AD patients. The pharmacokinetics of donanemab in patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD) was investigated in a population PK analysis. The dataset included 2131 patients with a mean age of 74 years (range 54 – 88 years) and a mean body weight of 73.8 kg (range 31.8 – 157 kg). The majority (89.9%) of the patients were White and APOE4 carriers (66.4%). Of these, 52.2% were heterozygotes and 14.2% were homozygotes.

Most of the patients (47.9%) had mild renal impairment. The dataset included 16.3% of patients with normal renal function, 34.8% of patients with moderate renal impairment, 18 patients (0.8%) with severe renal impairment and 2 patients (0.1%) with end-stage renal disease (ESRD).

Most of the patients (95.1%) had normal hepatic function based on the NCI classification. The dataset included 95 (4.5%) patients with mild hepatic impairment, 6 patients (0.3%) with moderate hepatic impairment and no patients with severe hepatic impairment.

There were 70.2%, 24.7%, and 5.03% of donanemab ADA titres that were 1:5-1:2560, 1:5120 - 1:20480, and >1:20480, respectively in the dataset.

Covariates to be investigated for their possible impact on donanemab PK included age, body weight (already included in the base model), sex, race, ethnic origin, creatinine clearance, serum bilirubin, serum albumin, C-reactive protein, AST, ALT, AP, baseline tau, tau pathology, renal function, hepatic function, ADA/NAB status or titre, study and formulation.

The final pop PK model was a 2-compartment model with zero-order input (i.v. infusion) and first-order elimination. The only covariate reaching statistical significance in the covariate analysis was the ADA titre as a covariate of donanemab clearance (CL). The base model already included allometric body weight scaling with fixed factors on volume and clearance terms.

Donanemab exposures decreased with increasing ADA titres. At high titres, a 32.1% decrease of AUC and more donanemab concentrations below the threshold for plaque reduction were predicted. Assuming continuous treatment with donanemab for 76 weeks, at least 98% of the patients maintained average plasma/serum drug concentrations (Cavg) above 15.2 µg/mL over the entire treatment period. Assuming dosing per protocol, cessation of donanemab treatment in patients who met the respective criteria resulted in a decrease of the percentage of patients maintaining Cavg above 15.2 µg/mL (82% to 89% in week 52, 65% to 69.5% in week 72. The impact of ADA titre appeared to be relatively small.

Donanemab exposures also increased with decreasing body weight. A comparison of the donanemab exposures after weight-based and fixed dosing showed comparable AUC and Ctrough values, but higher Cmax values after fixed dosing. Within weight quartiles, the differences of Cavg,ss and Cmax,ss were ≤30% for weight-based and flat dosing. However, for the extreme body weights, the differences between weight-based and flat dosing were higher: for low-weight patients, median Cavg,ss and Cmax,ss were 1.55-fold and 1.72- fold higher after flat dosing. For high-weight patients, median Cavg,ss and Cmax,ss after flat dosing were 54% and 60% of the values after weight-based dosing.

After fixed dosing, the 5th percentile of Cavg,ss was still >15.2 µg/mL in patients with a body weight of 157 kg and high ADA titres but low-weight patients are likely to have a higher ARIA-E risk after flat dosing.

The population PK dataset was updated with the 24-week data from standard and enhanced titration arms of study AACQ. The purpose of this analysis was to compare donanemab exposures for both treatment arms. According to the modelling report, the enhanced titration arm was associated with a significant reduction of the ARIA-E risk.

The demographic data of the 841 newly included patients were similar to the data of previous patient population described above. The final population PK model was applied to the new data with fixed parameters from the prior analysis described above. It described the AACQ data without further modifications reasonably well.

The population PK model was used to simulate donanemab exposures over 12 weeks for both treatment arms. Donanemab AUC(0-12 weeks) was slightly lower for the enhanced titration arm, but overall the exposures for both treatment arms were largely overlapping. In summary, comparable PK between the standard and the enhanced titration treatment arm over the first 12 weeks (where the treatments were different) was demonstrated.

Interactions
No interaction studies were done for donanemab due to the biological nature of the molecule and because its mechanism of action does not affect cytokines.

Pharmacodynamics
Secondary pharmacology (safety)
No dedicated tQT study was performed. An exposure-response analysis of the data obtained in study AACD (dose range 10 mg/kg to 40 mg/kg SD and up to 20 mg Q2W MD) was conducted. No relationship between donanemab serum concentrations and QRS or QTcF was detected. The predicted ΔΔ QRS for the predicted C_{max} after 1400 mg Q4W in study AACG was -0.151 ms (90% CI: -0.628, 0.327). The predicted ΔΔ QTcF for the predicted C_{max} after 1400 mg Q4W in study AACG was -0.961 ms (90% CI: -2.01,0.09).

6.2 Dose finding and dose recommendation

Clinical pharmacology aspects: The measurements of cerebral amyloid plaques by florbetapir PET scanning in study AACC showed that only the highest dose of 10 mg/kg administered resulted in a clear reduction from baseline compared to placebo. The administration of higher doses in study AACD indicated that 10 mg/kg Q2W did not lead to better results than the 10 mg/kg Q4W dose. Similarly, the benefit of the 20 mg/kg Q4W dose over the 10 mg/kg Q4W dose was only minimal.

Clinical aspects:
No dedicated clinical dose response studies were performed.

The dosing regimen of donanemab in the pivotal study AACI (TRAILBLAZER-ALZ2) was based on the dose-ranging studies AACC and AACD. A dose of 1400 mg Q4W (20 mg/kg in a 70 kg patient) was chosen as the target dose since doses <10 mg/kg Q4W (700 mg in a 70 kg patient) did not achieve sufficient amyloid plaque reduction, whereas a single dose of 40 mg/kg Q4W (2800 mg in a 70 kg patient) was associated with an elevated ARIA risk. According to the original protocol (dated 30 Jan. 2020), no titration period was foreseen. With protocol amendment (a) (dated 14 Dec. 2020), a titration scheme (i.e. 700 mg for the first three doses) was introduced at the end of the first year of study conduct after two cases of symptomatic ARIA had been reported for the initial dosing regimen. The first Phase 2 study AACG (TRAILBLAZER-ALZ), protocol dated 30 Aug. 2017, had already used a titration scheme of 3 x 700 mg Q4W, followed by 1400 mg Q4W for up to 72 weeks from the start of study conduct.

During the ongoing evaluation process, the applicant submitted an interim clinical study report (CSR) with 24-week interim data from study AACQ (TRAILBLAZER-ALZ 6) and a population PK/PD analysis that compared three alternative dosing regimens (enhanced titration (350 mg, 700 mg, 1050 mg Q4W, then 1400 mg Q4W), dose skipping (700 mg Q8W, then 1400mg Q4W), and Cmax (6 x 350mg Q2W, 2 x 700mg Q2W, then 1400 mg Q4W) to the standard dosing used in the pivotal study AACI (3 x 700 mg Q4W, then 1400 mg Q4W), analysing exposure metrics and amyloid plaque reduction to support a PK/PD bridging between the two dosing regimens. Study AACQ did not include any efficacy data; it used PK/PD bridging instead for the extrapolation to the former standard dosing. The submitted data included interim safety, immunogenicity, PK and PD data from baseline to Week 24 comparing three alternative dosing regimens to the standard dosing regimen.

Together with the responses to the preliminary decision, the applicant then submitted the finalised CSR of study AACQ:
Of 842 treated study participants, 677 participants had completed the 76-week study period.

Among the alternative dosing regimens investigated, the enhanced titration group was the only dosing group that met the 24-week primary objective of Study AACQ on ARIA-E frequency reduction. This group showed a 41% relative risk reduction in ARIA-E (reducing ARIA-E to 14% compared to 24% in the standard arm), while demonstrating comparable cumulative exposure and similar observed brain amyloid plaque reduction at Week 24 and at Week 76.
Introducing the enhanced titration dosing regimen was therefore accepted by Swissmedic.

6.3 Efficacy

The clinical efficacy of donanemab is mainly based on a single pivotal study: I5T-MC-AACI (**AACI**, **TRAILBLAZER-ALZ2**).
AACI had originally been designed as a Phase 2 study (protocol dated 30 Jan. 2020). With protocol amendment (b) (dated 17 Feb. 2021), it was then converted into a Phase 3 study.

AACI was a multicentre, randomised, parallel-group, double-blind placebo-controlled study over 76 weeks in the double-blind period including 1736 adult patients with early symptomatic AD (defined as mild cognitive impairment or mild dementia, both due to AD) AND evidence for amyloid and tau brain pathology.

Inclusion criteria comprised among others: 60 to 85 years of age, Mini-Mental State Examination (MMSE) score of 20 to 28; a P-tau criterion in the flortaucipir F18 scan[1] (inclusion of patients with evidence for high tau load in PET imaging) AND an amyloid criterion in the florbetapir F18 or florbetaben F18 scan[2].
Based on the individual MMSE score at screening, study participants were assigned to the clinical categories of MCI due to AD (MMSE≥27) or mild AD (MMSE = 20-26).

Patients with presence of ARIA-E, >4 cerebral microhaemorrhages, >1 area of superficial siderosis, any macrohaemorrhage or severe white matter disease in the centrally read MRI at screening were excluded from study participation. Patients with no/very low tau pathology (defined as a negative visual read or a moderate positive visual read [PET signal limited to temporal lobe] with Standardised Uptake Value ratio (SUVr)) were also excluded.

At screening, amyloid pathology had to be confirmed by florbetapir (amyloid plaque fibrils) or florbetaben (amyloid plaque accumulation) PET scanning that was evaluated using the Centiloid (CL) method. The amyloid re-accumulation rate (median, 95% CI) was estimated at 2.80 (2.16, 3.11) CL/year; after having achieved an amyloid load below 24.1 CL (i.e. the threshold for the diagnosis of AD) with Kisunla, it would take 10 to 15 years for amyloid plaque levels to return to baseline (assuming a linear increase over time). Hence, little benefit is to be expected from continued donanemab treatment once amyloid plaque clearance has been achieved.
Tau burden was quantified by flortaucipir PET scan at screening using the SUVr method with the cerebellum as the reference region. Based on the individual SUVrs, study participants were attributed to subgroups of intermediate and high tau load.

Participants who met entry criteria were equally randomised to the donanemab group (700 mg IV Q4W for the first 3 doses and then 1400 mg IV Q4W) or the placebo group (IV Q4W).

Prespecified dose modification of investigational product were permitted in this study for participants who developed ARIA during the titration period, or for participants whose amyloid plaque reduction met criteria for dose cessation:

Donanemab-treated participants could switch to placebo in a blinded manner during the study if they met either 1 of the 2 criteria at Week 24, 52, or 76 (when further amyloid PET scans were performed):

1. amyloid level was <11 CL at any single amyloid PET scan, or
2. amyloid level was ≥11 to <25 CL in 2 consecutive amyloid PET scans.

Disposition
In total, 8240 adults were screened for inclusion. 1736 (21.1%) finally met screening criteria and were randomised to treatment (876 subjects to placebo and 860 subjects to donanemab). 1727 subjects

[1] Tau PET levels at baseline were defined using a SUVr value and visual read:
Low-medium (or intermediate) tau 1.10 ≤ SUVr ≤ 1.46, with a topographic deposition pattern consistent with moderate AD (AD+), **OR** SUVr ≤ 1.46, with a topographic deposition pattern consistent with advanced AD (AD++)
High tau SUVr > 1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++)
[2] Amyloid pathology: florbetapir/florbetaben PET estimate of **amyloid burden >37 CL**.
Background: The 37 CL amyloid PET inclusion threshold was chosen to be beyond the range of variability for the 24 CL amyloid PET positivity threshold in order to facilitate the assessment of the amyloid-lowering potential of donanemab. Examination of scatter plots from 3 studies with amyloid and tau PET data (including Studies AACG and AACI) suggested that few patients in a screening/clinical population would expect to have amyloid PET values between 24 and 37 CL, and that most patients with a flortaucipir PET SUVr >1.10 would be expected to have an amyloid burden > 37 CL.

were actually treated with the investigational product (donanemab or placebo). The majority of screening failures resulted from florbetapir PET out of range (n=1601, 24.6%), flortaucipir PET out of range (n=1631, 25.1%), and MMSE out of range (n=1510, 23.2%).

A total of 1320 participants (donanemab, n = 622; placebo, n = 698) completed the 76-week placebo-controlled treatment period (AACI-PC), while 404 participants (donanemab, n = 231; placebo, n = 173) discontinued treatment.
A higher proportion of participants discontinued the treatment due to AEs in the donanemab treatment arm as compared to the placebo treatment arm (5.8% vs. 2.4%).

1258 participants (donanemab, n = 584; placebo, n = 674) who had continued the DB period entered the LTE period (AACI-LTE).

Baseline Characteristics
Baseline demographics, clinical, and biomarker characteristics were generally balanced between both treatment arms. Mean age at study entry was 73.0 years in both groups. In the donanemab and placebo groups, 57.3% and 57.4% were female, 90.9% and 92.1% were White, and 69.8% and 71.2% carried an APOE ε4 allele with 16.7% homozygous carriers in both groups. Around 50% of all patients were using concomitant AChE inhibitors (predominantly donepezil), and around 20% were using concomitant memantine. Hypertension, anxiety/depression, arthritis/osteoarthritis represented very common comorbidities in the overall population. 17 to 22% of subjects had a history of malignant or unspecified tumours, thyroid disease, obesity or diabetes. 12.7% of subjects had been diagnosed with ischaemic heart disease. While around one third of subjects used aspirin (donanemab n=279, placebo n=286) and 10% (donanemab n=84, placebo n=88) reported comedication with anticoagulants (including heparins, warfarin, and direct oral anticoagulants), the use of non-aspirin antiplatelets [(donanemab n=52 (6.1%), placebo n=33 (3.8%)] and the use of thrombolytics [(donanemab n=1 (0.1%), placebo n=2 (0.2%)], were less frequent.

Mean (SD) iADRS score at baseline (Visit 2) in the overall population was 103.8 (14.2), CDR-SB was 3.9 (2.1), ADAS-Cog13 score was 29.0 (8.0), ADCS-ADL score was 66.4 (8.5), ADCS-iADL score was 47.8 (7.9), and MMSE score was 22.3 (3.9). Almost all participants (96.7%) had CDR-G scores of 0.5 to 1. Mean (SD) amyloid PET Centiloid at baseline was 102.5 (34.5) and the AD signature-weighted neocortical flortaucipir SUVr was 1.3 (0.3).

Efficacy Analyses
Primary efficacy endpoint (PE): Integrated Alzheimer`s Disease Rating Scale (iADRS)
To determine whether treatment with donanemab slows disease progression at Week 76 as measured on the iADRS compared to placebo regardless of any initiation or change to standard treatment and regardless of stopping the study drug in the intermediate brain tau or overall (intermediate or high tau pathology) study population.
The PE has been changed from the Clinical Dementia Rating—Sum of Boxes (CDR-SB) to iADRS in AACI protocol amendment (b), dated 17 Feb. 2021 (first patient enrolled 19.06.2020) to replicate and confirm the results of the primary outcome from the Phase 2 Study AACG. In contrast to previous clinical studies with monoclonal amyloid antibodies (mABs) in AD, the CDR-SB was not used as primary endpoint in the final study protocol to assess the effect of donanemab at Week 76. Instead, the newly developed iADRS was used to assess cognition and function. In 2015, the iADRS had been developed as a novel outcome measurement primarily for the use in clinical dementia studies and not for the use in daily clinical practice.
iADRS represents a linear compound of selected parts of two other established clinical dementia scales, the Alzheimer's Disease Assessment Scale–Cognitive Subscale 13 (ADAS-Cog-13, cognition), and the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale (ADCS-iADL function, items 6a and 7-23) scale and therefore combines cognitive and functional aspects of daily

living. In this study, the 2022 version of the iADRS was used (Wessels AM et al, 2022, https://doi.org/10.1002/trc2.12312).

The total iADRS score is calculated as follows: iADRS = ADCS-iADL + (– 1 (ADAS-Cog13) + 85).

ADAS-Cog13 scores range from 0 to 85, with higher scores indicating greater deficit of global cognition while ADCS-iADL scores range from 0 to 59, with lower scores indicating greater impairment. To compensate for this opposite scaling, the ADAS-Cog score is multiplied by (-1) in the calculation of the integrated scale. To anchor the ADAS-Cog at 0, a constant (85) is added. iADRS scores range from 0 to 144, with maximum scores indicating no impairment.

Secondary efficacy endpoints
The original primary endpoint of change from baseline over 76 weeks in the CDR-SB score was re-defined as the key secondary outcome. Additional secondary endpoints included the change from baseline through week 76 in ADAS-Cog13 score, ADCS-iADL score, MMSE score and brain amyloid plaque and brain tau deposition.

Tertiary and exploratory endpoints
These included the change from baseline through week 76 in blood-based biomarkers such as neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), phosphorylated (p)tau and Aβ levels. The change in the digit symbol substitution test (DSST, medicines version) score and the change in the CDR-global (CDR-G) score were also collected.

The PE and analysis method had been prespecified in the statistical analysis plan (SAP) prior to the database lock. A natural cubic spline (NCS) analysis with 2 degrees of freedom (DF) was used to assess the primary outcome. The primary efficacy analysis was conducted on (1) the intermediate tau population at baseline and (2) the overall (intermediate and hight tau at baseline) population.
PE was the change from baseline in the iADRS through Week 76 in at least one of both, the intermediate tau pathology population or the overall tau population vs. PBO treated subjects.

Efficacy results
iADRS - Intermediate tau population
At Week 76, the LS mean (±SE) change from baseline in the iADRS score in the intermediate tau population was -9.27±0.49 in the placebo group and -6.02±0.50 in the donanemab group, with an LS mean difference (±SE) between both groups of 3.25±0.70, 95% CI 1.88, 4.62, p<0.001 in favour of donanemab. This corresponds to a 35% (95%CI 19.9, 50.2) slowing of clinical progression in donanemab-treated participants vs. placebo-treated participants.

iADRS - Overall tau population
The LS mean (±SE) change from baseline in the iADRS score in the overall population was -13.11±0.50 in the placebo group and -10.19±0.53 in the donanemab group, with an LS mean difference (±SE) between the groups of 2.92±0.72, 95% CI 1.51, 4.33, p<0.001. This corresponds to a 22% (95%CI 11.4, 33.2) slowing of clinical progression in donanemab-treated patients vs. placebo-treated patients.

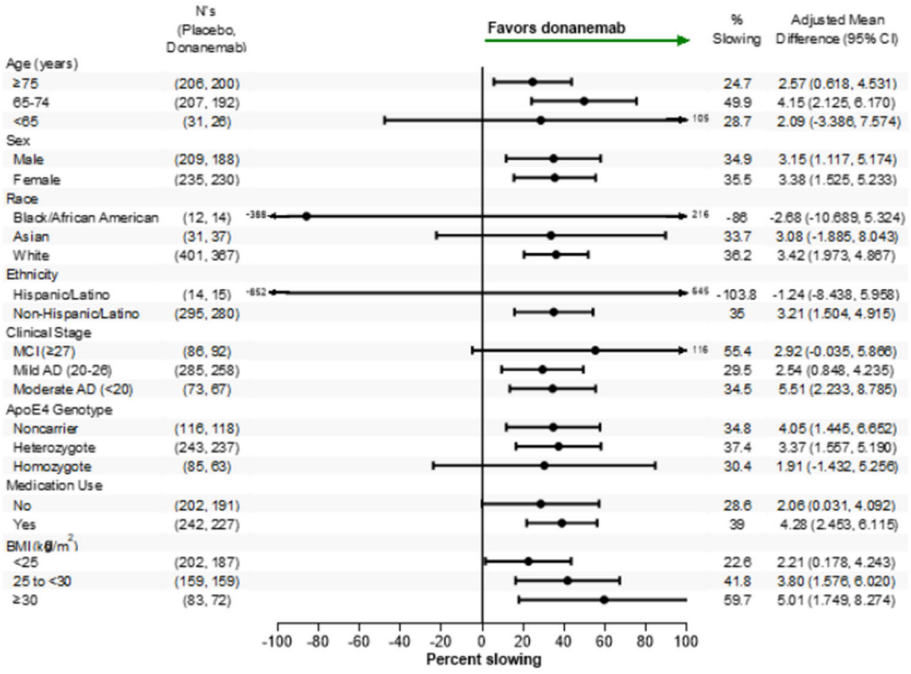
So, the study met its primary endpoint as donanemab-treated patients had a statistically significantly slowed clinical progression on the primary outcome, iADRS, compared with placebo in both intermediate tau (35% slowing; p<0.001) and overall (22.3% slowing; p<0.001) populations at 18 months. This treatment effect in the overall population was mainly driven by the intermediate tau population.

iADRS - Minimally Clinical Important Difference (MCID)
The applicant had predefined the thresholds for MCID on the iADRS in the AD population in an earlier study as follows:

- MCI: 5 points decrease from baseline
- Mild dementia: 9 points decrease from baseline

The difference donanemab vs. placebo on the primary endpoint does not reach either MCID threshold.

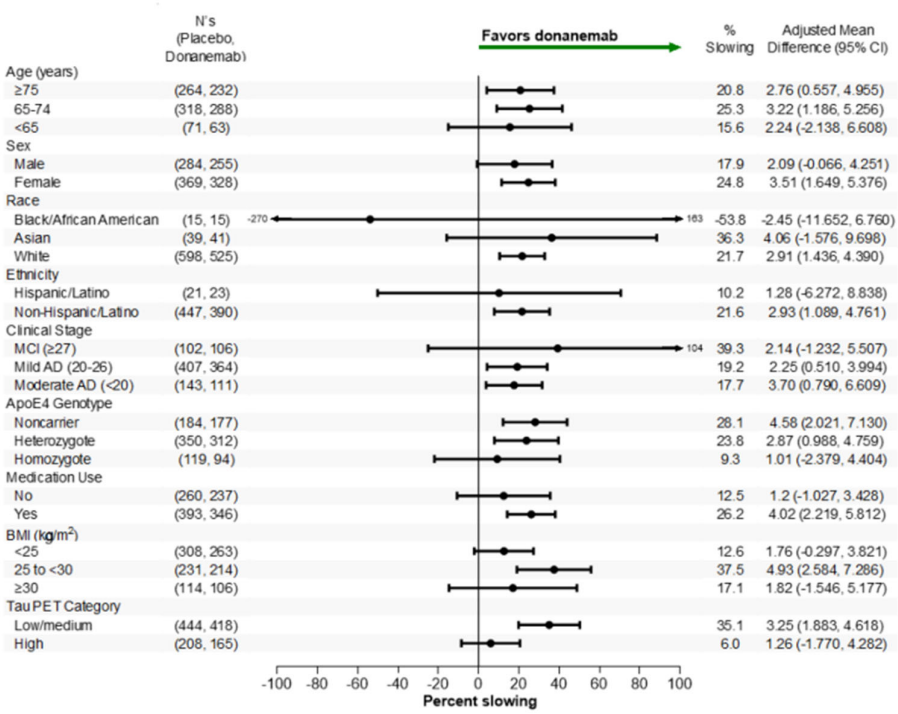
Subgroup analyses
While subgroup analyses showed consistent results and nominally favoured donanemab in terms of iADRS across most subgroups, uncertainties remained regarding clinical efficacy in patients with MCI, patients with a high tau load at baseline as well as in homozygous APOE ε4 carriers:



Abbreviations: AD = Alzheimer's disease; ApoE4 = apolipoprotein E allele 4; BMI = body mass index; CI = confidence interval; LS = least squares; iADRS = integrated Alzheimer's Disease Rating Scale; MCI = mild cognitive impairment; PC = placebo-controlled.

Figure AACI.5.15. iADRS: Subgroup analysis by demographic and baseline characteristics, intermediate tau population (AACI-PC period).

(Source: AACI-04-CSR, p. 176/2611)



Abbreviations: AD = Alzheimer's disease; ApoE4 = apolipoprotein E allele 4; BMI = body mass index; CI = confidence interval; LS = least squares; iADRS = integrated Alzheimer's Disease Rating Scale; MCI = mild cognitive impairment; PC = placebo-controlled.

Figure AACI.5.16. iADRS: Subgroup analysis by demographic and baseline characteristics, overall population (AACI-PC period).

(Source: AACI-04-CSR, p. 177/2611)

Disease progression

On the iADRS, the delay of disease progression at Week 76 in the overall tau population, was estimated at 1.4 months for donanemab (assessed on the iADRS, using a model with proportionality assumption). In the intermediate tau population, the estimated delay of 4.4 months was statistically significant. Using the CDR-SB, the delay in disease progression at Week 76 was 7.5 and 5.4 months, respectively, in the intermediate tau and overall tau population (estimated by a model with proportionality assumption).

The postulated slowing of disease progression has only been shown for the first 18 months. There is no data regarding the time thereafter.

Secondary efficacy analyses

The results of the primary analyses were supported by all secondary outcomes including the CDR-SB and the change in brain amyloid load. Brain tau deposition was not changed significantly (see table below, statistically significant results are given in bold).

Clinical Endpoint	Low-Medium Tau Population		Overall Population	
	Donanemab N=588	Placebo N=594	Donanemab N=860	Placebo N=876
CDR-SB[1]				
Mean baseline	3.72	3.64	3.92	3.89
Change from baseline	1.20	1.88	1.72	2.42
Difference donanemab vs. placebo (%)	**-0.67 (36%) P<0.001**	-	**-0.70 (29%) P<0.001**	-
ADAS-Cog$_{13}$[2]				
Mean baseline	27.41	27.60	28.53	29.16
Change from baseline	3.17	4.69	5.46	6.79
Difference donanemab vs. placebo (%)	**-1.52 (32%) P<0.001**	-	**-1.33 (20%) P<0.001**	-
ADCS-iADL[3]				
Mean baseline	48.20	48.56	47.96	47.98
Change from baseline	-2.76	-4.59	-4.42	-6.13
Difference donanemab vs. placebo (%)	**1.83 (40%) P<0.001**	-	**1.70 (28%) P<0.001**	-
MMSE Score[4]				
Mean baseline	23.11	22.88	22.52	22.20
Change from baseline	-1.61	-2.09	-2.47	-2.94
Difference donanemab vs. placebo (%)	**0.48 (22.9%) P=0.016**	-	**0.47 (16.1%) P=0.012**	-
Brain Amyloid Centiloid Change				
Mean baseline	103.00	100.94	104.02	101.75
Change from baseline	-88.03	0.18	-87.03	-0.67
Difference donanemab vs. placebo (%)	**-88.21 P<0.0001**	-	**-86.37 P<0.0001**	-
Brain Tau Deposition (Frontal SUVr Change)				
Mean baseline	1.1696	1.1709	1.2775	1.2738
Change from baseline	0.0273	0.0271	0.0401	0.0442
Difference donanemab vs. placebo (%)	0.0002 P=0.9684	-	-0.0041 P=0.4522	-

MCIDs for cognitive scoring tools are defined as follows (Ebeli M et al. 2024, https://doi.org/10.1370/afm.3050):

[1] CDR-SB: 1 to 2 points on a range 0 to 18 points.

[2] ADAS-Cog$_{13}$: 3.75 points on a range 0 to 85 points.

[3] ADCS-iADL: no MCID published, range 0 to 59 points.

[4] MMSE: 1 to 3 points on a range 0 to 30 points.

Volumetric MRI (vMRI)
Several vMRI measurements were conducted. In both, the intermediate tau and overall tau populations, the vMRI at Week 76 showed a greater decrease in the whole brain volume (nominal p<0.001) and a greater compensatory increase in ventricular volume (nominal p<0.001) in donanemab-treated participants compared to placebo-treated participants.
A smaller decrease in the hippocampal volume was observed in donanemab-treated participants compared with placebo-treated participants (nominal p=0.061 in the intermediate tau and nominal p=0.002 in the overall population).
Accelerated neurodegeneration with pronounced brain atrophy and compensatory ventricular enlargement has been described in AD patients receiving anti-β-amyloid therapy (Alves F et al. 2023, Belder CRS et al. 2024). The underlying mechanism and the (long-term) impact of these amyloid-removal-related brain volume changes are largely unknown.

Dose cessation criteria based on amyloid level
Exploratory analyses of donanemab-treated participants who met the dose cessation criteria were conducted. At Week 76, approximately 74% participants in the intermediate tau population and 69% participants in the overall population showed a significant reduction in amyloid plaque and met the dose cessation criteria. At Week 24, approximately 20% and 17% (intermediate tau and overall) and at Week 52, approximately 52% and 47% (intermediate tau and overall) fulfilled the criteria.

Key supportive studies
Swissmedic (SMC) considers only AACI as pivotal while Phase 2 study I5T-MC-AACG (**AACG, TRAILBLAZER-ALZ**) can be considered as supportive, the more so as it has relevant protocol amendments with major implications for data integrity.

AACG was a double-blind, placebo-controlled study to evaluate donanemab in patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with presence of intermediate brain tau burden demonstrated by flortaucipir PET. It aims to assess whether removal of existing amyloid plaques can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment, followed by final study assessments at 76 weeks.

It is to note that inclusion criteria did not require any clinical diagnosis of MCI due to AD or mild dementia, nor a CDR-SB score of 0.5-1.0. Instead, a gradual and progressive change in memory function reported by patients or informants for ≥ 6 months (CogState Brief Battery (learning/working memory score of 82 to 90) was required, and 18F flortaucipir scan (central read) criteria and 18F florbetapir scan (central read) criteria had to be met).

In contrast to study AACI (which included patients with evidence for a high tau load in PET imaging), study AACG only included patients with low to medium tau load. This impairs potential lumping of both study populations as tau is considered a marker of irreversible neurodegeneration due to neuronal loss and disintegration of the axonal cytoskeleton.
In total, 272 participants were randomised (N=126 placebo, N=131 donanemab-M (monotherapy), N=15 donanemab-C (donanemab in combination with an inhibitor of beta-secretase 1, However, the combination therapy was discontinued. These participants remained blinded and were allowed to receive monthly monotherapy with donanemab)), N=271 participants were treated, and N=199 participants completed the study (N=93 placebo, N=94 donanemab-m).
As in AACI, the PE of AACG was defined as the change in iADRS scores from baseline at Week 76.

Results
Formally, the study met its primary endpoint as donanemab-treated participants had statistically significantly less decline in cognition/function than placebo-treated participants as evaluated on the iADRS at Week 76 (LS mean change difference ± SE: 3.20 ± 1.56, p=0.042). The results equal a 32% reduction in cognitive/functional decline on the iADRS for donanemab-treated participants compared to

placebo. These statistically significant results appear mainly driven by the ADAS-Cog13 component of the iADRS total score (see table below, significant results are given in bold). While ADAS-Cog13 equals a 39% reduction of disease progression, the effect on the ADCS-iADL is estimated at a 23% reduction compared with placebo.

Secondary outcome measure	**Placebo** (N=120)	**Donanemab** (N=125)	**LS mean difference**
CDR-SB	1.58±0.18	1.22±0.18	-0.36±0.24, 95% CI -0.83, 0.12; NS
ADAS-Cog13	4.77±0.66	2.91±0.66	**-1.86±0.90, 95% CI -3.63, 0.09; p=0.040**
ADCS-iADL	-5.2±0.74	-3.98±0.74	1.21 ± 1.009, 95% CI -0.77, 3.20; NS
MMSE	-2.98±0.39	-2.35±0.39	0.64 ± 0.525, 95% CI -0.40, 1.67; NS

6.4 Safety

Main safety data were derived from the placebo-controlled studies AACG and AACI (“Dona-PC, LY only”). Additional safety data from ongoing studies were included in a larger safety pool (“All Dona”).

In the pivotal study AACI, 853 adults received at least one dose of donanemab. Of these, 710 patients are covered by the approved indication (ApoE ε4 heterozygotes or non-carriers): 29.9% (255/853) non-carriers, 53.0% (452/853) heterozygotes, and 0.4% (3/853) with genotype unknown.

An overview of the treatment-emergent adverse events (TEAEs) in the donanemab-placebo-controlled study (Dona-PC) and all donanemab (All Dona) is provided in the following table. The safety profile listed below refers to the dosing regimen of 3 infusions of 700 mg followed by infusions of 1400 mg of donanemab or the corresponding infusions of placebo.

	DONA-PC		ALL DONA
	Placebo N=999	Donanemab N=984	Donanemab N=2727
	n (%)	n (%)	n (%)
Deaths[b]	12 (1.2)	17 (1.7)	32 (1.2)
SAEs	153 (15.3)	168 (17.1)	411 (15.1)
DCAE	47 (4.7)	152 (15.4)	265 (9.7)
TEAEs	831 (83.2)	878 (89.2)	2129 (78.1)
ARIA-E/-H[a,*]	142 (14.2)	364 (37.0)	825 (30.3)
ARIA-E*	19 (1.9)	240 (24.4)	531 (19.5)
Symptomatic ARIA-E*	1 (0.1)	57 (5.8)	117 (4.3)
ARIA-H*	130 (13.0)	308 (31.3)	699 (25.6)
Macrohaemorrhage*	2 (0.2)	3 (0.3)	9 (0.3)
Anaphylactic reaction	0	3 (0.3)	8 (0.3)
IRR	4 (0.4)	84 (8.5)	225 (8.3)

Abbreviations: ARIA-E = amyloid-related imaging abnormality-oedema/effusions; ARIA-H = amyloid-related imaging abnormality-haemorrhage/haemosiderin deposition; DCAE = discontinuation of study treatment due to adverse event; Dona = donanemab; IRR = infusion-related reaction; MRI = magnetic resonance imaging; N = number of participants; n = number of subjects with at least 1 adverse event; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Participants may be counted in more than 1 category.

b Deaths are also included as SAEs and discontinuations due to adverse event.

* Based on MRI or TEAE cluster output.

(Source: 2.7.4 clin-safety-sum-eu, p. 22/261)

The most frequently reported TEAEs for donanemab-treated participants include ARIA-E (24.4%), ARIA-H (18.2%), infusion related reaction (IRR) (8.5%), nausea (5.2%), and headache (13.1%). Most of the TEAEs were of mild (34.9%) or moderate severity (41.9%).

The only severe TEAE that occurred at a frequency of at least 1% and reported in more than one patient in the donanemab treatment group was ARIA-E (placebo, 0%; donanemab, 2.1%).
Serious AEs related to ARIA events occurred at a frequency of 1.6%, with serious ARIA-E reported in 15 (1.5%) and serious ARIA-H reported in 4 (0.4%) donanemab-treated patients, compared with no serious ARIA-E/-H events in the placebo-treated patients. 14 of the 15 serious ARIA-E cases were also symptomatic. Three participants in the donanemab-treated group experienced fatal SAEs related to ARIA events: One (0.1%) death was attributed to an ARIA-E event, another (0.1%) to an ARIA-H event, and the third participant died after an incident of serious ARIA-E and ARIA-H.
ARIA events are of major clinical importance. They are generally managed symptomatically. Major clinical signs and symptoms are often absent or subtle, a scenario described as ‘clinically silent’. In these cases, ARIA diagnosis requires adequate imaging studies. Based on MRI imaging diagnosis, ARIA events were actually quite common in donanemab treated subjects (ARIA-E 24.4% of donanemab vs. 1.8% of placebo treated subjects, ARIA-H 31.2% vs. 12.4% and concurrent ARIA-E&H events in 16.4% vs. 0.6%).
Negative long-term sequelae of ARIA events cannot be excluded, even if instant changes in functional cognitive parameters may be subtle and remain inapparent during a timely limited controlled study period.
As ARIA incidence depends largely on the intensity of the MRI schedule and the MRI protocol, MRI field strength, MRI sequences, slice thickness (n.b.: partial volume effects) as well as other MRI parameters (e.g. positioning of the patient) have to be clearly defined and described in the Information for Healthcare Professionals. MRI follow-ups should be performed preferably on the same MRI scanner and evaluated by the same neuroradiologist.

ARIA risk factors
ARIA risk factors refer to baseline MRI abnormalities such as microhaemorrhages and superficial siderosis, white matter disease (WMD), and APOE ε4 genotype. They were associated with a higher incidence of ARIA-E, symptomatic ARIA-E, and ARIA-H.
The relative contribution to the overall ARIA-E risk across key baseline characteristics was as follows: APOE ε4 homozygosity 37%, presence of 2, 3 or 4 microhaemorrhages 21%, presence of superficial siderosis 18%, a mean arterial pressure (MAP) ≥107 mmHg 14%, and an amyloid PET load ≥198 CL 11%. Regarding the overall ARIA-E and ARIA-H incidence, homozygous APOE ε4 carriers were characterised by the highest risk (58.3% donanemab vs 21.3% placebo), followed by APOE ε4 heterozygous carriers (37.4% donanemab vs 13.4% placebo). Non-carriers had the lowest risk (24.1% donanemab vs 11.3% placebo) while controlling for other potential risk factors. For symptomatic ARIA-E, the risk was similar for APOE ε4 homozygous and heterozygous carriers, but higher than for non-carriers (symptomatic ARIA-E occurred in 4.1% of APOE ε4 non-carriers, 6.1% of heterozygotes, 7.7% of homozygotes). Serious events of ARIA occurred in approximately 0.7% of APOE ε4 non-carriers, 1.7% of heterozygotes and 3% of homozygotes.
These findings underline the need for mandatory APOE ε4 genotyping prior to the start of donanemab treatment and support the exclusion of homozygous APOE ε4 carriers from donanemab treatment.

Other TEAEs of clinical importance included hypersensitivity, anaphylaxis and IRR, immunogenicity and hypersensitivity, hepatic safety and suicidal ideation and behaviour. The incidence of IRR was higher in donanemab-treated participants compared to placebo-treated participants. Nonetheless, the events were transient and the majority resolved on the same day (median 0.5 days, mean 0.7 days). Almost 60% of the first-onset IRRs occurred by the third or fourth infusion, and the rates of individual TEAEs anaphylactic reaction and hypersensitivity in donanemab-treated participants were low (≤1.0%). A total of 88.1% of donanemab-treated participants developed ADAs although the majority did not have IRR.

A total of 4 SAEs of suicidal ideation and suicidal behaviour were reported in the donanemab group (placebo group: two SAEs). Three of these SAEs were fatal: two in the donanemab group and one in the placebo group. Overall, these rates are within respective background rates in the AD population.

The incidence of discontinuation due to AEs was lower in the placebo-treated group (4.7%) compared with the donanemab-treated group (15.4%). Events reported in at least 1% of participants in donanemab-treated participants that led to permanent discontinuation of study treatment were in the SOCs of Nervous system disorders and Injury, poisoning and procedural complications.

The incidence of deaths was similar between both treatment arms: 12 (1.2%) deaths were reported in in the placebo-treated and 17 deaths (1.7%) in the donanemab-treated group. Five deaths were considered as related to study treatment by the investigator (four deaths in the donanemab-treated group (thalamic haemorrhage, death, ARIA-E and ARIA-H) and one death in the placebo-treated participants (atherosclerosis)).

6.5 Final clinical benefit risk assessment

The demonstration of efficacy of donanemab is mainly based on data from the pivotal Phase 3 Study AACI. During the ongoing review, the applicant themselves suggested a restriction to symptomatic ApoE ε4 non-carriers and heterozygous carriers and proposed an extended dosing regimen supported by TRAILBLAZER-ALZ6 (AACQ) results.

Based on newly submitted long-term data from AACI, the final study report from AACQ, and provided that extensive additional risk minimising measures are implemented (e.g. treatment exclusively in specialised centres, close clinical monitoring of patients under donanemab treatment, guidelines for

treating/diagnosing specialists, manual for PET and MRI imaging, patient leaflet, information material for patients, relatives and caregivers, post-authorisation safety studies (PASS), and Controlled Access Programme (CAP)), the benefit-risk ratio was considered to be positive in AD patients who are ApoE ε4 non-carriers or heterozygous carriers.
The duration of treatment is to be limited to a maximum of 18 months. Treatment should be discontinued earlier if amyloid PET load falls below a critical threshold (i.e. < 24 Centiloids) as further benefit is not to be expected from continued donanemab therapy while safety risks remain. To identify potential candidates for early treatment stop, amyloid PET is warranted at baseline and between month 6 and 12 of donanemab treatment. Similarly, treatment should be stopped in case of progression to a more advanced clinical AD stage.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Kisunla was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

IMPORTANT WARNING for the use of KISUNLA: Amyloid-related Imaging Abnormalities

Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is often asymptomatic, although serious and life-threatening events can occur. Furthermore, ARIA may occur during the entire duration of treatment, and events can also recur. Symptoms may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E. Systemic lysis with a thrombolytic must not be carried out during treatment with donanemab.

ApoE ε4 carriers

KISUNLA is not indicated in apolipoprotein Eε4 (ApoE ε4) homozygous patients. Approximately 15% of Alzheimer's disease patients are apolipoprotein E ε4 (ApoE ε4) homozygotes and when treated with this class of medications, including KISUNLA, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers (see section Warnings and precautions). Testing for ApoE ε4 status is required prior to initiation of treatment to inform the risk of developing ARIA. Prior to genotype testing, prescribers should discuss with patients the risk of ARIA across all genotypes and the implications of genetic testing results. Consider the benefit of donanemab for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with donanemab.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

KISUNLA®

Composition

Active substances

Donanemab (produced in Chinese Hamster Ovary (CHO) cells by genetic engineering).

Excipients

Citric acid
Polysorbate 80
Sodium citrate, dihydrate
Sucrose
Water for injection

Each 20 ml vial of Kisunla contains 11.5 mg of total sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (intravenous infusion).
A Kisunla 20 ml vial contains 350 mg of donanemab (17.5 mg/mL).
The solution is clear to opalescent, colourless to slightly yellow to slightly brown. The solution must not be

Indications/Uses

Kisunla is indicated for slowing the progression of symptomatic Alzheimer's disease (AD) in adult patients with proven Alzheimer's-type amyloid-beta pathology and a clinical diagnosis of mild cognitive impairment or mild dementia, who are heterozygotes or non-carriers of the apolipoprotein E ε4 (ApoE ε4) allele (see sections “Contraindications”, and “Clinical efficacy”).

Dosage/Administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of Alzheimer’s disease. The infusion of donanemab should be initiated and supervised by a healthcare professional. Prompt access to an MRI must be ensured. The treatment with donanemab has to take place under the supervision of an experienced multidisciplinary team that is trained on the diagnosis, monitoring, and treatment of ARIA and experienced in diagnosis and treatment of infusion-related reactions.

Before the start of treatment, the following must be available:
- ApoE Ɛ4 genetic testing, including appropriate genetic counseling prior to testing per the applicable national or local regulations.
- Baseline MRI-imaging (not older than 3 months, based on a standardized protocol)
- Amyloid-PET, evaluated by the Centiloid method

- Tau-PET (if available)

A Neuroimaging Manual and a Magnetic Resonance Imaging Manual for Donanemab are available below for consultation.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Beta amyloid evidence
Beta amyloid evidence consistent with AD should be confirmed using a validated test (e.g., amyloid PET).

Dosage
Administer donanemab every 4 weeks. The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, 1050 mg for the third dose (350/700/1050 mg), followed by 1400 mg every 4 weeks. This regimen is based on the pharmacokinetic and pharmacodynamic bridging data between the recommended dose studied in the Phase 3b TRAILBLAZER-ALZ 6 trial and the Phase 3 pivotal trial TRAILBLAZER-ALZ 2. It is not the schedule used for the first 3 doses in the pivotal phase 3 trial (see pharmacokinetics section and efficacy section).

Treatment duration
Treatment should be maintained until amyloid plaques are cleared as confirmed using a validated method and continued for a maximum of up to 18 months.
It should be discontinued early, as soon as a progression to a higher clinical disease stage occurs. Therefore, the cognitive status should be evaluated before initiation of therapy and afterwards every three months with a suitable, validated cognitive test procedure that reliably records the stages of Alzheimer's disease, and an assessment of the clinical symptoms should be carried out. The results must be documented in writing.
Monitoring cognition and the progression of symptoms should be carried out to evaluate whether the patient experienced a progression of the underlying disease and/or whether the clinical cause suggests, for other reasons, that Kisunla has not shown efficacy in this patient.
An amyloid-PET must be completed between month 6 and month 12 to determine the amyloid load and, if PET negativity occurs, to end the therapy. The duration of treatment is recommended to a maximum of 18 months. If PET negativity is achieved before 18 months, there is a lack of clinical response or in the individual case the next higher clinical stage of the disease is reached, treatment must be discontinued.

The benefit-risk may depend on the level of baseline tau. Numerically higher levels of efficacy have been observed in patients with low-medium tau load compared to high tau (see

section Pharmacodynamics). The results of tau PET imaging, if performed, should be taken into consideration when deciding whether or not to administer donanemab.

Monitoring and dosing interruption for amyloid-related imaging abnormalities

Access to magnetic resonance imaging (MRI) must be ensured throughout treatment with Kisunla. Obtain baseline (within 3 months) MRI prior to initiating treatment. Perform an MRI prior to the second infusion, prior to third infusion, prior to the fourth infusion, and prior to the seventh (month 6). An additional MRI at one year of treatment (prior to the twelfth dose) in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and/or patients with previous ARIA events in treatment, should be performed. If patients report symptoms suggestive for ARIA, at any time of treatment a clinical examination including MRI imaging may take place.
In the Study TRAILBLAZER-ALZ 2 protocol (AACI), FLAIR sequence on MRI was recommended to detect ARIA-E, while T2* gradient-recalled echo was recommended to detect ARIA-H. Susceptibility-weighted imaging is also acceptable to detect ARIA-H.

The recommendations for dosing interruptions for patients with amyloid-related imaging abnormalities-oedema/effusions (ARIA E) and haemorrhage/hemosiderin deposition (ARIA-H) are provided in Table 1.

Table 1: Dosing recommendations for patients with ARIA-E and ARIA-H

	ARIA-E and ARIA-H severity[b] on MRI		
Clinical symptom	**Mild**	**Moderate**	**Severe**
Asymptomatic	Consider suspending dosing	Suspend dosing[a]	Discontinue dosing
Symptomatic	Suspend dosing[a]	Suspend dosing[a]	Discontinue dosing

[a] Suspend until MRI demonstrates radiographic resolution (ARIA-E) or stabilization (ARIA-H) and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution (ARIA-E) or stabilization (ARIA-H) 2 to 4 months after initial identification. Resumption of dosing or discontinuation should be guided by clinical judgment. A new assessment of risk factors must be carried out before resuming treatment. Supportive therapy, including corticosteroids, may be given for ARIA-E. However, the efficacy of this treatment has not been proven.
[b] See Table 2 for ARIA MRI radiographic severity classification criteria

In the event of radiographically or clinically symptomatic severe ARIA-E or ARIA-H, treatment with donanemab should be permanently discontinued.

Donanemab should be permanently discontinued after clinically serious ARIA-E, serious ARIA-H or intracerebral haemorrhage greater than 1 cm. Treatment with donanemab should be permanently

discontinued following recurrent clinically symptomatic or radiographically moderate or severe ARIA events.

Mode of administration

Kisunla 350 mg is for intravenous infusion only. Each vial is for single use only. It should be administered over at least 30 minutes. Patients should be observed post-infusion for a minimum of 30 minutes. For instructions on dilution of the medicinal product before administration, see section “Special precautions for storage”.
Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use Kisunla if it is cloudy or there are visible particles.

Missed dose

If an infusion is missed, the missed dose should be administered at the next possible occasion. Then, resume the recommended dosing regimen every 4 weeks.

Elderly

No dose adjustment is required for the elderly (see section “Pharmacokinetics”).

Patients with impaired renal function
In the case of mild to moderate renal impairment, no dose adjustment is required. Only limited data are available for patients with severely impaired renal function (see "Pharmacokinetics").

Patients with impaired hepatic function
In case of mildly impaired hepatic function, no dose adjustment is required. There are only limited data for patients with moderately impaired hepatic function and no data for patients with severe hepatic impairment (see "Pharmacokinetics").

Patients undergoing concurrent plasmapheresis

The timing between donanemab administration and the plasmapheresis should be coordinated to minimize donanemab removal (see section “Interactions”).

Paediatric population

Kisunla is not authorised for use in the paediatric population. No dosage recommendation can therefore be given.

Contraindications

- Hypersensitivity to donanemab or to any of the excipients (see section “Composition”).

Imaging findings indicating an increased risk for ARIA or intracerebral hemorrhage, such as

- initial MRI findings of:
  - a previous intracerebral hemorrhage of more than 1 cm
  - more than 4 microhemorrhages (defined as ≤1 cm in diameter on the T2* sequence)
  - any superficial siderosis, vasogenic edema (ARIA-E) or other findings that suggest a cerebral amyloid angiopathy with associated inflammation (CAA-ri)
  - more than 2 lacunar infarctions or strokes affecting a large vascular area
  - severe subcortical hyperintensities corresponding to a Fazekas score of 3
- severe white matter disease
- Other serious pathologies that can cause cognitive impairment
- MRI evidence of non-AD dementia
- Stroke or transient ischemic attack within 1 year prior to initiation of therapy
- Poorly controlled hypertension
- Blood clotting disorder that is not adequately controlled (including a platelet count <50,000 or an International Normalized Ration [INR] >1.5 for patients not taking anticoagulants)
- Treatment with anticoagulants
- Systemic lysis with a thrombolytic
- Unstable medical findings that interfere with or may interfere with donanemab therapy.
- Any finding that could prevent a satisfactory MRI evaluation for safety monitoring.
- Active epilepsy within 1 year before starting therapy.
- Pregnancy or women of childbearing potential without adequate contraception

Warnings and precautions

Controlled access programme

In order to promote the safe and effective use of donanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme.

Educational materials

Prescribers should be familiar with the educational material prepared for the detection and management of ARIA and discuss the benefits and risks of donanemab therapy with the patient/caregiver. MRT images, signs, or symptoms of possible side effects must be explained to the patient/caregiver. Furthermore, they must be instructed when an emergency consultation must take

place. The patient information and the patient card are handed over to the patient and explained. The patient card must always be carried along.

Amyloid-related imaging abnormalities (ARIA)
Serious cases of amyloid-related imaging abnormalities (ARIA) have been observed in donanemab clinical studies and some have been fatal (see section “Undesirable effects”). ARIA includes amyloid-related imaging abnormalities-edema/effusions (ARIA-E; also known as cerebral vasogenic edema) and amyloid-related imaging abnormalities hemorrhage/hemosiderin deposition (ARIA-H; includes cerebral microhemorrhage ≤ 10 mm, and cortical superficial siderosis). Intracerebral hemorrhage greater than 1 cm has been observed. ARIA-H usually occurs in association with ARIA-E.
ARIA can be detected by magnetic resonance imaging (MRI).
ARIA-events were very common in clinical studies with donanemab. Most ARIA events were first observed within 24 weeks of initiation of treatment and were usually asymptomatic although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Most of the serious ARIA events occurred within 12 weeks of initiation of treatment. See section “Undesirable effects” for information on incidence of ARIA. Further MRI scans should be performed during treatment with donanemab. Perform an MRI at baseline (within 3 months to initiating treatment), prior to the second infusion, prior to the third infusion, prior to the fourth infusion, prior to the seventh infusion. An additional MRI at one year of treatment (prior to the twelfth infusion) in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and/or patients with previous ARIA events earlier in treatment, should be performed (see Section “Dosage/Administration”). Additional MRI is indicated if ARIA symptoms occur. Symptoms may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures. ARIA should always be considered as a possible aetiology in these neurological symptoms. Symptoms associated with ARIA usually resolve over time. After an initial ARIA event, the relapse rate at resumption of treatment is very common: 24.3% with ARIA-E and 35.9% with ARIA-H (see section «Undesirable effects»).
ARIA-E typically resolve in MRI imaging over time. ARIA-H can persist and stabilize.
Emergency access to MRI imaging must be ensured throughout the entire duration of treatment.

A careful benefit risk evaluation should be conducted prior to initiating treatment with donanemab.

MRI-Monitoring for ARIA
For recommendations on MRI-imaging see section “Dosage/Administration“.
If symptoms are suspicious of ARIA, a clinical examination and an additional MRI must be performed.

Recommendations for Dosing Interruptions in Patients with ARIA
Recommendations for dosing interruptions for patients with ARIA-E and ARIA-H are provided in section “Dosage/Administration”. In the case of serious ARIA-E, serious ARIA-H, intracerebral

hemorrhage ≥1 cm, recurrent symptomatic or radiographically moderate or severe ARIA events, treatment with donanemab should be permanently discontinued.

Radiographic Severity

The radiographic severity of ARIA associated with donanemab was classified by the criteria shown in Table 2.

Table 2: ARIA MRI Classification criteria

Aria Type			
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location < 5 cm.	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring < 10 cm.	FLAIR hyperintensity > 10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H microhaemorrhage	≤ 4 new incident microhaemorrhages	5 - 9 new incident microhaemorrhages	≥ 10 new incident microhaemorrhages
ARIA-H Superficial siderosis	1 new or expanding focal area of superficial siderosis	2 new or expanding focal areas of superficial siderosis	> 2 new or expanding focal areas of superficial siderosis

Abbreviations: FLAIR = fluid-attenuated inversion recovery; ARIA-E = amyloid-related imaging abnormalities oedema/effusions; ARIA-H = amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition

APOE ε4 Carrier Status and Risk of ARIA

Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. In the placebo-controlled (TRAILBLAZER-ALZ 2) analysis set, 16.8% (143/853) of patients in the donanemab arm were apolipoprotein E ε4 (ApoE ε4) homozygotes, 53.0% (452/853) were heterozygotes, and 29.9% (255/853) were non-carriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (55.9% on donanemab vs. 21.9% on placebo) than in heterozygotes (37.6% on donanemab vs. 14.1% on placebo) and noncarriers (24.7% on donanemab vs. 12.0% on placebo). Among patients treated with donanemab, symptomatic ARIA-E occurred in 8.4% of ApoE ε4 homozygotes compared with 6.6% of heterozygotes and 3.9% of noncarriers. Serious events of ARIA occurred in 2.8% of ApoE ε4 homozygotes, 1.8% of heterozygotes and 0.8% of noncarriers.

Intracranial hemorrhages were reported in 1.4% (10/710) of ApoE ε4 heterozygous and non-carriers after treatment with donanemab versus 0.8% (6/728) of placebo-treated AD patients in the indicated population. Intracerebral hemorrhages >1cm in diameter were observed in 0.4% (3/710) of patients treated with donanemab and in 0.3% (2/728) with placebo.

Testing for ApoE ε4 status is required prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.

A higher frequency of ARIA has also been observed in patients with pre-treatment microhaemorrhage and/or superficial siderosis.

Intracerebral Haemorrhage
In a placebo-controlled study (TRAILBLAZER-ALZ 2), intracerebral haemorrhage greater than 1 cm has been observed after treatment with donanemab in 0.4 % (3/853) compared to 0.2 % (2/874) for placebo.
Fatal events of intracerebral haemorrhage in patients taking donanemab have been observed.
In patients who received donanemab over 24 weeks in the Study TRAILBLAZER-ALZ 6 at the dosing regimen of 350/700/1050 mg, followed by 1400 mg every 4 weeks, intracerebral haemorrhage greater than 1 cm was reported in 0.9% (2/212) of patients treated with donanemab.

Other Risk Factors for Intracerebral Hemorrhage
Patients were excluded from enrollment in Study TRAILBLAZER-ALZ 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior intracerebral hemorrhage greater than 1 cm in diameter, more than 4 microhaemorrhages, more than 1 area of superficial siderosis, vasogenic edema, and severe white matter disease) (see Contraindications section). These and other lesions (aneurysm, vascular malformation) could potentially increase the risk of intracerebral hemorrhage.
The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy which has an increased risk for intracerebral haemorrhage.
Caution should be exercised when considering the use of donanemab in patients with factors that indicate an increased risk for intracerebral haemorrhage, and particularly in patients who require anticoagulant therapy, or in patients with MRI findings indicating a cerebral amyloid angiopathy.

Concomitant antithrombotic treatment
Patients who received donanemab and an antithrombotic medicine (acetylsalicylic acid, other antiplatelets, or anticoagulants), did not have an increased frequency of ARIA. The majority of exposures to antithrombotic medicines were to acetylsalicylic acid (80 %). The number of events and the limited exposure to non-acetylsalicylic acid antithrombotic medicines limit definitive conclusions about the risk of ARIA or intracerebral haemorrhage in patients taking antithrombotic medicines.
Because ARIA-H and intracerebral haemorrhage greater than 1 cm in diameter have been observed in patients taking donanemab, additional caution should be exercised when considering the administration of antithrombotics to a patient already being treated with donanemab. The use of concomitant aspirin and other antiplatelet therapy is permitted.

Because ARIA can cause focal neurologic deficits similar to those observed in an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA. Systemic lysis with

a thrombolytic as well as treatment with anticoagulants must not be carried out during therapy with donanemab (see section „Contraindications“).

Individual benefit-risk based on tau pathology
The benefit-risk may depend on the level of baseline tau. Numerically higher levels of efficacy have been observed in patients with low-medium tau compared to high tau (see section Clinical efficacy). The clinical efficacy in patients with no or very low levels of tau has not been established. The results of tau pathology testing, if performed, should be considered in individual patient benefit-risk discussions.

Hypersensitivity reactions
Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed with administration of donanemab (see section “Undesirable effects”). Signs and symptoms of these reactions include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnea, and changes in blood pressure. These reactions may be severe or life-threatening and typically occur during infusion or within 30 minutes. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy. Donanemab is contraindicated in patients with a history of hypersensitivity to donanemab or to any of the excipients. In the event of a nonserious infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Pre-treatment with antihistamines, acetaminophen, or corticosteroids prior to subsequent dosing may be considered.

Infusion-Related Reactions,
Infusion-related reactions (IRR) and anaphylaxis have been observed with administration of donanemab (see section “Undesirable effects”). These reactions may be severe or life-threatening and typically occur during infusion or within 30 minutes. Signs and symptoms of these reactions may include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnea, and changes in blood pressure. For information on frequencies of infusion related reactions see section “Undesirable effects”.
If serious infusion-related reactions or anaphylaxis occur, discontinue administration of donanemab immediately and initiate appropriate treatment. After an infusion-related reaction of grade 3 or higher that does not improve or regress after treatment, therapy with donanemab must be permanently stopped.

In the event of a nonserious infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated.

If there are signs of tissue damage as part of a hypersensitivity reaction (e.g. arthritis, glomerulonephritis or mononeuritis multiplex), therapy with donanemab must be permanently discontinued.

Immunogenicity
In placebo-controlled clinical trials, 88.1% of patients treated with donanemab developed antibodies to donanemab (anti-drug antibodies, ADA). In all of these patients, it was neutralizing antibodies. All patients with IRR had ADA. A higher ADA titer was associated with an increased incidence of IRR and infusion-related hypersensitivity.

Patients excluded from the clinical study program
Patients with Down syndrome may be associated with a higher rate of CAA (cerebral amyloid angiopathy) and ARIA events. Patients with Down syndrome have not been studied in clinical trials with donanemab. The safety and efficacy of donanemab in these patients is not known.

Sodium
This medicinal product contains 11.5 mg sodium per vial of 350 mg Donanemab (20 ml) and 46 mg sodium per 1‘400 mg dose, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

No formal drug interaction studies have been performed with donanemab. No pharmacokinetic drug interactions are expected based on the characteristics of donanemab.
A concomitant use of donanemab and intravenous immunoglobulins, plasmapheresis, or immunoadsorption may result in a reduced efficacy of donanemab. The time between these applications should be coordinated to minimize the elimination of donanemab. After administration of donanemab, a wait of at least nine weeks should be applied before such a therapy is carried out. After previous treatment with intravenous immunoglobulins, the time interval to the donanemab administration should be three weeks. In patients who regularly need one of these therapies, the therapeutic decision should consider this interaction with foresight and needs a decision according to medical necessity (see section “posology/use”).

Pregnancy, lactation

Women of childbearing potential

The pregnancy status of women of childbearing potential should be checked before initiating treatment with donanemab. Women of childbearing potential must use effective contraception during and up to two months after treatment.

Pregnancy

There are no available data on the use of donanemab in pregnant women. No animal embryofetal development studies have been conducted with donanemab. Human IgG is known to pass through the placenta after the first trimester of pregnancy. So, donanemab can potentially be transferred from the mother to the developing fetus. Use of donanemab is not recommended during pregnancy.

Lactation

Lactation studies have not been conducted in animals. Human immunoglobulin G (IgG) is known to be transferred into human milk; therefore, donanemab may be transmitted from the mother to the breastfed infant. The risks for a breastfed infant are unknown. Administer donanemab to nursing women only if the potential benefit outweighs the potential risk for the mother and the infant.

Fertility

There are no data on the effect of donanemab on human fertility. No animal studies have been performed to test donanemab for potential fertility impairment.

Effects on ability to drive and use machines

There have been no studies conducted to determine the effects of donanemab on the ability to drive and use machines.

Undesirable effects

Summary of safety profile

In a placebo-controlled study (TRAILBLAZER-ALZ 2, phase 3) in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease (AD), 853 adults received at least one dose of donanemab. Of these,710 patients were in the indicated population (ApoE ε4 heterozygotes or non-carriers): 29.9% (255/853) non-carriers, 53.0% (452/853) heterozygotes, and 0.4% (3/853) with genotype unknown.

The most frequently reported undesirable effects in the indicated population were ARIA-E (20.6%), ARIA-H (27.6%), headache (14.6%), and infusion-related reactions (8.3%). The most important serious undesirable effects were serious ARIA-E (1.3%), serious ARIA-H (0.3%), and serious

hypersensitivity, including infusion-related reactions (0.4%). Anaphylaxis was uncommonly reported (0.4%) (see section “warnings and precautions”).

List of adverse reactions in the overall population

Adverse reactions from clinical studies are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing severity. The corresponding frequency category for each reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Nervous system Disorders

Very common: ARIA-E[a,b] (24.0%), ARIA-H[a,b,c] (31.4%), headache (14.0%)

[a] As assessed by MRI
[b] Possible associated symptoms: Headaches, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, seizures
[c] Includes: Microhaemorrhage and superficial siderosis

Uncommon: intracerebral hemorrhage (> 1cm) [d]

[d] Includes: cerebral hemorrhage and hemorrhagic stroke

Gastrointestinal disorders

Common: Nausea, vomiting

Immune system disorders

Common: Hypersensitivity

Uncommon: Anaphylactic reaction

General disorders and administration site conditions

Common: Infusion-related reactions[e], Hypersensitivity

Uncommon: Anaphylactic raction

[e] includes Erythema, chills, nausea, vomiting, sweating, headache, chest tightness, shortness of breath, and changes in blood pressure

Description of selected undesirable effects

Amyloid-related Imaging Abnormalities and Intracerebral Hemorrhage in the indicated population

TRAILBLAZER-ALZ-2

ARIA (ARIA-E or ARIA-H) was observed in 33% (234/710) of patients (heterozygotes or non-carriers) treated with donanemab, compared to 13.5% (98/728) of patients on placebo in the placebo-controlled study (Dosing regimen 700 mg donanemab every 4 weeks for the first 3 doses, afterwards 1400 mg donanemab every 4 weeks). Symptomatic ARIA occurred in 6.1% of patients on

donanemab. Clinically serious ARIA events were reported for 1.4% (10/710) of patients treated with donanemab. Three participants (0.4%) had serious ARIA and subsequently died.

ARIA-E (*amyloid-related imaging abnormalities-edema/effusions*,also known as cerebral vasogene edema) was observed in 20.6% of patients treated with donanemab compared with 1.8% of patients on placebo. The maximum radiographic severity for ARIA-E was mild in 6.2% of patients, moderate in 12.7% of patients, and severe in 1.4% of patients. The median time to radiological resolution of ARIA-E was approximately 8.3 weeks. Symptomatic ARIA-E was reported for 5.6% of patients treated with donanemab in placebo-controlled clinical trials.
Clinical symptoms associated with ARIA-E resolved in approximately 80.0% of patients, with a median time to clinical symptom resolution of 3.9 weeks.
In heterozygotes, ARIA-E was observed in 23.2% (105/452) of patients treated with donanemab, compared to 2.1% (10/474) of patients on placebo. The maximum radiographic severity for ARIA-E in heterozygotes treated with donanemab was mild in 6.6% of patients, moderate in 14.2% of patients, and severe in 2.0% of patients. Symptomatic ARIA-E was reported for 6.6% of heterozygotes treated with donanemab. In noncarriers, ARIA-E was observed in 15.7% (40/255) of patients treated with donanemab, compared to 0.8% (2/250) of patients on placebo. The maximum radiographic severity for ARIA-E in noncarriers treatment with donanemab was mild in 5.1% of patients, moderate in 10.2% of patients, and severe in 0.4% of patients. Symptomatic ARIA-E was reported for 3.9% of noncarriers treated with donanemab.

ARIA-H (*amyloid-related imaging abnormalities hemorrhage/hemosiderin*, these include cerebral microhaemorrhages and cortical superficial siderosis) can occur spontaneously in patients with AD independent of treatment. ARIA-H was observed in 27.6% of patients treated with donanemab compared with 12.2% of patients on placebo. The maximum radiographic severity for ARIA-H was mild in 14.4% of patients, moderate in 5.5% of patients, and severe in 7.6% of patients. Symptomatic ARIA-H was reported for 1.1% of patients treated with donanemab compared with 0.3% of patients on placebo. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 12.4% of donanemab-treated patients compared to 11.5% on placebo.

In heterozygotes, ARIA-H was observed in 32.5% (147/452) of patients treated with donanemab, compared to 12.9% (61/474) of patients on placebo. The maximum radiographic severity for ARIA-H in heterozygotes was mild in 15.0% of patients, moderate in 7.7% of patients, and severe in 9.5% of patients. Symptomatic ARIA-H was reported for 1.5% of heterozygotes treated with donanemab compared with 0.2% of patients on placebo. Isolated ARIA-H was observed in 14.2% of donanemab-treated heterozygotes compared to 11.2% of heterozygotes on placebo. In noncarriers, ARIA-H was observed in 18.8% (48/255) of patients treated with donanemab, compared to 11.2% (28/250) of

patients on placebo. The maximum radiographic severity for ARIA-H in noncarriers was mild in 12.9% of patients, moderate in 1.6% of patients, and severe in 4.3% of patients. Symptomatic ARIA-H was reported for 0.4% of noncarriers treated with donanemab compared with 0.4% of patients on placebo. Isolated ARIA-H was observed in 9.0% of donanemab-treated noncarriers compared to 11.2% of noncarriers on placebo.

The majority of first ARIA radiographic events in the placebo-controlled studies occurred early in treatment (within 24 weeks of initiation of treatment), although ARIA can occur at any time during treatment and patients can have more than one episode.

Intracerebral haemorrhage greater than 1 cm was observed in 0.4% (3/710) of donanemab-treated patients and in 0.3 % (2/728) in placebo treated patients. Additionally, in a participant with baseline superficial siderosis treated with donanemab in the pivotal study, fatal ARIA-H was reported with concurrent intracerebral haemorrhage.

TRAILBLAZER-ALZ 6

In Study TRAILBLAZER-ALZ 6 at 76 weeks, ARIA (ARIA-E or ARIA-H) was observed in 28.8% of patients (heterozygotes or non-carriers) treated with donanemab at the dosing regimen of 350/700/1050 mg, followed by 1400 mg every 4 weeks (n=191). Clinically serious ARIA events were reported for 0.5% of patients on donanemab.
ARIA-E was observed in 14.7% of patients treated with donanemab. The maximum radiographic severity for ARIA-E was mild in 5.8% of patients, moderate in 8.9% of patients, and severe in 0% of patients. The median time to radiological resolution of ARIA-E was approximately 8.4 weeks. Symptomatic ARIA-E was reported for 3.1% of patients treated with donanemab. Clinical symptoms associated with ARIA-E resolved in approximately 83.3% of patients, with a median time to symptom resolution of 1.6 weeks.

ARIA-H was observed in 25.1% of patients treated with donanemab. The maximum radiographic severity for ARIA-H was mild in 18.3% of patients, moderate in 3.1% of patients, and severe in 3.7% of patients. Symptomatic ARIA-H was reported for 0.5% of patients treated with donanemab.

Intracerebral haemorrhage was reported in 1% (2/191) of ApoE ε4 heterozygotes and non-carrier patients after treatment with donanemab. Of these, serious intracerebral haemorrhage greater than 1 cm was observed in 0.5% (1/191) of donanemab-treated patient. This participant with ARIA-E was treated with a thrombolytic for stroke-like symptoms and had a fatal intracerebral hemorrhage.

Infusion-related reactions

In *TRAILBLAZER-ALZ-2* infusion reactions were observed in 8.7% of patients treated with donanemab compared to 0.5% on placebo. Anaphylaxis was uncommonly reported (0.4%). Serious infusion reactions or hypersensitivity occurred in 0.4% of patients treated with donanemab compared to 0.1% on placebo. The majority of infusion reactions and hypersensitivity reactions have mostly occurred within the first 4 doses of donanemab, although they can occur at any time.

Treatment discontinuations occurred with donanemab due to IRR (3.6%), hypersensitivity (0.5%), and anaphylaxis (0.4%), but not with placebo.

A re-exposure resulted in a subsequent IRR/hypersensitivity in 47.5% of patients, and the severity and type of symptoms were thereby usually comparable to the first event.

Premedication before a subsequent therapy did not affect IRR.

Immunogenicity
In placebo-controlled clinical studies, 88.1% of donanemab-treated patients developed anti-drug antibodies (ADA) and all of the patients with ADA had neutralizing antibodies. Although donanemab exposure decreased with increasing ADA titer, the development of ADA was not associated with loss of clinical efficacy of donanemab. All patients reporting infusion-related reactions had ADA.

Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Single doses up to 40 mg/kg (approximately 2800 mg in a 70 kg person) have been administered. ARIA-E occurred in 2 out of 4 patients administered this dose and resolved. In case of an overdose, initiate supportive therapy.

Properties/Effects

ATC code

ATC code: N06DX05
Pharmacotherapeutic group: Nervous system, psychoanaleptics, anti-dementia drugs, other antidementia drugs.

Donanemab is a recombinant monoclonal humanised antibody produced in Chinese Hamster Ovary (CHO) cells.

Mechanism of action

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble, pyroglutamate-modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present only in brain amyloid plaques. Donanemab binds to N3pG Aβ and aids plaque removal through microglial-mediated phagocytosis.

Pharmacodynamics

Reductions in cerebral amyloid plaques, as measured by amyloid positron emission tomography (PET), were observed among patients receiving donanemab. Donanemab reduced tau pathophysiology, as measured by plasma P-Tau217.
The percentage of donanemab treated patients who achieved amyloid clearance (that is, less than 24.1 Centiloids) in Study TRAILBLAZER-ALZ 2 was 32.5 % at week 24, 69.5 % at week 52 and 80.8 % at week 76 in the indicated population.

In study TRAILBLAZER-ALZ 2, the difference between donanemab and placebo in the change from baseline amyloid level at week 76 was statistically significant in the indicated population (-89.24 Centiloids).

In Study TRAILBLAZER-ALZ 6, similar amyloid plaque reduction was observed at week 24 for the dosing regimen of 350/700/1 050 mg, then 1 400 mg every 4 weeks thereafter, when compared with the dosing regimen of 700 mg for the first three infusions, then 1 400 mg every 4 weeks thereafter, studied in the pivotal study.

Donanemab exposure decreased with increasing ADA titre. Amyloid beta reduction was found irrespective of ADA titre. No association was observed between the presence of ADA and outcomes on the iADRS and CDR-SB (see also Warnings and precautions and Undesirable effects sections).

Clinical efficacy

The safety and efficacy of donanemab were evaluated in a Phase 3 (TRAILBLAZER-ALZ 2) study. This was a double-blind, placebo-controlled, parallel-group study. It was conducted in patients at an age between 60 and 85 years, with early symptomatic AD (Mild Cognitive Impairment (MCI) or mild dementia due to AD and an MMSE-value of 20 to inclusive 28. Patients had to have evidence of amyloid beta pathology confirmed by amyloid PET scan. The participants also had evidence of pathologic tau deposition on a flortaucipir PET scan.

Supportive data are available from a phase 2 study (TRAILBLAZER-ALZ) with a comparable design. The dosing regimens used in these studies are different from the approved dosing regimen (see section “Pharmacokinetics”).

For the safety analysis, patients were followed for up to 76 weeks or end of treatment plus 57 days.

TRAILBLAZER-ALZ 2 was originally designed as a phase 2 Study and later converted to phase 3 Study. Main amendments included: Addition of a titration period of 700 mg for the first three doses; adaptations from a phase 2 to a phase 3 Study including increase in the sample size and change in the primary analysis from “CDR-SB in overall population or intermediate tau population” to “iADRS in the intermediate tau population”; addition of a long-term extension phase to further evaluate the efficacy and safety of donanemab over time.

Phase 3 Study TRAILBLAZER-ALZ 2
In this study, 1736 patients were randomized 1:1 to receive 700 mg of donanemab every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks via intravenous infusion (N=860) or placebo (N=876) for a total of up to 72 weeks. The study included a double-blind extension period of 78 weeks duration. Dosing was continued until study completion or amyloid plaque was cleared, defined as demonstrating a plaque level of less than 25 Centiloids for two consecutive amyloid PET scans or a single PET scan demonstrating a plaque level of less than 11 Centiloids.

Additionally, dose suspension was allowed for treatment-emergent ARIA. If patients were already on symptomatic treatment (acetylcholinesterase inhibitors, AChEI) and/or the N-Methyl-D-aspartate inhibitor, memantine) at study entry, these treatments could continue. Symptomatic treatments could be added or changed during the study, at the investigator’s discretion. The study excluded patients with preexisting ARIA-E, greater than 4 microhaemorrhages, more than 1 area of superficial siderosis, any intracerebral haemorrhage >1 cm or severe white matter disease. At baseline, mean age was 73 years, with a range of 59 to 86 years, with a mean (SD) baseline weight of 71.7 kg (15.7), with a gradual and progressive change in memory function for at least 6 months and a Mini–Mental State Examination (MMSE) score of 22.29 (3.88). 57.4% of the participants were female, 91.5% were White, 5.7% were of Hispanic or Latino ethnicity, 6.0% were Asian, and 2.3% were Black. 80.0% of patients were enrolled in North America, 13.9% in Europe, 5.1% in Japan and 1.0% in Australia. 29% were ApoEε 4 non-carriers, 54% heterozygotes, and 17% homozygotes.

55.6% of patients were on AChEI, and 20.3% on memantine. 61% of patients were on either AChEI or memantine use.

The average (mean, SD) of amyloid in the Centiloids at baseline was 102.5 (34.5).

There were two primary analysis populations based on tau PET imaging at screening with flortaucipir: 1) low-medium tau level population (total percentage 68.2%), and 2) combined population with low-medium as well as high tau levels (total percentage 31.8%).

Overall, 24.7% of patients discontinued treatment early (29.3% with Donanemab, 20.1% with placebo).

The primary efficacy endpoint was change in cognition and function as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is an integrated assessment of cognition and daily function comprised of items from the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13, score 0-85) and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL, score 0-59) scale, measuring the core domains across the AD clinical continuum. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints included Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB), ADAS-Cog13, ADCS-iADL.

Important findings from the study for the indicated population are presented in Table 3 below.

In the indicated population, 717 participants were randomized to donanemab, 414were female and 303 were male, and 70 were <65 years old, 320 were 65-74 years old, and 327 were >= 75 years old.

In the indicated population, 730 participants were randomized to placebo, 426 were female and 304 were male, and 66 were <65 years old, 311 were 65-74 years old, and 353 were >= 75 years old

Table 3: Efficacy analysis results of donanemab study TRAILBLAZER ALZ 2 at week 76, in the indicated population (ApoE ε4 heterozygotes and non-carriers)

Clinical Endpoint	ApoE ε4 heterozygotes and noncarriers	
	Dona	Placebo
iADRS (NCS)		
Mean baseline (SD)	104.66 (14.12)	103.83 (14.03)
LS Mean change from baseline	-10.21 (0.57)	-13.59 (0.55)
Difference from placebo (95 % CI)	3.38 (1.83, 4.92)	
Female		
Mean baseline (SD)	104.92 (14.02)	103.75 (13.38)
LS Mean change from baseline	-10.98 (0.76)	-14.77 (0.72)
Difference from placebo (95 % CI)	3.80 (1.77, 5.83)	
Male		
Mean baseline (SD)	104.32 (14.26)	103.95 (14.87)
LS Mean change from baseline	-9.18 (0.87)	-11.92 (0.85)
Difference from placebo (95 % CI)	2.73 (0.36, 5.10)	
<65 years old		
Mean baseline (SD)	105.19 (15.46)	107.14 (14.19)
LS Mean change from baseline	-12.74 (1.77)	-14.21 (1.86)
Difference from placebo (95 % CI)	1.47 (-3.51, 6.45)	
65-74 years old		
Mean baseline (SD)	106.05 (12.88)	105.09 (13.59)

LS Mean change from baseline	-9.33 (0.86)	-13.69 (0.83)
Difference from placebo (95 % CI)	4.35 (2.03, 6.68)	
≥ 75 years old		
Mean baseline (SD)	103.20 (14.83)	102.11 (14.19)
LS Mean change from baseline	-10.48 (0.86)	-13.37 (0.80)
Difference from placebo (95 % CI)	2.89 (0.61, 5.17)	
CDR-SB (MMRM)		
Mean baseline (SD)	3.96 (2.10)	3.94 (2.04)
LS Mean change from baseline	1.67 (0.11)	2.43 (0.10)
Difference from placebo (95 % CI)	-0.77 (-1.04, -0.49)	
Female		
Mean baseline (SD)	4.03 (2.11)	3.97 (1.98)
LS Mean change from baseline	1.66 (0.12)	2.49 (0.15)
Difference from placebo (95 % CI)	-0.83 (-1.20, -0.45)	
Male		
Mean baseline (SD)	3.87 (2.08)	3.89 (2.13)
LS Mean change from baseline	1.48 (0.15)	2.15 (0.14)
Difference from placebo (95 % CI)	-0.66 (-1.07, -0.25)	
<65 years old		
Mean baseline (SD)	3.81 (2.05)	3.80 (1.54)
LS Mean change from baseline	2.53 (0.40)	2.81 (0.31)
Difference from placebo (95 % CI)	-0.28 (-1.19, 0.63)	
65-74 years old		
Mean baseline (SD)	3.78 (1.88)	3.66 (1.92)
LS Mean change from baseline	1.46 (0.14)	2.55 (0.16)
Difference from placebo (95 % CI)	-1.09 (-1.50, -0.68)	
≥ 75 years old		
Mean baseline (SD)	4.17 (2.30)	4.21 (2.19)
LS Mean change from baseline	1.48 (0.15)	2.04 (0.16)
Difference from placebo (95 % CI)	-0.56 (-0.96, -0.16)	
ADAS-Cog$_{13}$ (NCS)		
Mean baseline (SD)	28.43 (8.91)	29.00 (8.93)
LS Mean change from baseline	5.37 (0.31)	7.06 (0.29)
Difference from placebo (95 % CI)	-1.69 (-2.52, -0.86)	
Female		
Mean baseline (SD)	28.40 (9.15)	29.45 (8.61)
LS Mean change from baseline	5.59 (0.40)	7.20 (0.39)
Difference from placebo (95 % CI)	-1.61 (-2.71, -0.52)	
Male		
Mean baseline (SD)	28.46 (8.60)	28.40 (9.32)
LS Mean change from baseline	5.09 (0.47)	6.88 (0.45)
Difference from placebo (95 % CI)	-1.79 (-3.07, -0.52)	
<65 years old		
Mean baseline (SD)	27.82 (9.67)	27.11 (9.40)
LS Mean change from baseline	8.34 (0.94)	7.90 (0.96)

Difference from placebo (95 % CI)	0.44 (-2.19, 3.06)	
65-74 years old		
Mean baseline (SD)	27.82 (8.80)	28.74 (9.39)
LS Mean change from baseline	4.86 (0.45)	7.51 (0.44)
Difference from placebo (95 % CI)	-2.66 (-3.89, -1.42)	
≥ 75 years old		
Mean baseline (SD)	29.16 (8.83)	29.59 (8.36)
LS Mean change from baseline	5.21 (0.46)	6.47 (0.43)
Difference from placebo (95 % CI)	-1.26 (-2.49, -0.04)	

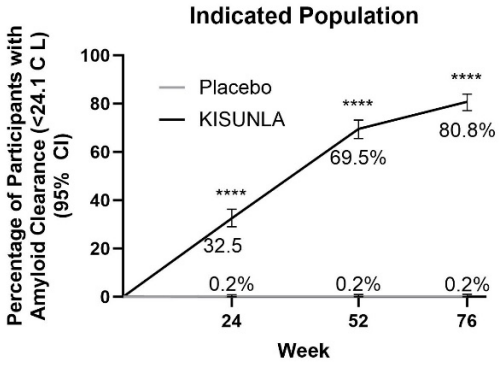
Abbreviations: ApoE ε4 = allele subtype 4 of the gene coding for apolipoprotein Class E; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; Dona=donanemab; iADRS = integrated Alzheimer's Disease Rating Scale; LS = Least-Square; MMRM = mixed model for repeated measures; SD = standard deviation.

Biomarkers

The percentage of donanemab treated patients with amyloid clearance (that is, less than 24.1 Centiloids or visually negative on an amyloid PET scan) in Study TRAILBLAZER-ALZ 2 is represented in Figure 2.

A reduction in plasma P-tau217 (log10) was observed with donanemab compared to placebo. In the low-medium tau population (498 participants received donanemab and 494 participants placebo), LS mean change difference ± SE was -0.19±0.012 and -0.26±0.015 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). Consistent with this, in the combined population, the mean change (log LS mean ± SE was -0.17±0.011 and -0.23±0.013 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points).

Figure 2: Percentage of donanemab treated patients in the indicated population achieving amyloid plaque clearance as monitored by amyloid PET over 76 weeks in study TRAILBLAZER-ALZ 2.



High tau population in the indicated population

In the high-tau population (218 participants received donanemab and 235 participants placebo), donanemab slowed clinical decline by 8% (1.55±1.66 [p=0.351]) on iADRS, and 18% (-0.60±0.28 [p=0.032]) on CDR-SB, at Week 76 compared with placebo.

Phase III Study TRAILBLAZER-ALZ 6

The donanemab dosing regimen of 350/700/1050 mg, followed by 1400 mg every 4 weeks was evaluated in a phase IIIb multicenter, randomized, double-blind, study in adults with early symptomatic AD (MCI due to AD or mild AD dementia, MMSE score 20 to 28 inclusive) and evidence of amyloid beta pathology confirmed by amyloid PET scan.

843 patients were randomized at a 1:1:1:1 ratio into four donanemab dosing regimens for a total of 72 weeks, 700 mg for the first three infusions, then 1400 mg every 4 weeks thereafter (n=207), or one of the three alternative dosing regimens (including the dosing regimen 350/700/1050 mg, followed by 1400 mg every 4 weeks; n=212), with the same total drug administered in all regimens.

The primary endpoint of the study was the proportion of participants with any occurrence of ARIA-E by week 24. The results showed that 14% of patients receiving 350/700/1050 mg, followed by 1400 mg every 4 weeks, compared with 24% receiving 700/700/700 mg, followed by 1400 mg every 4 weeks, experienced any occurrence of ARIA-E by week 24, a 41% lower relative risk. Similar amyloid plaque reductions were seen at 24 weeks in all dosing regimens.

Pharmacokinetics

The pharmacokinetics (PK) of KISUNLA were characterized using data following single or multiple dosing. Accumulation <1.3-fold occurs with every 4-week dosing; steady-state exposures are achieved after a single dose. In single doses from 350 mg to 2800 mg (~2 times the recommended dosage of 1400 mg for 70 kg of body weight), and multiple 350 and 1400 mg doses, exposures (Cmax and AUC) increased proportionally. Similar exposure was observed for dosing regimen

350/700/1050 mg, then 1400 mg every 4 weeks compared with the dosing regimen that established clinical efficacy (700 mg for the first three infusions, then 1400 mg every 4 weeks).

PK/PD bridging between the recommended titration studied in the Phase 3 TRAILBLAZER-ALZ 6 trial and the titration studied in the Phase 3 pivotal trial TRAILBLAZER-ALZ 2 is suppor2ed. The observed cumulative doses (0 to 12 weeks), cumulative $AUC_{(0\text{-}12\ weeks)}$, and average concentration at steady state ($C_{av,ss}$) for the recommended regimen and the regimen studied in the Phase 3 pivotal trial of Study TRAILBLAZER-ALZ 6 were similar and overlapping. Exposure ($C_{av,ss}$) noninferiority, defined as the lower bound of 90% confidence interval for the geometric mean ratio ≥0.8 for recommended titration compared with the titration studied in the Phase 3 pivotal trial, was demonstrated. Supportive data demonstrated similar observed PD (amyloid plaque reduction) at Weeks 24 and 52.

Absorption

Donanemab is for intravenous administration only.

Distribution

Following intravenous dosing, donanemab undergoes biphasic elimination. The central volume of distribution is 3.36 L with 18.7% inter-individual variability. Peripheral volume of distribution is 4.83 L, with 93.9% inter-individual variability.

Metabolism

Donanemab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous IgG, hence there is no metabolic inhibition or induction of enzymatic pathways. Donanemab is not expected to be metabolized by the cytochrome P450 families of enzymes responsible for the metabolism and elimination of small molecules. Therefore, active metabolites are not expected.

Elimination

The half-life of donanemab is approximately 12.1 days. Donanemab clearance was 0.0255 L/h (24.9% inter-individual variability).

Kinetics in specific patient groups

Age, gender and body weight

The PK of donanemab was not affected by age, sex, or race, based on a population PK analysis. While body weight was found to influence both clearance and volume of distribution, the resulting changes do not suggest a need for dose adjustment.

Renal and hepatic impairment

Renal and hepatic impairment did not affect the PK of donanemab based on population PK analysis.

Preclinical data

Safety pharmacology / toxicity after repeated dose

Based on conventional repeated dose studies, the preclinical data do not reveal any particular hazards for humans. No studies have been performed to test donanemab for potential of carcinogenicity, genotoxicity, or fertility impairment.

Other information

Incompatibilities

Not applicable.

Influencing diagnostic methods

Not known

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Unopened vial
Store in a refrigerator (2 °C to 8 °C) until time of use.
May be stored unrefrigerated for up to 3 days at room temperature (20 °C-25 °C).
Keep the vial in the outer carton in order to protect from light.
Do not freeze or shake.
Keep out of the reach of children

Diluted solution for infusion
The chemical and physical stability of the diluted solution has been demonstrated for a period of 72 hours at 2°C to 8°C or for 12 hours at room temperature (20°C to 25°C)

Storage times include the duration of infusion.

From a microbiological point of view, the diluted solution should be used immediately. If the solution is not used immediately, the storage conditions and duration of storage are the responsibility of the user and should not normally be more than 24 hours at 2 to 8°C, unless the dilution has taken place in controlled and validated aseptic conditions. If dilution has taken place in controlled and validated aseptic conditions, the donanemab dosing solution may be stored for up to 72 hours at 2°C to 8°C or for up to 12 hours at room temperature (20°C to 25°C).

Do not freeze the donanemab dosing solution.

Instructions for handling

Kisunla solution for infusion should be prepared and administered by a qualified healthcare Professional using aseptic technique.

Allow donanemab to equilibrate to room temperature for approximately 30 minutes before preparation.

Inspect the content of the vial for particulate matter and discoloration. If particulate matter or discolorations are identified, discard the vial.

After dilution and preparation in sodium chloride 9 mg/mL (0.9%) solution for injection, donanemab is administered as an intravenous infusion:

- Calculate the required volume of donanemab needed to prepare the infusion solution:
  For 350 mg of donanemab: 20 mL
  For 700 mg of donanemab: 40 mL
  For 1050 mg of donanemab: 60 mL
  For 1400 mg of donanemab: 80 mL
- Withdraw required volume of donanemab and further dilute into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, to a final concentration of 4 mg/mL to 10 mg/mL. Use only sodium chloride 9 mg/mL (0.9%) solution for injection for dilution.
- Gently invert the infusion bag to mix.
- Administer diluted solution over a period of at least 30 minutes.
- Administer the entire infusion solution.

Flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection at the end of the infusion.

Observe the patient post-infusion for a minimum of 30 minutes.

Authorisation number

69523 (Swissmedic)

Packs

Kisunla, concentrate for solution for infusion (intravenous infusion) with 350 mg donanemab in 20 mL: 1 vial (A)

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE.

Date of revision of the text

January 2026

Neuroimaging Manual for Donanemab

Abbreviations and Definitions

Term	Definition
2D	two-dimensional
3DT1	three-dimensional T1-weighted
Aβ	amyloid beta
AD	Alzheimer's disease
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
CL	Centiloid
DWI	Diffusion Weighted Imaging
FLAIR	Fluid-Attenuated Inversion Recovery
FORE	Fourier rebinning
GRE	Gradient Echo
IV	intravenous
MNI	Montreal Neurologic Institute
MRI	magnetic resonance imaging
MUBADA	multiblock barycentric discriminant analysis
NFT	neurofibrillary tangle
OSEM	ordered subset expectation maximisation
PET	positron emission tomography
RAMLA	row-action maximum likelihood algorithm
ROI	region of interest
SUVr	standardised uptake value ratio

Introduction

Amyloid plaques (extracellular, insoluble aggregations of Aβ peptides) and NFTs (hyperphosphorylated, misfolded tau aggregates) are key indicators of AD and are crucial for the neuropathologic diagnosis of AD (Hyman et al. 2012; Jack et al. 2024). Accumulation of Aβ peptide in the brain parenchyma is the earliest sign of AD and may lead to subsequent pathologic changes,

including tauopathy (Jack et al. 2024). In some cases, tau pathology can occur independently of Aβ accumulation, suggesting the existence of both amyloid-independent and amyloid-facilitated tauopathies (van der Kant et al. 2020).

Donanemab binds to the N-terminal truncated form of β-amyloid and aids plaque removal through microglial-mediated phagocytosis (DeMattos et al. 2012). Therefore, measurement of both amyloid and tau pathologies before and after donanemab treatment was included in clinical trials of donanemab (Mintun et al. 2021; Sims et al. 2023). PET constitutes a reference tool to visualise and quantify both Aβ plaque and NFT deposition in vivo.

MRI serves 2 main purposes for those undergoing assessment and treatment with amyloid-targeting therapies (By et al. 2025):

evaluation for exclusionary findings, and

safety monitoring to determine treatment-emergent neuroimaging abnormalities, in particular ARIA by amyloid-targeting therapies.

Based on these considerations, the TRAILBLAZER-ALZ 2 neuroimaging programme included amyloid and tau PET as well as several MRI measurements (Table 1). It should be noted that specific analyses of all PET and MRI scans, including visual and quantitative assessments, were conducted by centralised PET and MRI vendors, respectively.

A screen or baseline scan was obtained prior to treatment for determining eligibility or for monitoring treatment. *APOE* genotyping was also performed via blood sampling at screening unless country-specific laws and regulations prohibited this type of testing.

This neuroimaging manual highlights key elements of PET and MR imaging procedures implemented in the TRAILBLAZER-ALZ 2 trial. Additional details were specified in imaging vendors' standard operating procedures and site imaging manuals.

Table 1. Role of Imaging Modalities in TRAILBLAZER-ALZ 2 Trial

Modality		Screening/baseline	Follow-up
Amyloid PET		Presence of amyloid pathology, ≥37 CL (Q)	Amyloid plaque level and change in brain amyloid plaque level from baseline (Q)
Tau PET		Presence of tau pathology (VQ)	Change in brain amyloid plaque level from baseline (Q)
MRI	3DT1	Anatomical reference image for tau PET quantification	Change in volumetric MRI measures from baseline (Q)
	2D Axial Fluid-Attenuated Inversion Recovery (FLAIR)	Detection of cerebral oedema and white matter lesions (V)	Detection of cerebral oedema and white matter lesions (V)
	2D Axial T2* Gradient Echo (GRE)	Detection of haemosiderin deposits and other types of haemorrhagic lesions (V)	Detection of haemosiderin deposits and other types of haemorrhagic lesions (V)
	2D Axial T2 Turbo/Fast Spin Echo	Detection of white matter lesions and other MRI findings (V)	Detection of white matter lesions and other MRI findings (V)

Modality	Screening/baseline	Follow-up
2D Axial Diffusion Weighted Imaging (DWI)	Detection of acute infarcts and strokes (V)	Detection of acute infarcts and strokes (V)

Abbreviations: 2D = two-dimensional; 3DT1 = three-dimensional T1-weighted; CL = Centiloids; MRI = magnetic resonance imaging; PET = positron emission tomography; Q = quantitative assessment using specialised image processing and analysis software; V = visual assessment; VQ = visual and quantitative assessment.

Neuroimaging Manual

Amyloid PET

Amyloid PET scans with either 18F-florbetapir or 18F-florbetaben radiotracers were used to determine eligibility by assessing the participant's level of amyloid pathology. For eligible participants, follow-up amyloid PET scans were conducted at certain study visit intervals to assess

a) post-treatment amyloid level and switch donanemab treatment to placebo in a blinded procedure if the predetermined amyloid PET criteria were met, and
b) change in brain amyloid plaque deposition from baseline through Week 76.

For the 18F-florbetapir scan, the participant received a single IV bolus injection target dose of 370 MBq (10 mCi) of 18F-florbetapir followed by a saline flush and underwent a 20-minute scan (4 frames x 5 minutes) started approximately 50 minutes after injection. For the 18F-florbetaben scan, the participant received a single IV bolus injection target dose of 300 MBq (8.1 mCi) of 18F-florbetaben followed by a saline flush and underwent a 20-minute scan (4 frames x 5 minutes) started approximately 90 minutes after injection.

PET images were reconstructed using scanner-specific protocols with the following parameter selections: iterative reconstruction algorithm (FORE, OSEM or RAMLA), 3 to 6 iterations, 16 to 33 subsets. Post-reconstruction Gaussian filters of 3 to 5 mm were applied (except for Philips scanners where the 'Normal' or 'Sharp' relaxation parameter setting was used).

In the TRAILBLAZER-ALZ 2 trial, only quantitative assessment of amyloid PET images was performed.

1.1.1 Screening/Baseline Amyloid PET Scan

The 5-minute PET images were motion-corrected and then averaged into a single static image (Shcherbinin et al. 2016; Pontecorvo et al. 2019). The averaged screening/baseline amyloid PET image was spatially normalised to the reference amyloid PET template in the standard brain space (MNI space). No MR image was used to conduct quantitative assessment for eligibility.

Quantitative assessment of both 18F-florbetapir or 18F-florbetaben images in the TRAILBLAZER-ALZ 2 trial followed the most used technique of an estimation of SUVr. SUVr constitutes a ratio of the average PET signal in a neocortical composite region (target region) scaled by the average PET signal in a reference region that is typically spared of amyloid plaques, for example, cerebellum. To calculate SUVr, all target and reference ROIs were applied onto the participant's spatially normalised PET image in the MNI space. According to previously developed amyloid PET methodology, SUVr was calculated as an unweighted average of 6 cortical regions (mesial orbital frontal, anterior

cingulate, precuneus, posterior cingulate, parietal, and temporal) and used the whole cerebellum as a reference region (Joshi et al. 2015).

To harmonise amyloid level measurements conducted using different PET tracers, 18F-florbetapir or 18F-florbetaben, previously validated procedures were used to convert tracer-specific SUVr measures to a common frame of reference, the CL scale (Klunk et al. 2015). The CL scale allows interpretation of the amyloid PET SUVr according to 2 anchor points: 0 CL (average amyloid PET signal in young [≤45 years], cognitively unimpaired people) and 100 CL (average amyloid PET signal in patients with typical mild-to-moderate AD) (Klunk et al. 2015; Iaccarino et al. 2025). Different transformation formulas were used to convert 18F-florbetapir and 18F-florbetaben SUVr measures to CL units, enabling implementation of identical CL thresholds for both amyloid PET radiotracers.

In the TRAILBLAZER-ALZ 2 trial, eligible participants had amyloid pathology (≥37 CL) assessed with 18F-florbetapir or 18F-florbetaben (Sims et al. 2023).

1.1.2 Follow-up Amyloid PET Scan

Follow-up amyloid PET scans in the TRAILBLAZER-ALZ 2 trial were conducted at 24, 52, and 76 weeks. Analogously to the screening/baseline analyses, the follow-up amyloid PET images were motion-corrected and averaged. However, the spatial normalisation to the reference amyloid PET template was conducted differently to assess

a) post-treatment amyloid level and switch donanemab treatment to placebo in a blinded procedure if the predetermined amyloid PET criteria were met, and
b) change in brain amyloid plaque deposition from baseline through Week 76.

For the post-treatment amyloid level assessment, the averaged follow-up image was directly normalised to the reference amyloid PET template analogously to the procedure applied to the screening/baseline scan. If amyloid plaque level at 24 or 52 weeks was less than 11 CL on any single amyloid PET scan or less than 25 but greater than or equal to 11 CL on 2 consecutive amyloid PET scans, donanemab was switched to placebo in a blinded procedure (Sims et al. 2023).

To assess the change in brain amyloid plaque deposition from baseline through Week 76 for each individual participant, the averaged image was first aligned with the corresponding baseline amyloid PET image and then to the standard brain template using the same co-registration parameters as the baseline PET scan. In addition to the change in amyloid plaque level from baseline, the percentage of participants reaching amyloid clearance (<24.1 CL) was calculated. A cut threshold of 24.1 CL was used based on previously established discrimination of none or sparse versus moderate to frequent plaques in autopsy-confirmed data between amyloid-positive and amyloid-negative cases (Joshi et al. 2015; Navitsky et al. 2018).

No MR image was used to conduct quantitative assessments of follow-up amyloid PET images.

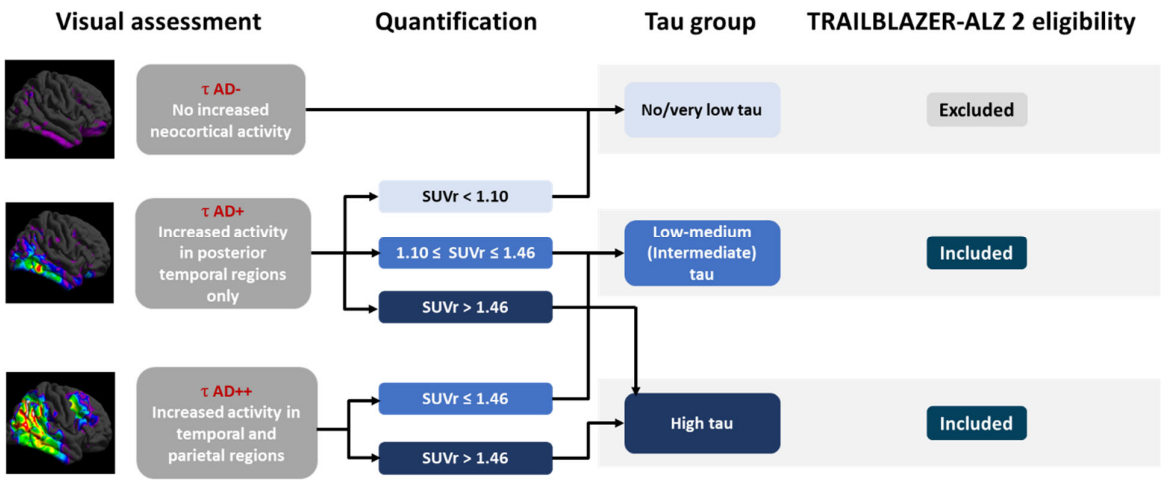
Tau PET

Tau PET with 18F-flortaucipir was used to determine eligibility by assessing the participant's level of tau pathology. For eligible participants, follow-up tau PET scans were conducted at 76 weeks to assess the effect of donanemab versus placebo on brain tau deposition.
In the TRAILBLAZER-ALZ 2 trial, participants received a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir followed by a saline flush and a dynamic 30-minute brain scan (6 frames x 5 minutes) was acquired approximately 75 minutes after injection.
PET images were reconstructed using scanner-specific protocols with the following parameter selections: iterative reconstruction algorithm (FORE, OSEM or RAMLA), 3 to 6 iterations, 16 to 33 subsets. Post-reconstruction Gaussian filters of 3 to 5 mm were applied (except for Philips scanners where the 'Normal' or 'Sharp' relaxation parameter setting was used).
For the quantitative analysis of flortaucipir images, the 5-minute PET images were motion-corrected, as well as corrected for the acquisition time and then averaged into a single static image. Correction for acquisition time was conducted because flortaucipir SUVr values may not reach a stable plateau by 75 minutes after injection, rather they may continue increasing throughout the potential imaging window (Shcherbinin et al. 2016). Consequently, differences in the injection-to-scan acquisition times across the baseline and Week 76 scans could affect SUVr analyses. Details of the correction for acquisition time were previously described (Pontecorvo et al. 2019).

1.1.3 Screening/Baseline Tau PET Scan

Screening/baseline flortaucipir scans were both visually and quantitatively evaluated to confirm the presence of tau pathology in TRAILBLAZER-ALZ 2 participants.
Scans were interpreted by visual examination as having regional patterns of tracer uptake that were moderate (τAD+) or advanced (τAD++) tau pattern or were not (negative [τAD-] tau pattern) consistent with AD (Fleisher et al. 2020; Lu et al. 2021). The τAD- tau pattern was defined as no increased neocortical activity or increased neocortical activity restricted to the mesial temporal, anterolateral temporal, and/or frontal regions. Moderate τAD+ tau pattern was defined as increased neocortical activity in the posterolateral temporal or occipital region. Advanced τAD++ tau pattern was defined as either increased neocortical activity in the parietal or precuneus region or increased activity in the frontal region together with increases in the posterolateral temporal, parietal, or occipital regions.
Readers were physicians with expert knowledge in the trial-specific disease indication(s) and with experience in clinical trial review. Before evaluating any trial images, the readers completed specific training with re-training during the trial as required.
Quantitative assessment of both baseline and follow-up 18F-flortaucipir images in the TRAILBLAZER-ALZ 2 trial followed the most commonly used technique, an estimation of SUVr. SUVr constitutes a ratio of the average PET signal in a neocortical composite region (target region) scaled by the average PET signal in a reference region that is typically spared of NFTs, for example, cerebellum or white matter. To calculate SUVr, all target and reference ROIs were applied onto the participant's

spatially normalised PET image in the MNI space. Different spatial normalisation techniques and SUVr measures were applied to make eligibility decisions using screening/baseline scans and to assess change in tau deposition for each individual participant using follow-up scans.
For the quantitative eligibility assessment, the averaged screening/baseline flortaucipir image was spatially normalised to the reference tau PET template in the MNI space. No MR image was used to conduct quantitative eligibility assessment. The global neocortical tau level was quantitatively measured using a previously published AD-signature weighted neocortical tau SUVr (MUBADA, Devous et al. 2018) with respect to a reference signal intensity in subject-specific white matter (PERSI, Southekal et al. 2018).
The eligibility decision (tau positivity assessment) was based on both visual and quantitative assessments (see Figure 1). According to the combined visual and quantitative eligibility method (tauVQ), TRAILBLAZER-ALZ 2 participants with either (1) τAD+ patterns and AD-signature weighted neocortical tau SUVr ≥1.10 or (2) τAD++ patterns were deemed to have a positive tau level. Scans with the τAD- pattern were considered to have an inadequate tau level and were excluded from the trial without an image quantification. If a τAD+ scan was unable to be quantitatively analysed, the scan was assessed using visual assessment to determine eligibility, which was performed by an independent reviewer.



Abbreviations: SUVr = standardised uptake value ratio.

Figure 1. Tau PET eligibility assessment in TRAILBLAZER-ALZ 2 trial.

1.1.4 Follow-up Tau PET Scan

Follow-up tau PET scans in the TRAILBLAZER-ALZ 2 trial were conducted at 76 weeks.
For the longitudinal tau PET analysis, more rigorous spatial normalisation involving individual baseline 3DT1 MR image was implemented. First, the baseline averaged tau PET image was co-registered to the participant's 3DT1 MR image. The 18-month tau PET image was motion- and time-corrected and averaged, then aligned first to the baseline PET image and then to the corresponding baseline MR image using the same co-registration parameters as the baseline tau PET scan. Finally, the baseline

3DT1 MR image was normalised to the MNI space, and the same MRI-to-atlas transformation matrix was used for spatial normalisation of the previously co-registered both baseline and 18-month flortaucipir PET images.
For longitudinal tau PET analyses, regional and global SUVr values with respect to the previously developed (Pontecorvo et al. 2017) cerebellar grey reference region were used. In the reference region, a cerebellar grey matter region derived from the cerebellar crustaneous ROI was modified by translating it inferiorly by 6 mm was chosen. This modification was performed to avoid possible overlap with inferior cortical areas and supratentorial cerebrospinal fluid. In longitudinal analyses, target ROIs included all automated anatomical labelling (Tzourio-Mazoyer et al. 2002) regions as well as additional custom regions. In particular, MUBADA SUVr (Devous et al. 2018) with respect to cerebellar grey reference region was used to measure change in the global neocortical tau deposition.

MRI

MRI was applied at screening and follow-up visits. Eligibility assessments were performed to evaluate potential MRI-based exclusionary criteria. At follow-up visits, volumetric MRI measurements were conducted to assess the effect of donanemab versus placebo on brain region volumes. Moreover, safety assessments to evaluate the occurrence of MRI findings were conducted at all visits.
Eligible MRI scanners had a magnetic field strength of 1.5 Tesla or 3.0 Tesla only.
Each MRI procedure consisted of the following MRI sequences:

- 3DT1: Magnetisation-Prepared Rapid Gradient-Echo (Siemens)/Inversion Recovery-Prepped Fast Spoiled Gradient-Recalled Echo (General Electric)/3D Turbo Field Echo (Philips)
- 2D FLAIR
- 2D Axial T2* GRE
- 2D Axial T2 Turbo/Fast Spin-Echo, and
- 2D Axial DWI.

The purposes of these sequences are highlighted in Table 1. The exact acquisition parameters depended upon the manufacturer, scanner model, installed hardware and software, as well as magnetic field strength. All scanners were qualified by the MRI vendor, and the acquisition parameters had to meet requirements set by the MRI vendor.

1.1.5 Screening/Baseline MRI Scan

Key MRI-based exclusion criteria included (Sims et al. 2023)

- presence of ARIA of oedema/effusion (2D Axial FLAIR)
- more than 4 cerebral microhaemorrhages (2D Axial T2* GRE)
- more than 1 area of superficial siderosis (2D Axial T2* GRE)
- any intracerebral haemorrhage greater than 1 cm (2D Axial T2* GRE), and
- severe white matter disease (age-related white matter changes = 3 in any hemisphere of the regions evaluated within the scoring paradigm, 2D Axial T2 Turbo/Fast Spin Echo; Wahlund et al. 2001).

1.1.6 Follow-up MRI Scan

Follow-up MRI scans were performed at Week 4, Week 12, Week 24, Week 52, and Week 76/Early Termination. Unscheduled visits were also performed as needed.

Assessments at follow-up visits included safety assessments to evaluate safety and tolerability of donanemab as assessed by MRI (ARIA and emergent radiological findings, such as cerebral oedema, haemosiderin deposits, white matter disease, or any other MRI abnormality and other incidental findings).

Safety and tolerability of donanemab were assessed using follow-up MRI scans using the following parameters:

- presence, radiographic severity, and location of ARIA of oedema/effusion (2D Axial FLAIR, 2D Axial T2)
- presence, number, and location of microhaemorrhages (2D Axial T2* GRE)
- presence and location of intracerebral haemorrhages greater than 1 cm (2D Axial T2* GRE)
- presence and location of superficial siderosis (2D Axial T2* GRE)
- presence and radiographic severity of ARIA-H haemorrhagic (2D Axial T2*GRE)
- presence and radiographic severity of white matter disease (2D Axial FLAIR, 2D Axial T2), and
- presence and location of any other MRI abnormalities (2D DWI, 2D Axial T2).

Any participant with detected ARIA had imaging every 4 to 6 weeks until resolution or stabilisation (Sims et al. 2023). ARIA management and treatment interruption guidelines depended upon the radiographic severity and symptoms. If infusions were paused, investigators were advised to await resolution of ARIA of oedema/effusion on radiographic imaging and stabilisation of ARIA of microhaemorrhages and haemosiderin deposits before resuming infusions. Permanent discontinuation was advised for intracerebral haemorrhages greater than 1 cm or serious ARIA. Investigators made final ARIA management decisions. ARIA Preferred Term groupings, severity evaluation, and event definitions were published (Zimmer et al. 2025).

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Synopsis of the Magnetic Resonance Imaging Protocol for Donanemab

Abbreviations and Definitions

Term	Definition
1.5T	magnetic field strength of 1.5 Tesla
2D	two-dimensional
3T	magnetic field strength of 3 Tesla
3DT1	three-dimensional T1-weighted
DWI	Diffusion Weighted Imaging
FLAIR	Fluid-Attenuated Inversion Recovery
GRE	Gradient Echo
MRI	magnetic resonance imaging
PET	positron emission tomography

Introduction/Background

MRI serves 2 main purposes for those undergoing assessment and treatment with donanemab:

- evaluation for exclusionary findings, and
- safety monitoring to determine treatment-emergent neuroimaging abnormalities, in particular amyloid-related imaging abnormalities and intracerebral hemorrhage greater than 1 cm.

This synopsis of the MRI protocol highlights key elements of magnetic resonance imaging procedures.

MRI modalities implemented in the TRAILBLAZER-ALZ 2 trial are highlighted in Table 1.

Table 1. Role of MRI Modalities in TRAILBLAZER-ALZ 2 Trial

Modality	Screening/baseline	Follow-up
DT1	Anatomical reference image for tau PET quantification	Change in volumetric MRI measures from baseline (Q)
2D Axial Fluid-Attenuated Inversion Recovery (FLAIR)	Detection of cerebral oedema and white matter lesions (V)	Detection of cerebral oedema and white matter lesions (V)
2D Axial T2* Gradient Echo (GRE)	Detection of haemosiderin deposits and other types of haemorrhagic lesions (V)	Detection of haemosiderin deposits and other types of haemorrhagic lesions (V)
2D Axial T2 Turbo/Fast Spin Echo	Detection of white matter lesions and other MRI findings (V)	Detection of white matter lesions and other MRI findings (V)
2D Axial Diffusion Weighted Imaging (DWI)	Detection of acute infarcts and strokes (V)	Detection of acute infarcts and strokes (V)

Abbreviations: 2D = two-dimensional; 3DT1 = three-dimensional T1-weighted; MRI = magnetic resonance imaging; PET = positron emission tomography; Q = quantitative assessment using specialised image processing and analysis software; V = visual assessment.

Synopsis of the MRI Protocol for Donanemab

Eligible MRI scanners in the TRAILBLAZER-ALZ 2 trial had a magnetic field strength of 1.5 Tesla or 3.0 Tesla only. Each MRI procedure consisted of the following MRI sequences in chronological order of acquisition:

- 3DT1 (3 to 4 mins): Magnetization-Prepared Rapid Gradient-Echo (Siemens)/Inversion Recovery-Prepped Fast Spoiled Gradient-Recalled Echo (General Electric)/3D Turbo Field Echo (Philips)
- 2D FLAIR (2.5 to 4.5 mins)
- 2D Axial T2* GRE (3 to 4 mins)
- 2D Axial T2 Turbo/Fast Spin-Echo (1 to 2 mins), and
- 2D Axial DWI (less than 1 min).

The purposes of these sequences are highlighted in Table 1. The exact acquisition parameters depended upon the

- manufacturer
- scanner model
- installed hardware and software, and
- magnetic field strength.

Specific MRI scanner parameters used in the TRAILBLAZER-ALZ 2 trial are proprietary to the MRI vendor and were standardized across MRI manufacturers and field strengths to allow the comparison of images acquired at different scanner models and field strengths. Sequences/modalities used for safety assessments in donanemab clinical trials are routinely used in neurodegenerative MRI protocols (Di Muzio et al. 2015; Benzinger and Jindal 2023; Harper et al. 2014).
Published consensus clinical protocol recommendations are provided below (Benzinger [WWW]; Cogswell et al 2022; Cogswell et al 2025; Lawson et al 2023; Philips [WWW]). These have compatibility with images acquired during trials. Detailed parameter settings for each sequence are provided in an appendix. Table 2 provides links to reference tables containing the parameters.

Table 2. MRI Parameters Locator Table

Magnetic Field Strength (T)	Location
GE 1.5 T	Appendix 1
GE 3 T	Appendix 2
Siemens 1.5 T	Appendix 3
Siemens 3 T	Appendix 4
Philips 1.5T	Appendix 5
Philips 3T	Appendix 6

Abbreviations: GE = General Electric; T = Tesla.

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Appendices: Quick Reference Guide for MRI Parameters

Appendix 1. General Electric 1.5T

Parameter	T1	FLAIR	T2*	T2	DWI
Imaging Mode	3D	2D	2D	2D	2D
Pulse Sequence	MP-RAGE	FSE-XL	Gradient Echo	FSE	Spin Echo
Orientation	-	Axial	Axial	Axial	Axial
FOV (cm)	25.6	22.0	22.0	22.0	24.0
Slice Thickness (mm)	0.5	4.0	4.0	4.0	4.0
Slice Spacing (mm)	-	0.4	0.4	0.4	0.4
Number of Slices	1 (slab)	36	36	36	36
Frequency Matrix	256	300	224	300	120
Phase Matrix	256	200	200	200	160
Phase FOV	1.0	1.0	0.9	1.0	1.0
NEX	1.0	1.0	1.0	1.0	2.0
Flip Angle (°)	12.0	160 (auto)	20.0	160 (auto)	-
TE (ms)	3.1	130.0	25.0	130.0	Minimum
TR (ms)	7.7	10000.0	600.0	10000.0	9163.0
TI (ms)	799	2687	-	2687	-
Echo Train Length	-	20	-	20	-
Fat/Water Saturation	-	Fat	-	Fat	Fat

Full protocol can be found at: https://signapulse.gehealthcare.com/autumn-2023/optimizing-the-aria-imaging-protocol-on-ge-healthcare-mr-systems

Appendix 2. General Electric 3.0T

Full

Parameter	T1	FLAIR	T2*	T2	DWI
Imaging Mode	3D	2D	2D	2D	2D
Pulse Sequence	MP-RAGE	FSE-XL	Gradient Echo	FSE	Spin Echo EPI
Orientation	-	Axial	Axial	Axial	Axial
FOV (cm)	25.6	22.0	22.0	22.0	24.0
Slice Thickness (mm)	0.5	4.0	4.0	4.0	4.0
Slice Spacing (mm)	-	0.4	0.4	0.4	0.4
Number of Slices	1 (slab)	36	36	36	36
Frequency Matrix	256	300	300	300	160
Phase Matrix	256	200	220	200	160
Phase FOV	1.0	0.9	0.9	0.9	1.0
NEX	1.0	1.0	1.0	1.0	1.0
Flip Angle (°)	8.0	160 (auto)	20.0	160 (auto)	-
TE (ms)	3.0	130.0	15.0	130.0	Minimum
TR (ms)	7.3	9000.0	800.0	9000.0	7500.0
TI (ms)	1000	2473	-	2473	-
Echo Train Length	-	23	-	23	-
Fat/Water Saturation	-	Fat	-	Fat	Fat

protocol can be found at: https://signapulse.gehealthcare.com/autumn-2023/optimizing-the-aria-imaging-protocol-on-ge-healthcare-mr-systems

Appendix 3. Siemens 1.5T

Parameter	T1	FLAIR	T2*	T2	DWI
Mode	3D	2D	2D	2D	2D
Sequence	3D MPRAGE	2D TSE FLAIR	2D T2* Gradient Echo	2D TSE	2D EPI Spin Echo
Orientation	Sagittal	Transversal (axial)	Transversal (axial)	Transversal (axial)	Transversal (axial)
Voxel Size (mm)	1.3 × 1.3 × 1.3	0.5 × 0.5 × 4.0	0.5 × 0.5 × 4.0	0.9 × 0.9 × 5.0	1.9 × 1.9 × 4.0
FOV Read (mm)	240	240	240	240	240
Slice Thickness (mm)	1.3	4.0	4.0	5.0	4.0
Slices	192	30	30	28	30
TR (ms)	2400	10000	608	4700	4700
TE (ms)	2.24	114	35	111	79
TI (ms)	1000	2600	-	-	-
Flip Angle (°)	8	150	20	180	-
Bandwidth (Hz/Px)	190	130	130	190	1220
Acceleration	GRAPPA 2	GRAPPA 2	GRAPPA 2	GRAPPA 2	GRAPPA 2
Averages	1	1	1	1	1
Concatenations	1	2	2	2	1
Turbo/EPI Factor	224 (Turbo)	16 (Turbo)	-	26 (Turbo)	128 (EPI)
Fat Saturation	Standard	Fat Sat Strong	Standard	Standard	Fat Sat Strong

Full protocol can be found at: https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/neurology-neurography/asnr

Appendix 4. Siemens 3T

Parameter	T1	FLAIR	T2*	T2	DWI	Full
Mode	3D	2D	2D	2D	2D	
Sequence	3D MPRAGE	2D TSE FLAIR	2D T2* Gradient Echo	2D TSE	2D EPI Spin Echo	
Orientation	Sagittal	Transversal	Transversal	Transversal	Transversal	
Voxel Size (mm)	1.0 × 1.0 × 1.0	0.5 × 0.5 × 4.0	0.5 × 0.5 × 4.0	0.9 × 0.9 × 5.0	1.9 × 1.9 × 4.0	
FOV Read (mm)	256	240	240	230	240	
Slice Thickness (mm)	1.0	4.0	4.0	5.0	4.0	
Slices	176	30	30	25	30	
TR (ms)	2300	9000	597	5140	6700	
TE (ms)	2.98	96.0	35.0	78.0	72.0	
TI (ms)	900	2500	-	-	-	
Flip Angle (°)	9	150	20	120	-	
Bandwidth (Hz/Px)	240	199	200	260	1698	
Acceleration	GRAPPA 2	GRAPPA 3	GRAPPA 2	GRAPPA 3	GRAPPA 2	
Averages	1	1	1	1	1	
Concatenations	1	2	2	2	1	
Turbo/EPI Factor	176 (Turbo)	16 (Turbo)	-	26 (Turbo)	128 (EPI)	
Fat Saturation	None	Fat Sat Strong	None	None	Fat Sat Strong	

protocol can be found at: https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/neurology-neurography/asnr

Appendix 5. Philips 1.5T

Parameter	T1	FLAIR	T2*	DWI
Mode	3D	2D	2D	2D
Sequence Type	3D FFE, TFE, T1W	IR, TSE, FLAIR	FFE, T2*	SE, DWI, EPI
Orientation	Sagittal	Transverse (axial)	Transverse (axial)	Transverse (axial)
Voxel Size (mm)	1.05 × 1.05 × 1.10	0.90 × 1.12 × 4.00	0.90 × 1.12 × 4.00	1.51 × 2.17 × 4.00
Recon Voxel Size (mm)	0.64 × 0.64 × 1.10	0.65 × 0.65 × 4.00	0.90 × 0.90 × 4.00	1.20 × 1.20 × 4.00
FOV (mm)	FH 256, AP 238, RL 159	AP 230, RL 183, FH 129	AP 230, RL 183, FH 129	RL 230, AP 230, FH 129
Slice Thickness (mm)	1.10	4.00	4.00	4.00
Slices	145	26	26	26
TR (ms)	7.4	11000	910	3498
TE (ms)	3.4	150	28	85
TI (ms)	950	2800	-	-
Flip Angle (°)	8	60–120	18	90
Bandwidth (Hz)	217.1	217.0	108.7	18.9
Acceleration	SENSE (2.2)	SENSE (1)	SENSE (1.5)	SENSE (2)
Echo Train/EPI Factor	TFE: 216	TSE: 41	-	EPI: 53
Fat Saturation	None	SPIR (strong)	None	SPIR (strong)
Water-Fat Shift (pixels)	1.0	Maximum	2.0	11.482
Averages	1	2	2	1

Full protocol can be found at: https://www.mriclinicalcasemap.philips.com/global/case/291/i

Appendix 6. Philips 3T

Parameter	T1	FLAIR	T2*	DWI
Mode	3D	2D	2D	2D
Sequence	3D FFE, TFE, T1W	IR, TSE, FLAIR	FFE, T2*	SE, DWI, EPI
Orientation	Sagittal	Transverse (axial)	Transverse (axial)	Transverse (axial)
Voxel Size (mm)	1.00 × 1.00 × 1.00	0.65 × 1.00 × 4.00	0.90 × 1.12 × 4.00	1.31 × 1.32 × 4.00
Recon Voxel Size (mm)	0.47 × 0.47 × 1.00	0.45 × 0.45 × 4.00	0.53 × 0.53 × 4.00	0.96 × 0.96 × 4.00
FOV (mm)	FH 240, AP 240, RL 170	AP 230, RL 186.9, FH 139	AP 230, RL 183.1, FH 139	RL 230, AP 230, FH 119
Slice Thickness (mm)	1.00	4.00	4.00	4.00
Slices	170	28	28	24
TR (ms)	6.6	8000	835	2965
TE (ms)	3.0	135	16	55
TI (ms)	1060	2500	-	-
Flip Angle (°)	8	100	18	90
Bandwidth (Hz)	271.3	227.3	217.0	13.2
Acceleration	SENSE (AP 1, RL 2.2)	SENSE (RL 2.4)	None	SENSE (AP 2.2)
Echo Train/EPI Factor	TFE: 204	TSE: 35	-	EPI: 79
Fat Saturation	None	SPIR (weak)	None	SPIR (strong)
Water-Fat Shift (pixels)	1.6	1.911	2.002	32.925
Averages	1	2	1	1

Full protocol can be found at: https://www.mriclinicalcasemap.philips.com/global/case/291/i

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