# Summary Report of Benefit-Risk Assessment

## LORMALZI CONCENTRATE FOR SOLUTION FOR INFUSION 350MG/20ML

## NEW DRUG APPLICATION

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| **Active Ingredient(s)** | Donanemab |
| **Product Registrant** | DKSH Singapore Pte. Ltd. |
| **Product Registration Number** | SIN17201P |
| **Application Route** | Full evaluation |
| **Date of Approval** | 11 March 2025 |

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## A INTRODUCTION

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

The active substance, donanemab, is an immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against an 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.

Lormalzi is available as a concentrate for solution for infusion containing 350mg/20ml of donanemab. Other ingredients include citric acid anhydrous, polysorbate 80, sodium citrate dihydrate, sucrose and water for injection.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, donanemab, is manufactured at Eli Lilly Kinsale Limited, Cork, Ireland. The drug product, Lormalzi Concentrate for Solution for Infusion 350mg/20mL, is manufactured at Lilly France, Fegersheim, France.

**Drug substance:**

Adequate controls have been presented for the starting materials, intermediates, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance [redacted] The packaging is a [redacted] polycarbonate container with a white polypropylene copolymer [redacted] closure.

**Drug product:**

The manufacturing process involves formulation, prefiltration, sterile filtration followed by filling and utilises aseptic processing. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at 2-8ºC, as well as the shelf-life after dilution with 0.9% sodium chloride solution of 72 hours when stored at 2-8ºC or 12 hours at 20-25ºC. The container closure system is a 20ml type I glass vial with chlorobutyl elastomeric stopper, aluminium seal and polypropylene flip top.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of donanemab to slow disease progression in adult patients with AD was based on a Phase III study AACI and a Phase IIIb study AACQ, as well as a Phase II study AACG.

Studies AACI and AACG were randomised, double-blind, placebo-controlled studies in patients with early symptomatic AD [mild cognitive impairment (MCI) or mild dementia] who had confirmed amyloid beta pathology by amyloid positron emission tomography (PET) scan and evidence of pathologic tau deposition on a flortaucipir PET scan. The studies were similarly designed except that Study AACI included patients with low-medium (intermediate) and high tau levels whereas study AACG included only patients with low-medium tau level. Also, Study AACI had a larger sample size (N = 1,736) compared to Study AACG (N = 272).

The patients in the studies were randomised in a 1:1 ratio to receive donanemab IV 700 mg every 4 weeks (Q4W) for the first 3 doses, then 1400 mg Q4W or placebo. 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. The use of placebo as comparator was considered appropriate as there was no disease modifying agent approved for the treatment of AD at the time of the studies.

The primary endpoint in both studies was the change from baseline to Week 76 in the integrated Alzheimer's Disease Rating Scale (iADRS) score. The iADRS is a combination of two validated scales that measure cognition and function: Alzheimer's Disease Assessment Scale – 13-item cognitive subscale (ADAS-Cog13); and Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale (ADCS-iADL). Key secondary endpoints were change from baseline to Week 76 in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog13, ADCS-iADL and Mini-Mental State Examination (MMSE) scores, as well as change from baseline to Week 76 in brain amyloid plaque deposition via florbetapir (F18) PET, brain tau deposition via flortaucipir (F18) PET, and volumetric magnetic resonance imaging (vMRI) measures. The endpoints and statistical methods employed were considered appropriate and multiplicity was controlled via graphical approaches.

The demographics and baseline characteristics were balanced between groups. A total of 257 patients were randomised in study AACG: 131 patients in the donanemab group and 126 in the placebo group. The mean age was 75 years (range: 61 to 86 years). Approximately half (51.8%) of the patients were female and 94.6% were White. A total of 1,736 patients were

randomised in the larger study AACI: 860 patients in the donanemab group and 876 in the placebo group. The mean age was 73 years (range: 59 to 86 years). A total of 57.4% of the patients were female and 91.5% were White. In both studies, the mean baseline iADRS scores ranged from 103.8 to 106.2 and CDR-SB scores ranged from 3.5 to 3.9. In addition, 70.5% to 73.3% of the patients were APOE4 carriers.

The results of the studies AACG and AACI were as follows and summarised in Table 1.

Study AACG met its primary endpoint in patients with early symptomatic AD (MCI and mild dementia) with presence of intermediate brain tau burden. Donanemab-treated patients had statistically significantly less decline in cognition/function than placebo-treated patients as assessed by the iADRS at Week 76 (LS mean change difference ± SE: 3.20 ± 1.56; p=0.042). The results demonstrated a 32% reduction in cognitive/functional decline for donanemab-treated patients compared with placebo.

When stratified by AD stages (MCI and mild AD), donanemab-treated patients with mild AD (N=88) had significantly less cognitive and functional decline, as measured by iADRS, compared with placebo-treated patients (LS mean difference: 3.99; p=0.029). The treatment difference favouring donanemab treatment was similar in the smaller MCI stratum (N=45) but not significant (LS mean difference: 4.35; p=0.223). The lack of demonstration of statistical significance in the MCI group could be due to the smaller sample size and was unlikely to be concerning given that the effect size remained consistent with the mild AD subgroup and was numerically larger than the primary analysis, suggesting that the non-significant result may be attributable to reduced statistical power rather than a difference in treatment effect.

In terms of the secondary endpoints, donanemab-treated patients had statistically significantly lesser decline in cognition than placebo-treated patients as assessed by the ADAS-Cog13 at Week 76 (LS mean change difference ± SE: -1.86 ± 0.898; p=0.040). The results demonstrated a 39% reduction in cognitive decline for donanemab-treated patients compared with placebo. Statistical significance was not achieved for donanemab versus placebo in other secondary endpoints including CDR-SB score (LS mean change difference ± SE: -0.36 ± 0.239; p=0.139; 23% reduction in cognitive/functional decline); ADCS-iADL score (LS mean change difference ± SE: 1.21 ± 1.009; p=0.230; 23% reduction in functional decline); and MMSE score (LS mean change difference ± SE: 0.64 ± 0.525; p=0.227; 21% reduction in cognitive decline), likely attributed to the small sample size. Nevertheless, a favorable trend of numerical improvement with donanemab versus placebo was observed.

As with Study AACG, Study AACI met its primary endpoint with donanemab-treated patients had a statistically significantly slower clinical progression on the primary outcome, iADRS, compared with placebo in both intermediate tau (LS mean change difference ± SE: 3.25 ± 0.70; p<0.001; 35% slowing of clinical progression) and overall (LS mean change difference ± SE: 2.92 ± 0.72; p<0.001; 22% slowing of clinical progression) populations at Week 76.

Subgroup analyses showed consistent results favouring donanemab in terms of iADRS across the clinical stages (39.3% to 55.4% slowing of clinical progression in MCI and 19.2% to 29.5% slowing of clinical progression in mild AD) in the intermediate tau and overall populations. Similar to the findings in Study AACG, treatment difference favouring donanemab was observed in the smaller MCI stratum but not statistically significant [intermediate tau population: LS mean difference = 2.92 (95% CI: -1.232, 5.507); overall population LS mean difference = 2.14 (95% CI: -1.232, 5.507)]. It was noted that the MCI stratum showed numerically greater slowing of progression than in the overall population, thus the lack of

demonstration of statistical significance in the MCI stratum may likewise be attributed to the smaller sample size (N=251).

Donanemab also demonstrated statistically significant efficacy in slowing clinical progression on all the secondary outcome measures compared with placebo. The results for the secondary endpoints were consistent with the primary outcome. The analyses of CDR-SB score showed statistically significantly less decline in clinical progression with donanemab in both intermediate tau (36% slowing; $p<0.001$) and overall (29% slowing; $p<0.001$) populations compared with placebo at Week 76. In addition, there were statistically significantly less decline in clinical progression with donanemab as assessed by ADAS-Cog13 score (range: 20% to 32% slowing) and ADCS-iADL score (range: 28% to 40% slowing) in the intermediate tau and overall populations at Week 76.

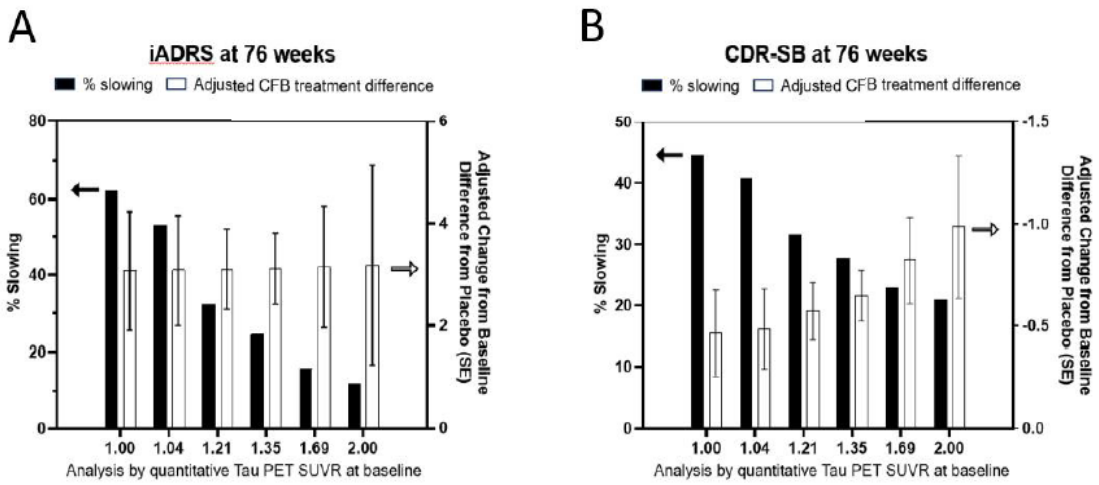
The clinical significance of delaying clinical progression based on the various scales was further supported by time-based analyses. When stratified by tau levels (intermediate and high tau), donanemab statistically significantly delayed disease progression time by 4.4 months in the intermediate tau population and 1.4 months in the overall population as assessed by iADRS at Week 76. In addition, a similar delay in disease progression by 7.5 and 5.4 months in the intermediate tau and overall populations, respectively, were observed when assessed by CDR-SB at Week 76.

The smaller treatment effect observed in the overall population could be attributed to the smaller reduction in clinical decline in the high tau subgroup compared with the intermediate tau population, where the LS mean difference observed on the iADRS in the high tau population was 1.26 compared to 3.25 in the intermediate population. The results were not unexpected given that the high tau subgroup had more advanced disease, which is harder to treat, suggesting that clinical benefit may be more pronounced with treatment initiation in early disease. The results in the high tau subgroup might also be confounded by a higher percentage of patients with baseline mild AD (90.6%) and worse clinical scores (mean CDR-SB score: 4.42; mean ADAS-Cog13 score: 31.88) as compared to the intermediate tau subgroup (mild AD: 80.4%; mean CDR-SB score: 3.71; mean ADAS-Cog13 score: 27.65).

In terms of CDR-SB, the magnitude of change was similar across the tau levels (-0.69 in the high tau population and -0.67 in the intermediate tau population). The results demonstrated a 39% and 37% lower risk of time progression to the next stage of the disease as assessed by CDR-global (CDR-G) scores compared with placebo at Week 76, in the intermediate tau population and overall population, respectively.

The impact of tau on clinical responses (iADRS and CDR-SB) are illustrated in the figures below. The absolute difference for iADRS was preserved across different tau levels, but there was a reduced slowing with increasing tau burden attributed to the increasingly rapid decline in patients with more advanced disease (Panel A). The CDR-SB data showed a different pattern, with patients having higher tau showing a greater absolute change in CDR-SB. However, the percent slowing of progression still indicated a decline as tau increased, suggesting that patients with high tau declined at a faster rate than the increase in absolute treatment difference (Panel B). Taken together, the results showed that early intervention is important.

**MMRM analysis of iADRS (Panel A) and CDR-SB (Panel B) at 76 weeks (18 months) according to SUVr**




Abbreviations: CFB = change from baseline; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MMRM = mixed model for repeated measures; PET = positron emission tomography; SE = standard error; SUVr = standardised uptake value ratio.

In terms of biomarkers, donanemab showed a statistically significant reduction in amyloid plaque compared to placebo in both the intermediate tau ($p<0.0001$) and overall ($p<0.0001$) populations. Overall, baseline plasma P-tau217, P-tau181 and glial fibrillary acidic protein (GFAP) levels were also reduced in the donanemab group at Weeks 24 and 76 in both the intermediate tau and overall populations ($p<0.0001$). A sizable proportion of donanemab-treated patients (34% and 30% in the intermediate tau and overall populations, respectively) had amyloid plaque clearance (<24.1 Centiloids) as early as Week 24. A total of 80% of donanemab-treated patients in the intermediate tau population and 76% in the overall population had clearance at Week 76. In addition, 47% and 36% of the patients remained stable (showed no decline in CDR-SB from baseline) compared with 29% and 23% of the patients in the placebo-treated patients at Week 52 in the intermediate tau and overall populations, respectively.

In both studies, donanemab treatment resulted in a greater decrease in the whole brain volume, a greater increase in ventricular volume, and a lesser decrease in the hippocampal volume compared with placebo. These paradoxical changes had similarly occurred post-treatment with other anti-amyloid therapies and had been linked to pseudoatrophy due to structural removal of protein aggregates or changes in blood-brain barrier (BBB) integrity and renormalisation of occluded lymphatic flow. Nonetheless, the slowing of clinical cognitive decline compared to placebo provided reassurance that the reduced brain volume did not translate into functional impairment.

**Table 1: Summary of key efficacy results**

| Study | Study design | Study population | Treatment arms | Results (Donanemab vs placebo) |
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| AACG (76 weeks)<br><br>*Sites included US and Canada | Phase II, randomised, double-blind, placebo-controlled (N=257) | Adult subjects (60-85 years old) with:<br>• Early symptomatic AD (MCI or mild dementia);<br>• MMSE score 20-28 | Equally randomised into:<br>• Donanemab IV 700 mg Q4W x 3 doses, then 1400 mg Q4W<br>• Placebo | **Primary endpoint – Change from baseline in iADRS score at Week 76:**<br>• -6.86 vs -10.06 (LS mean change difference ± SE: 3.20 ± 1.56; p=0.042)<br>• 32% reduction in cognitive/functional decline<br><br>**Secondary endpoint – Change from baseline in CDR-SB score at Week 76:** |

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| | | • Amyloid by PET<br>• Intermediate tau by PET | | • 1.22 vs 1.58 (LS mean change difference ± SE: -0.36 ± 0.239; p=0.139)<br>• 23% reduction in cognitive/functional decline<br><br>**Secondary endpoint – Change from baseline in ADAS-Cog13 score at Week 76:**<br>• 2.91 vs 4.77 (LS mean change difference ± SE: -1.86 ± 0.898; p=0.040)<br>• 39% reduction in cognitive decline<br><br>**Secondary endpoint – Change from baseline in ADCS-iADL score at Week 76:**<br>• -3.98 vs -5.20 (LS mean change difference ± SE: 1.21 ± 1.009; p=0.230)<br>• 23% reduction in functional decline<br><br>**Secondary endpoint – Change from baseline in MMSE score at Week 76:**<br>• -2.35 vs -2.98 (LS mean change difference ± SE: 0.64 ± 0.525; p=0.227)<br>• 21% reduction in cognitive decline<br><br>**Secondary endpoint – Brain amyloid plaque and via florbetapir PET and brain tau deposition via flortaucipir PET at Week 76:**<br>• Amyloid PET: -84.13 vs 0.93 (LS mean change difference ± SE: -85.06 ± 3.867; p<0.001)<br>• Tau PET: 0.09 vs 0.10 (LS mean difference: 0.01 (95% CI: -0.01, 0.03); p=0.560). There were significant (p<0.05) slowing of the tau increases in the frontal (60.8% slowing), parietal (46.3% slowing), and temporal (33.1% slowing), but not occipital lobes in the donanemab-treated patients compared to placebo-treated patients.<br><br>**Secondary endpoint – vMRI at Week 76:**<br>• Whole brain volume LS mean change difference ± SE: -4.58 ± 1.519 $cm^3$; p=0.003<br>• Bilateral ventricular volume LS mean change difference ± SE: 2.28 ± 0.581 $cm^3$; p<0.001 |
| AACI<br>(76 weeks)<br><br>*Sites included US, Canada, Australia, the Netherlands, Poland, the UK, Czech Republic, and Japan | Phase 3, randomised, double-blind, placebo-controlled (N=1,736) | Adult subjects (60-85 years old) with:<br>• Early symptomatic AD (MCI or mild dementia)<br>• MMSE score 20-28<br>• Amyloid by PET<br>• Intermediate (N=1,182) and high tau (N=554) by PET | Equally randomised into:<br>• Donanemab IV 700 mg Q4W x 3 doses, then 1400 mg Q4W<br>• Placebo | **Primary endpoint – Change from baseline in iADRS score at Week 76:**<br><u>Intermediate tau</u><br>• -6.02 vs -9.27 (LS mean change difference ± SE: 3.25 ± 0.70; p<0.001)<br>• 35% reduction in cognitive/functional decline<br><u>Overall</u><br>• -10.19 vs -13.11 (LS mean change difference ± SE: 2.92 ± 0.72; p<0.001)<br>• 22% reduction in cognitive/functional decline<br><br>**Secondary endpoint – Change from baseline in CDR-SB score at Week 76:**<br><u>Intermediate tau</u><br>• 1.20 vs 1.88 (LS mean change difference ± SE: -0.67 ± 0.141; p<0.001)<br>• 36% reduction in cognitive/functional decline<br><u>Overall</u><br>• 1.72 vs 2.42 (LS mean change difference ± SE: -0.70 ± 0.127; p<0.001)<br>• 29% reduction in cognitive/functional decline |

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| | | | | **Secondary endpoint – Change from baseline in ADAS-Cog13 score at Week 76:**<br><u>Intermediate tau</u><br>• 3.17 vs 4.69 (LS mean change difference ± SE: -1.52 ± 0.37; p<0.001)<br>• 32% reduction in cognitive decline<br><u>Overall</u><br>• 5.46 vs 6.79 (LS mean change difference ± SE: -1.33 ± 0.39; p=0.0006)<br>• 20% reduction in cognitive decline<br><br>**Secondary endpoint – Change from baseline in ADCS-iADL score at Week 76:**<br><u>Intermediate tau</u><br>• -2.76 vs -4.59 (LS mean change difference ± SE: 1.83 ± 0.47; p<0.001)<br>• 40% reduction in functional decline<br><u>Overall</u><br>• -4.42 vs -6.13 (LS mean change difference ± SE: 1.70 ± 0.44; p=0.0001)<br>• 28% reduction in functional decline<br><br>**Secondary endpoint – Change from baseline in MMSE score at Week 76:**<br><u>Intermediate tau</u><br>• -1.61 vs -2.09 (LS mean change difference ± SE: 0.48 ± 0.20; p=0.016)<br>• 23% reduction in cognitive decline<br><u>Overall</u><br>• -2.47 vs -2.94 (LS mean change difference ± SE: 0.47 ± 0.19; p=0.012)<br>• 16% reduction in cognitive decline<br><br>**Secondary endpoint – Brain amyloid plaque and via florbetapir F18 PET and brain tau deposition via flortaucipir PET at Week 76:**<br>• Amyloid PET: -88.03vs 0.18 [LS mean change difference ± SE: -88.21 ± 1.535; p<0.0001 (intermediate tau)]; -87.03 vs -0.67 [-86.37 ± 1.275; p<0.0001 (overall)]<br>• Tau PET: 0.0273 vs 0.0271 [LS mean difference: 0.0002 (95% CI: -0.0100, 0.0104) (intermediate tau)]; 0.0401 vs 0.0442 [-0.0041 (95% CI: -0.0148, 0.0066) (overall)]. The change from baseline to Week 76 in frontal tau deposition (frontal SUVr) did not differ significantly in the donanemab group compared with the placebo group (intermediate tau p=0.97, overall p=0.45).<br><br>**Secondary endpoint – vMRI at Week 76:**<br>• Whole brain volume LS mean change difference ± SE: -6.33 ± 0.627 $cm^3$; p<0.001 (intermediate tau); -6.66 ± 0.561 $cm^3$; p<0.001 (overall)<br>• Bilateral ventricular volume LS mean change difference ± SE: 2.40 ± 0.261 $cm^3$; p<0.001 (intermediate tau); 3.02 ± 0.256 $cm^3$; p<0.001 (overall)<br>• In both the intermediate tau and overall populations, the vMRI at Week 76 showed a greater decrease in the whole brain volume (nominal p<0.001) and a greater increase in |

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| | | | | ventricular volume (nominal p<0.001) in donanemab-treated patients compared with placebo-treated patients |

Abbreviations: MMSE = Mini-Mental State Examination; PET = positron emission tomography; IV = intravenous; Q4W = every 4 weeks; LS = least-squares; SE = standard error; iADRS = integrated Alzheimer's Disease Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; ADAS-Cog13 = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CI = confidence interval; SUVr = standardised uptake value ratio

The approved dosing regimen of 350/700/1050 mg (termed as the "modified titration dosing regimen"), followed by 1400 mg Q4W was evaluated in a Phase IIIb, multicentre, randomised, double-blind study (Study AACQ) in adults with MCI due to AD or mild AD dementia with confirmed amyloid beta pathology by amyloid PET scan. The objective of the study was to investigate the different donanemab dosing regimens and their effects on amyloid-related imaging abnormality (ARIA). The patients were randomly assigned in a 1:1 ratio to the standard dosing regimen (700 mg Q4W x 3 doses, then 1400 mg Q4W) or modified titration dosing regimen.

The primary endpoint of the study investigated safety by comparing the proportion of participants with any occurrence of ARIA-edema/effusions (ARIA-E) by Week 24 between the dosing regimens. The prespecified success criterion of the study was to achieve a probability of more than 80% that the modified titration dosing regimen reduced ARIA-E risk by at least 20% compared with the standard dosing regimen by 24 weeks. In addition, one of the secondary endpoints investigated efficacy based on the change from baseline in brain amyloid plaque deposition as measured by amyloid PET scan through Week 24.

A total of 420 patients were randomised: 208 patients on the standard dosing regimen and 212 patients on the modified titration dosing regimen. The demographics and baseline characteristics were balanced between groups. The mean age of patients was 73.6 years, 57.8% of the patients were females and 92.9% were White. In addition, 64.6% of the patients were APOE4 carriers.

The results showed that both dosing regimens resulted in similar and statistically significant decrease in amyloid mean change from baseline (all p<0.001). The LS mean change at Week 24 from baseline ± SE was -58.8 ± 1.8 (p<0.0001) for the standard dosing regimen and -56.3 ± 1.7 (p<0.0001) for the modified titration dosing regimen. In addition, both dosing regimens showed similar and statistically significant clearance of amyloid plaque. The proportion of patients that reached amyloid clearance at Week 24 were 56.7% (p<0.0001) for the standard dosing regimen and 50.7% (p<0.0001) for the modified titration dosing regimen.

In terms of safety, the modified titration group had a 41% lower ARIA-E risk compared to the standard dosing group (incidence 13.7% vs 23.7%, respectively), with a 94% probability that the relative risk reduction was at least 20%. Hence, the prespecified success criterion was met. Subgroup analyses also showed that in high-risk patients (with at least 1 copy of the APOE ε4 allele), the incidences of ARIA were lowered in the modified titration group compared with the standard dosing group. In APOE ε4 homozygotes and heterozygotes, the incidences of ARIA-E were reduced from 57% and 23% to 19% and 14%, respectively. For ARIA-H in APOE ε4 homozygotes, the incidence decreased from 43% to 29%. The results demonstrated that the modified titration regimen significantly reduced the incidence of ARIA-E, it was therefore selected as the final recommended dosing regimen based on its improved safety profile. Also, considering that the modified titration and standard dosing regimens showed comparable reductions in brain amyloid plaque levels, the efficacy demonstrated with the

standard dosing regimen in the pivotal clinical studies could be reasonably extrapolated to the modified titration dosing regimen.

Taken together, the results from the pivotal studies showed that donanemab could maintain patients in earlier stages of disease for a longer period compared to placebo and the results favoured donanemab regardless of the tau level.

The smaller magnitude of treatment effect in the high tau population was reflected in the package insert to allow physicians to assess the overall benefit-risk profile in the context of individual patient factors as well as to manage the expectations of patients and/or their caregivers.

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## D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of donanemab was based primarily on safety data derived from the placebo-controlled studies AACG and AACI, as well as the safety study AACQ. A total of 1,698 patients received at least three doses of donanemab in these studies.

In the placebo-controlled studies, the incidence of treatment emergent adverse events (TEAEs) was higher in the donanemab group compared to the placebo group (89.2% vs 83.2%). The common TEAEs which were observed at higher incidences in the donanemab group compared to the placebo group were ARIA-E (24.4% vs 1.8%), amyloid-related imaging abnormality-haemorrhage (ARIA-H, 18.2% vs 6.9%), infusion-related reaction (IRR, 8.5% vs 0.4%), nausea (5.2% vs 3.8%), and headache (13.1% vs 10.1%). Most of the TEAEs were mild to moderate in severity. There was a higher incidence of severe TEAEs in the donanemab group compared to placebo group (12.5% vs 9.5%). Severe TEAE that occurred at a frequency of at least 1% and were reported in more than 1 patient in the donanemab group was ARIA-E (2.1% vs 0%).

The incidence of serious adverse events (SAEs) was slightly higher in the donanemab group compared to the placebo group (17.1% vs 15.3%). The SAEs that occurred at a frequency of more than 0.5% in participants in the donanemab group (vs placebo) included ARIA-E (1.5% vs 0%), syncope (1.0% vs 1.1%), pneumonia (1.0% vs 0.6%), COVID-19 (0.8% vs 0.4%), and pulmonary embolism (0.6% vs 0.2%). No pattern or clear association of SAEs with donanemab was identified.

**Table 2: Incidence rates of adverse events (AEs)**

| | Donanemab placebo-controlled studies | | All donanemab studies |
|---|---|---|---|
| | Placebo (N=999) n (%) | Donanemab (N=984) n (%) | Donanemab (N=2,727) n (%) |
| **All TEAEs** | 831 (83.2) | 878 (89.2) | 2,129 (78.1) |
| **SAEs** | 153 (15.3) | 168 (17.1) | 411 (15.1) |
| **Treatment discontinuations due to AEs** | 47 (4.7%) | 152 (15.4%) | 265 (9.7%) |
| **Deaths** | 12 (1.2) | 17 (1.7) | 32 (1.2) |
| **AEs of Special Interest (AESIs)** | | | |
| ARIA-E | 18 (1.8) | 237 (24.1) | 527 (19.3) |
| ARIA-H | 124 (12.4) | 307 (31.2) | 697 (25.6) |
| ARIA-H microhaemorrhage | 109 (10.9) | 246 (25.0) | 576 (21.1) |
| ARIA-H superficial siderosis | 28 (2.8) | 157 (16.0) | 327 (12.0) |

ARIA is an AE of clinical importance for anti-amyloid therapies including donanemab. It is an expected AE based on the mechanism of action of the drug and what is known for other anti-amyloid therapies, In donanemab-treated patients, ARIA-E (24.1% vs 1.8%) and ARIA-H (31.2% vs 12.4%) occurred more frequently compared with placebo-treated patients. Concurrent ARIA-E and ARIA-H were observed in 16.4% of donanemab-treated patients compared with 0.6% of placebo-treated patients. ARIA-H microhaemorrhage (25.0% vs 10.9%) and ARIA-H superficial siderosis (ARIA-H SS) (16.0% vs 2.8%) also occurred more frequently in donanemab-treated patients compared with placebo-treated patients. The frequencies of macrohaemorrhage (intracerebral haemorrhage greater than 1 cm) were similar in the donanemab-treated and placebo-treated groups (0.3% vs 0.2%, respectively).

The maximum radiographic severity for ARIA-E was mild in 7.0% of patients, moderate in 14.8% of patients, and severe in 2.1% of patients. Symptomatic ARIA-E was reported for 5.8% of patients treated with donanemab. The maximum radiographic severity for ARIA-H was mild in 14.8% of patients, moderate in 6.0% of patients, and severe in 10.4% of patients. Symptomatic ARIA-H was reported for 1.0% of patients treated with donanemab. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 12.5% of donanemab treated patients compared to 11.7% on placebo.

The incidence of serious ARIA was generally low. Serious ARIA 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 in the placebo-treated patients. Of the 15 serious ARIA-E cases, 14 were symptomatic. Three patients in the donanemab-treated group reported serious ARIA and subsequently died. One (0.1%) death was attributed to ARIA-E, 1 (0.1%) death to ARIA-H, and the third patient had SAEs of ARIA-E and ARIA-H, was admitted to hospice and died. As part of the risk mitigation measures, the company is required to provide educational materials to physicians as well as “alert card” to patients and caregivers on the symptoms of ARIA so that medical attention could be promptly provided or sought.

It was observed that ARIA onset was mostly within 24 weeks of treatment initiation. A total of 54.9% of the donanemab-treated patients with ARIA-E (n=237) had their first ARIA-E event by Week 12 and 87.8% had the first event by Week 24. The majority of donanemab-treated patients with serious ARIA-E had their first event after receiving up to 5 infusions. In this regard, the MRI monitoring schedule prior to the second dose, prior to third dose, prior to fourth dose, and prior to the seventh dose was considered adequate to detect ARIA. The median time to radiographic resolution of ARIA-E was similar between groups at 52.5 days for placebo-treated patients and 59 days for donanemab-treated patients. More than 90% of severe ARIA-E events resolved radiographically and more than 73% had complete recovery (radiographic and with symptom resolution for symptomatic ARIA-E). Nearly 80% of severe ARIA-H events also stabilised radiographically.

Risk factors associated with ARIA included baseline MRI abnormality such as baseline microhaemorrhages and superficial siderosis-central nervous system (SS-CNS). These were associated with higher incidence of ARIA-E, symptomatic ARIA-E, and overall ARIA-H. A warning to exercise caution in patients with these baseline risk factors was included in the package insert to manage the risk of ARIA in susceptible patients.

In addition, apolipoprotein E ε4 (APOE ε4) genotype was identified as a predisposing factor for ARIA risk. APOE ε4 homozygote carriers had the highest risk, followed by APOE ε4 heterozygote carriers, and the noncarriers (incidence of ARIA-E: 41.1% vs 23.8% vs 14.8%, respectively; incidence of ARIA-H: 53.6%, 30.8%, and 18.9%, respectively). Testing for APOE

ε4 status is therefore mandatory to inform clinicians and patients of the risk of ARIA as well as aid the clinicians in their individualised benefit-risk assessment for their patients.

Aside from ARIA, the other AEs of clinical importance included anaphylaxis and infusion related reaction (IRR), immunogenicity and hypersensitivity, hepatic AEs, as well as suicidal ideation and behaviour. The incidence of IRR was higher in donanemab-treated patients compared to placebo-treated patients (8.5% vs 0.4%). Nonetheless, the events were transient and most resolved on the same day (median 0.5 days, mean 0.7 days). The majority (>59%) of the first-onset IRRs occurred by the third or fourth infusion and the incidences of anaphylactic reaction and hypersensitivity in donanemab-treated patients were low (≤1.0%). A total of 88.1% of donanemab-treated patients developed anti-drug antibodies (ADAs), however the majority did not have IRR. There were no differences in hepatic laboratory parameters related to hepatic function and injury between donanemab-treated patients and placebo-treated patients. One patient in the donanemab group discontinued from the study due to the AE of hepatic enzyme increased. A total of 4 cases of suicidal ideation and behaviour were reported as SAEs (2 in the donanemab group and 2 in the placebo group). Of these, 3 were fatal (2 in the donanemab group and 1 in the placebo group). Nonetheless, the overall incidences of suicidal ideation fell within background rates[1] in patients with AD.

The incidence of treatment discontinuation due to AEs was higher in the donanemab compared to placebo group (15.4% vs 4.7%). The AEs reported in at least 1% of participants in the donanemab group that led to permanent discontinuation of study treatment were IRR (3.9% vs 0%), ARIA-E (2.8% vs 0.4%), ARIA-H (1.0% vs 0.2%), and superficial siderosis (SS) (1.1% vs 0.1%).Overall, the incidences of ARIA-E, ARIA-H and IRR leading to discontinuation were low although these AEs occurred at higher incidences in the donanemab group compared to the placebo group, suggesting that donanemab was generally well tolerated.

There were 17 (1.7%) deaths in the donanemab group and 12 (1.2%) deaths in the placebo group. The events which were reported as the cause of death in 2 or more participants in the placebo group were pneumonia. In the donanemab group, the causes of death included ARIA (3 patients), completed suicide (2 patients), COVID-19 (2 patients, including 1 with pneumonia), and pulmonary embolism (2 patients). Five deaths were considered related to study treatment by the investigator. These included 4 cases in the donanemab group (1 case of thalamic haemorrhage, 1 case of ARIA-E, 1 case of ARIA-H, and 1 case of ARIA-E and ARIA-H which was admitted to hospice and died) and 1 case of atherosclerosis in the placebo group.

Overall, the safety profile of donanemab was consistent with what is known for the anti-amyloid class of drugs. ARIA is an AE of clinical importance and risk minimisation measures are necessary to mitigate the potential risks. These included physician educational materials and patient alert card to guide patients / carers to seek prompt medical attention if patients experience symptoms associated with ARIA as well as MRI monitoring. The package insert has also included information on dosing interruptions for patients with ARIA-E and ARIA-H until resolution. The resumption of dosing or discontinuation would be guided by clinical judgment and the risk factors should be re-evaluated prior to restarting treatment to ensure safeguard for patients.

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[1]Draper B et al., 1998. Age and Aging;27: 503-7 and Dubois B et al., 2016. Alzheimers Dement;12(3): 292-323

## E ASSESSMENT OF BENEFIT-RISK PROFILE

AD is a neurodegenerative disorder associated with a gradual deterioration in cognitive functions (such as memory, language, and thinking), leading to the eventual inability to carry out daily social and functional activities. With a rapidly aging population, the prevalence of AD is projected to rise. Existing drugs for AD such as cholinesterase inhibitors, e.g., donepezil, rivastigmine, and galantamine, and N-methyl-D-aspartic acid (NMDA) antagonist (memantine) primarily offer symptomatic relief but they do not alter the underlying pathological processes or slow the progressive neurodegeneration that characterises the disease. Given the progressive nature of the disease and the significant impact on patients' caregivers and society, there is a pressing need for more effective treatments that can slow the cognitive and functional decline associated with disease progression.

Benefits

The Phase II study, AACG, and Phase III study, AACI, met their primary endpoints as donanemab-treated patients demonstrated a statistically significant lesser decline in cognition/function (range: 22% to 35% slowing) than placebo-treated patients as assessed by the iADRS at Week 76.

Both studies demonstrated a slowing of cognitive/functional decline as measured by iADRS in the subgroups of mild AD (LS mean difference of 3.99 in Study AACG and 2.25 in Study AACI) and MCI (LS mean difference of 4.35 in Study AACG and 2.14 in Study AACI) compared to placebo. While the difference was not statistically significant in the MCI subgroup, this might be due to the reduced sample sizes in the MCI subgroup which possibly impacted the statistical power. It was noted that the results consistently favoured donanemab in terms of reduction in cognitive decline and that the percent slowing of progression was greater in MCI patients (39.3% to 55.4%) compared to mild AD patients (19.2% to 29.5%), indicating a greater benefit of treatment when the drug was initiated at an earlier stage.

The secondary endpoints in both the studies supported the primary endpoints. In Study AACG, the results favoured donanemab compared to placebo for secondary endpoints including CDR-SB score (23% reduction in cognitive/functional decline; p=0.139), ADCS-iADL score (23% reduction in functional decline; p=0.230), and MMSE score (21% reduction in cognitive decline; p=0.227) although statistical significance was not reached. The lack of statistical significance in Study AACG might be due to the small sample size, whereas the larger study AACI showed a statistically significant reduction in clinical progression with donanemab in both the intermediate tau and overall populations compared to placebo at Week 76 for CDR-SB score (ranging from 29% to 36% slowing), ADAS-Cog13 score (ranging from 20% to 32% slowing), and ADCS-iADL score (ranging from 28% to 40% slowing). The trend towards slower decline in cognitive impairment by donanemab in both studies, coupled with statistical significance demonstrated in Study AACI which also included high tau patients signifying more progressive disease, provided reassurance on the robustness of the data.

In the time-based analysis, Study AACI showed that donanemab delayed disease progression time by 4.4 months in the intermediate tau population and 1.4 months in the overall population as assessed by iADRS at Week 76; and by 7.5 and 5.4 months in the intermediate tau and overall populations, respectively, as assessed by CDR-SB at Week 76. While the faster progression of AD in subjects with high tau led to smaller percent slowing of clinical decline in the overall population, a similar magnitude of change in CDR-SB (-0.56 in the high tau population and -0.67 in the intermediate tau population) as well as lower risk of progression to the next stage of the disease (39% and 37% lower risk in the intermediate tau and the overall

population, respectively, based on CDR-G) across different tau levels were observed. The results with respect to the magnitude of treatment effect based on tau level has been reflected in the package insert to guide physicians in assessing the overall benefit-risk profile and managing patient and caregiver expectations.

In terms of biomarkers, a reduction in plasma P-tau217, P-tau181 and GFAP levels were observed in the donanemab group compared to the placebo group with the reduction in amyloid plaque. A notable proportion of donanemab-treated patients (34% and 30%) experienced amyloid plaque clearance (<24.1 Centiloids) as early as 6 months in the intermediate tau and overall populations, respectively. By 18 months, 80% of donanemab-treated patients in the intermediate tau population and 76% in the overall population had achieved clearance. Additionally, 47% and 36% of donanemab-treated patients remained stable (showing no decline in CDR-SB from baseline) at 1 year in the intermediate tau and overall populations, respectively.

Despite paradoxical brain changes, including a greater decrease in whole brain volume, a greater increase in ventricular volume, and a lesser decrease in hippocampal volume which pointed to increased brain atrophy compared with placebo, donanemab slowed clinical decline compared to placebo in both studies. The results indicated that brain changes did not impact cognitive function. Although the cellular mechanisms remained unclear, these changes had also occurred post-treatment with other anti-amyloid therapies and had been linked to pseudoatrophy due to structural removal of protein aggregates or changes in blood-brain-barrier integrity and renormalisation of occluded lymphatic flow.

Overall, the data from both studies showed that donanemab resulted in significant amyloid clearance which is a hallmark of AD, and the results supported the use of the drug in early AD (MCI and mild dementia) based on demonstration of clinically relevant reductions in cognitive decline with donanemab compared to placebo across various validated AD scales.

Risks

The most frequently reported TEAEs for donanemab-treated patients were ARIA-E (24.4%), ARIA-H (18.2%), IRR (8.5%), nausea (5.2%), and headache (13.1%). Most of the TEAEs were of mild (34.9%) or moderate (41.9%) in severity. Severe TEAEs that occurred at a frequency of at least 1% and were reported in more than 1 patient in the donanemab treatment group was ARIA-E (placebo: 0%; donanemab: 2.1%).

ARIA is an AE of clinical importance and it is generally managed symptomatically. ARIA-E (24.1% vs 1.8%), ARIA-H (31.2% vs 12.4%), concurrent ARIA-E and ARIA-H (16.4% vs 0.6%), ARIA-H microhaemorrhage (25.0% vs 10.9%), and ARIA-H SS (16.0% vs 2.8%) occurred more frequently in donanemab-treated patients compared to placebo-treated patients.

Symptomatic ARIA-E was reported in 5.8% and symptomatic ARIA-H was reported in 1.0% of donanemab-treated patients. The majority of severe ARIA-E events (90%) resolved radiographically, with over 73% experiencing complete recovery (radiographic and symptom resolution for symptomatic ARIA-E), and nearly 80% of severe ARIA-H events stabilised radiographically.

The incidence of serious ARIA-E and ARIA-H was generally low (range: 0.4% to 1.5%). Fourteen of the 15 serious ARIA-E cases were symptomatic. Three deaths occurred in association with ARIA: 1 case of ARIA-E, ARIA-H, and concurrent ARIA-E and ARIA-H each.

Overall, although the incidences of AEs such as ARIA-E, ARIA-H and IRR were higher in the donanemab group compared to the placebo group, the incidences of such AEs leading to discontinuation were generally low (range: 1.0% to 3.9%).

Given that the majority (87.8%) of the donanemab-treated patients with ARIA-E (n=237) had their first ARIA-E event by Week 24 after receiving up to 5 infusions, the proposed MRI monitoring schedule prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose was considered adequate to detect ARIA.

APOE ε4 genotype has been identified as a risk factor for ARIA, and testing for APOE ε4 status is recommended. The other risk factors identified for ARIA included baseline MRI abnormality such as microhaemorrhages and SS-CNS. A warning has been included in the package insert to exercise caution in patients with these baseline risk factors to manage the risk of ARIA.

The other AEs of clinical importance included hypersensitivity, anaphylaxis and IRR, immunogenicity and hypersensitivity, as well as hepatic safety, which were generally clinically manageable. The incidence of suicidal ideation and behaviour fell within background rates in patients with AD.

In all, the safety profile of donanemab was consistent with what is known for the anti-amyloid class of drugs and was considered to be clinically manageable given that the donanemab treatment would be initiated and followed up in specialised clinical setting. Based on the data demonstrating that the modified titration regimen significantly reduced the incidence of ARIA while maintaining efficacy compared to the standard dosing regimen, this dosing regimen was approved as it provided an improved safety profile that further supported the favourable benefit-risk profile of donanemab. The risk mitigation measures were also strengthened to include MRI monitoring, testing for risk factors as well as the distribution of physician and patient educational materials.

Based on the overall weight of evidence, the benefits of donanemab in slowing disease progression of AD in patients with MCI or mild dementia, thereby enabling patients to retain cognition and function for a longer period of time, were considered to outweigh the risks. The risks were considered clinically manageable and could be reasonably mitigated through risk minimisation measures and product labelling.

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## F CONCLUSION

Based on the review of the efficacy and safety data as well as the risk minimisation measures to guide clinicians on the management of ARIA, the benefit-risk profile of Lormalzi to slow disease progression in adult patients with AD, with evidence of amyloid beta pathology and either mild cognitive impairment or mild dementia, was deemed favourable and approval of the product registration was granted on 11 March 2025.

## APPROVED PACKAGE INSERT AT REGISTRATION

## 1. NAME OF THE MEDICINAL PRODUCT

Lormalzi Concentrate for Solution for Infusion 350mg/20mL

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 350 mg donanemab in 20 mL (17.5 mg/mL)

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

Excipient(s) with known effect

Each 20 mL vial contains 11.5 mg sodium.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The solution is clear to opalescent, colourless to slightly yellow to slightly brown with a pH of 5.5 – 6.5 and an osmolarity of approximately 300 mOsm/L.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of 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.

Beta amyloid evidence

Beta amyloid evidence consistent with AD should be confirmed using a validated test.

Posology

The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, and 1050 mg for the third dose, followed by 1400 mg, every 4 weeks. Treatment should be maintained until amyloid plaques are cleared, as confirmed using a validated method, up to a maximum of 18 months.

Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible (see section 5.1).

The benefit-risk of treatment should be reassessed at regular intervals on an individual basis. Consideration should be given to discontinuing treatment if donanemab would no longer be expected to be effective.

Monitoring and dosing interruption for amyloid related imaging abnormalities

Obtain a recent (within 1 year) brain magnetic resonance imaging (MRI) prior to initiating treatment. Perform an MRI prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose (see section 4.4).

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

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

| Clinical Symptom | ARIA-E and ARIA-H Severity[b] on MRI | | |
|---|---|---|---|
| | **Mild** | **Moderate** | **Severe** |
| **Asymptomatic** | Consider suspending dosing | Suspend dosing[a] | Suspend dosing[a] |
| **Symptomatic** | Suspend dosing[a] | | |

[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. Evaluation of risk factors again prior to restarting is recommended. Supportive treatment, including corticosteroids may be considered in case of ARIA-E.

[b] Refer to Table 2 for severity classification

Discontinue donanemab if intracerebral haemorrhage greater than 1 cm occurs.

Method of administration

Lormalzi 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 6.6.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use donanemab 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.

*Paediatric population*
There is no relevant use of Lormalzi in the paediatric population for the treatment of Alzheimer's disease.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients who were treated with Lormalzi. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

Infusion-Related Reactions

Infusion-related reactions, including anaphylaxis have been observed with administration of donanemab (see section 4.8. Undesirable Effects). These reactions may be severe or life-threatening and typically occur during infusion or within 30 minutes post infusion. Signs and symptoms of infusion-related reactions may include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnea, and changes in blood pressure.

If serious infusion-related reactions occur, discontinue administration of donanemab immediately and initiate appropriate treatment.

Amyloid-related imaging abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Lormalzi, can cause amyloid related imaging abnormalities (ARIA), characterised as ARIA with oedema (ARIA-E), which can be observed on MRI as brain oedema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhaemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer’s disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhaemorrhage or superficial siderosis. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, tremor, dizziness, nausea, vomiting, gait difficulty, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with Lormalzi.

Consider the benefit of Lormalzi for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with Lormalzi.

Serious cases of ARIA have been observed in donanemab clinical studies and some have been fatal (see section 4.8 Undesirable Effects). Intracerebral haemorrhage > 1 cm has been observed. ARIA can be detected by MRI.

Most ARIA events were first observed within 24 weeks of initiation of treatment. Access to MRI should be available during the treatment period of donanemab. Perform an MRI at baseline (within 1 year to initiating treatment), prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose (see section 4.2). MRI may also be indicated if ARIA symptoms occur.

Most serious ARIA events occurred within 12 weeks of initiation of treatment and an additional MRI prior to the third dose may aid in earlier detection of ARIA, particularly for patients with ARIA risk factors such as apolipoprotein E ε4 allele (APOE ε4) carriers, baseline cerebral microhaemorrhages and superficial siderosis.

APOE ε4 carriers have a higher frequency (homozygotes greater than heterozygotes) of ARIA-E and ARIA-H compared to non-carriers. In study TRAILBLAZER-ALZ-2, 17% (143/850) of patients in the Lormalzi arm with known genotype were apolipoprotein E ε4 (ApoE ε4) homozygotes, 53% (452/850) were heterozygotes, and 30% (255/850) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (55% on Lormalzi vs. 22% on placebo) than in heterozygotes (36% on Lormalzi vs. 13% on placebo) and noncarriers (25% on Lormalzi vs. 12% on placebo). Among patients treated with Lormalzi, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes compared with 7% of heterozygotes and 4% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, 2% of heterozygotes and 1% of noncarriers. The recommendations for management of ARIA do not differ between ApoE ε4 carriers and noncarriers [see section 4.2 Posology and method of administration]. Testing for ApoE ε4 status must be performed prior to initiation of treatment to inform the risk of developing ARIA. A higher frequency of ARIA has also been observed in patients with pre-treatment cerebral microhaemorrhage and/or superficial siderosis.

Neuroimaging findings that may indicate cerebral amyloid angiopathy (CAA) include evidence of prior intracerebral haemorrhage, cerebral microhaemorrhage, and cortical superficial siderosis. CAA has an increased risk for intracerebral haemorrhage. The presence of an ApoE ε4 allele is also associated with CAA. In Study TRAILBLAZER-ALZ-2, the baseline presence of at least 2 microhaemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, were identified as risk factors for ARIA.

The safety of donanemab has not been established in patients with pre-treatment MRI showing ARIA-E, more than 4 microhaemorrhages, more than 1 area of superficial siderosis, severe white matter disease or intracerebral haemorrhage greater than 1 cm. Caution should be exercised when initiating donanemab treatment in patients with these baseline risk factors.

*Monitoring and dose management guidelines in Patients with ARIA*
Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity [see Section 4.2 Posology and method of administration]. Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity [see Section 4.2 Posology and method of administration]. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

Baseline brain MRI and periodic monitoring with MRI are recommended [see Section 4.2 Posology and method of administration]. Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with Lormalzi. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data for dosing patients who have experienced recurrent episodes of ARIA-E.

If symptoms of ARIA-H occur, it is often in the presence of ARIA-E and managed as for ARIA-E. The recommendations for dosing interruptions for patients with ARIA-E and ARIA-H are provided in Table 1 (see section 4.2).

Discontinue donanemab if intracerebral haemorrhage greater than 1 cm occurs.

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

The majority of ARIA-E radiographic events in Study TRAILBLAZER-ALZ-2 occurred early in treatment (within the first 24 weeks), although ARIA can occur at any time and patients can have more

than one episode. The maximum radiographic severity of ARIA-E in patients treated with Lormalzi was mild in 7% (59/853) of patients, moderate in 15% (128/853) of patients, and severe in 2% (14/853) of patients. Resolution on MRI after the first ARIA-E event occurred in 63% of patients treated with Lormalzi by 12 weeks, 80% by 20 weeks, and 83% overall after detection. The maximum radiographic severity of ARIA-H microhaemorrhage in patients treated with Lormalzi was mild in 17% (143/853) of patients, moderate in 4% (34/853) of patients, and severe in 5% (40/853) of patients. The maximum radiographic severity of ARIA-H superficial siderosis in patients treated with Lormalzi was mild in 6% (47/853) of patients, moderate in 4% (32/853) of patients, and severe in 5% (46/853) of patients. Among patients treated with Lormalzi, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 3% (4/143) compared to heterozygotes 2% (9/452) or noncarriers 0.4% (1/255). Among patients treated with Lormalzi, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 22% (31/143) compared to heterozygotes 8% (38/452) or noncarriers 4% (9/255).

**Table 2: ARIA MRI Classification criteria**

| ARIA Type | Radiographic Severity | | |
|---|---|---|---|
| | **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 [a] | 1 new focal area of superficial siderosis | 2 new focal areas of superficial siderosis | > 2 new 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
[a] Includes new or increased focal areas of superficial siderosis

Concomitant antithrombotic treatment

In Study TRAILBLAZER-ALZ-2, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed. 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 (81 %). The incidence of ARIA-H was 30% (106/349) in patients taking Lormalzi with a concomitant antithrombotic medication within 30 days compared to 29% (148/504) who did not receive an antithrombotic within 30 days of an ARIA-H event. The incidence of intracerebral haemorrhage greater than 1 cm in diameter was 0.6% (2/349 patients) in patients taking Lormalzi with a concomitant antithrombotic medication compared to 0.4% (2/504) in those who did not receive an antithrombotic. 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 haemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with donanemab.

One fatal intracerebral haemorrhage occurred in a patient taking Lormalzi in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent. Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue

plasminogen activator) to a patient already being treated with Lormalzi. Because ARIA can cause focal neurologic deficits similar to those observed in an ischaemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy in a patient being treated with donanemab.

Caution should be exercised when considering the use of Lormalzi in patients with factors that indicate an increased risk for intracerebral haemorrhage and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of cerebral amyloid angiopathy.

Sodium

This medicinal product contains 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.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No pharmacokinetic drug interactions are expected based on the characteristics of donanemab.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of donanemab in pregnant women. Animal embryofetal developmental toxicity studies have not been conducted with donanemab. Donanemab is an IgG1-based antibody and may be transferred to the fetus during the third trimester.

Lormalzi is not recommended during pregnancy.

Breast-feeding

Lactation studies have not been conducted in animals. Human immunoglobulin G (IgG) is known to be excreted in human milk; therefore, donanemab may be transmitted from the mother to the breastfed infant. The risks to a breast-fed infant are unknown.

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.

## 4.7 Effects on ability to drive and use machines

Lormalzi has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were ARIA-E (24.4 %), ARIA-H (31.3 %) and headache (13.1 %). The most important serious adverse reactions were: Serious ARIA-E (1.5 %), serious ARIA-H (0.4 %), and serious hypersensitivity including infusion-related reactions (0.6 %). Anaphylaxis was uncommonly reported (0.3 %) (see section 4.4).

Tabulated list of adverse reactions

In two placebo-controlled studies (see section 5.1) in patients with AD, a total of 984 adult subjects received at least one dose of donanemab.

Adverse reactions from clinical studies (Table 3) 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 seriousness. In addition, 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).

**Table 3. Adverse reactions**

| System organ class | Very common | Common | Uncommon |
|---|---|---|---|
| Gastrointestinal disorders | | Nausea<br>Vomiting | |
| Injury, poisoning and procedural complications | | Infusion-related reaction | Anaphylactic reaction |
| Nervous system disorders | ARIA-E[a]<br>ARIA-H[a,b]<br>Headache | | |

[a] As assessed by MRI.
[b] Includes microhaemorrhage and superficial siderosis

Hepatic laboratory observations

Participants in both treatment groups experienced elevated AST or ALT ⩾5x ULN; 2 placebo patients (0.2%) and 1 donanemab treated patient (0.1%).

Description of selected adverse reactions

*Amyloid-related Imaging abnormalities*
ARIA (ARIA-E or ARIA-H) was observed in 37 % of patients treated with donanemab, compared to 14.2 % of patients on placebo in the placebo-controlled studies. Serious ARIA events were reported for 1.6 % of patients treated with donanemab. Clinical symptoms associated with ARIA-E resolved in approximately 80 % of patients.

ARIA-E was observed in 24.4 % of patients treated with donanemab compared with 1.9 % of patients on placebo. The maximum radiographic severity for ARIA-E was mild in 7.0 % of patients, moderate in 14.8 % of patients, and severe in 2.1 % of patients. Symptomatic ARIA-E was reported for 5.8 % of patients treated with donanemab in placebo-controlled clinical trials. The median time to resolution of ARIA-E was approximately 9 weeks.

ARIA-H can occur spontaneously in patients with AD independent of treatment. ARIA-H was observed in 31.3 % of patients treated with donanemab compared with 13 % of patients on placebo. The maximum radiographic severity for ARIA-H was mild in 14.8 % of patients, moderate in 6.0 % of patients, and severe in 10.4 % of patients. Symptomatic ARIA-H was reported for 1.0 % 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 12.5 % of donanemab-treated patients compared to 11.7 % on placebo.

In Study TRAILBLAZER-ALZ 6, ARIA-E was observed in 14% of patients treated with donanemab at the dosing regimen of 350/700/1050 mg, followed by 1400 mg every 4 weeks (n=212), for 24 weeks. Symptomatic ARIA-E occurred in 3%. Clinical symptoms associated with ARIA-E resolved in approximately 83% of patients. ARIA-H was observed in 20% of patients and symptomatic ARIA-H occurred in less than 1%.

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 and patients can have more than one episode.

In placebo-controlled studies, intracerebral haemorrhage greater than 1 cm has been observed after treatment with donanemab in 0.3 % compared to 0.2 % for placebo.

In Study TRAILBLAZER-ALZ 6, intracerebral haemorrhage greater than 1 cm was reported in 1% (2/212) of patients treated with donanemab for 24 weeks at the dosing regimen of 350/700/1050 mg, followed by 1400 mg every 4 weeks.

*Infusion-related reactions*
Infusion reactions were observed in 8.5 % of patients treated with donanemab compared to 0.4 % on placebo. Anaphylaxis was uncommonly reported (0.3 %). Serious infusion reactions or hypersensitivity occurred in 0.6 % of patients treated with donanemab compared to 0.2 % on placebo.

The majority of infusion reactions and hypersensitivity reactions have occurred within the first 4 doses of donanemab, although they can occur at any time.

*Immunogenicity*
In 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. In Study TRAILBLAZER-ALZ-2, approximately 10% of Lormalzi-treated patients who developed ADA reported infusion-related reactions compared to 2% of patients who did not develop ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

### 4.9 Overdose

Single doses up to 40 mg/kg (approximately 2 800 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 if necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Mechanism of action

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against an 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. The accumulation of beta amyloid plaque in the brain is one of the defining pathophysiological features of Alzheimer’s disease but its role in the pathogenesis of the disease has not been fully elucidated.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The safety and efficacy of donanemab were evaluated in a Phase III (TRAILBLAZER-ALZ 2) and a Phase II (TRAILBLAZER-ALZ) study, both double-blind placebo-controlled, parallel-group, in patients with early symptomatic AD (Mild Cognitive Impairment (MCI) or mild dementia due to AD) and evidence of amyloid beta pathology confirmed by amyloid PET scan. The participants also had evidence of pathologic tau deposition on a flortaucipir PET scan. The Phase III study confirmed the efficacy and safety results observed in the Phase II Study.

*Phase III Study TRAILBLAZER-ALZ 2*
In this study, 1 736 patients were randomized 1:1 to receive 700 mg of donanemab every 4 weeks for the first 3 doses, and then 1 400 mg every 4 weeks via intravenous infusion (N = 860) or placebo (N = 876) for a total of up to 72 weeks. The study includes 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 pre-existing ARIA-E, greater than 4 microhaemorrhages, more than 1 area of superficial siderosis, any intracerebral haemorrhage > 1 cm or severe white matter disease. Patients with significant neurological disease affecting the central nervous system other than AD that may affect cognition (such as other dementias or epilepsy), history of cancer within 5 years (unless low risk of recurrence or spread), or potentially confounding psychiatric diagnoses (including schizophrenia or chronic psychosis) were excluded.

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 20 to 28 (inclusive). 57.4 % were female, 91.5 % were White, 5.7 % were of Hispanic or Latino ethnicity, 6.0 % were Asian, and 2.3 % were Black. 55.6 % of patients were on AChEI, and 20.3 % on memantine. 61 % of patients were on either AChEI or memantine use.

There were two primary analysis populations based on tau PET imaging at screening with flortaucipir: 1) low-medium tau level population, and 2) combined population (low-medium plus high tau level population).

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-$Cog_{13}$) and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) 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-$Cog_{13}$, ADCS-iADL.

Treatment with donanemab statistically significantly slowed clinical decline compared to placebo at week 76, with consistency across measures of cognition and function (Figure 1 and Table 4).

Treatment effect in subgroups (age, BMI, gender, race, APOE ε4carrier status, disease severity [MCI or mild dementia due to AD], tau terciles and concomitant symptomatic treatment) was consistent with the results in the combined study population.

**Figure 1: iADRS Mean change from baseline in the combined and in the low-medium tau population through 76 weeks in Study TRAILBLAZER-ALZ 2.**

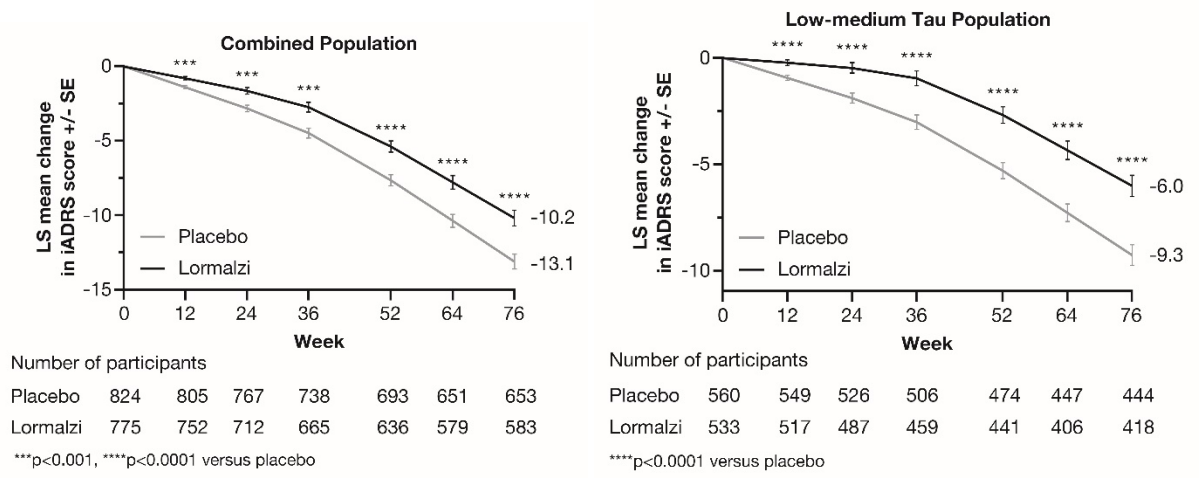



**Table 4: Secondary clinical outcomes of donanemab study TRAILBLAZER-ALZ 2 at week 76***

| | **Combined Tau Population** | | **Low-Medium Tau Population** | |
|---|---|---|---|---|
| **Clinical endpoints** | Donanemab (N = 860) | Placebo (N = 876) | Donanemab (N = 588) | Placebo (N = 594) |
| **CDR-SB[b]** | | | | |
| Mean baseline | 3.92 | 3.89 | 3.72 | 3.64 |
| Change from baseline | 1.72 | 2.42 | 1.20 | 1.88 |
| Difference from placebo (%) | -0.70 (29 %) | - | -0.67 (36 %) | - |
| p-value | p < 0.0001 | | p < 0.0001 | |
| **ADAS-Cog$_{13}$[a]** | | | | |
| Mean baseline | 28.53 | 29.16 | 27.41 | 27.60 |
| Change from baseline | 5.46 | 6.79 | 3.17 | 4.69 |
| Difference from placebo (%) | -1.33 (20 %) | - | -1.52 (32 %) | - |
| p-value | p = 0.0006 | | p < 0.0001 | |
| **ADCS-iADL[a]** | | | | |
| Mean baseline | 47.96 | 47.98 | 48.20 | 48.56 |
| Change from baseline | -4.42 | -6.13 | -2.76 | -4.59 |
| Difference from placebo (%) | 1.70 (28 %) | - | 1.83 (40 %) | - |
| p-value | p = 0.0001 | | p < 0.0001 | |

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale - Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; NCS2 = natural cubic spline with 2 degrees of freedom; MMRM = mixed model for repeated measures

[a] Assessed using NCS2 analysis.

[b] Assessed using MMRM analysis.

* Statistically significant with adjustment for multiplicity in the graphical testing scheme

Patients treated with donanemab also had a 39 % and 37 % lower risk of progressing to the next stage of disease as measured by the CDR-global score (HR: 0.61, $p < 0.001$; and HR: 0.63, $p < 0.0001$) through Week 76 in the low-medium tau and in the combined population, respectively.

At Week 76, donanemab treatment statistically significantly delayed disease progression by 4.4 months and 7.5 months as assessed by iADRS and CDR-SB respectively in the low-medium tau population, and by 1.4 months and 5.4 months as assessed by iADRS and CDR-SB respectively in the combined population.

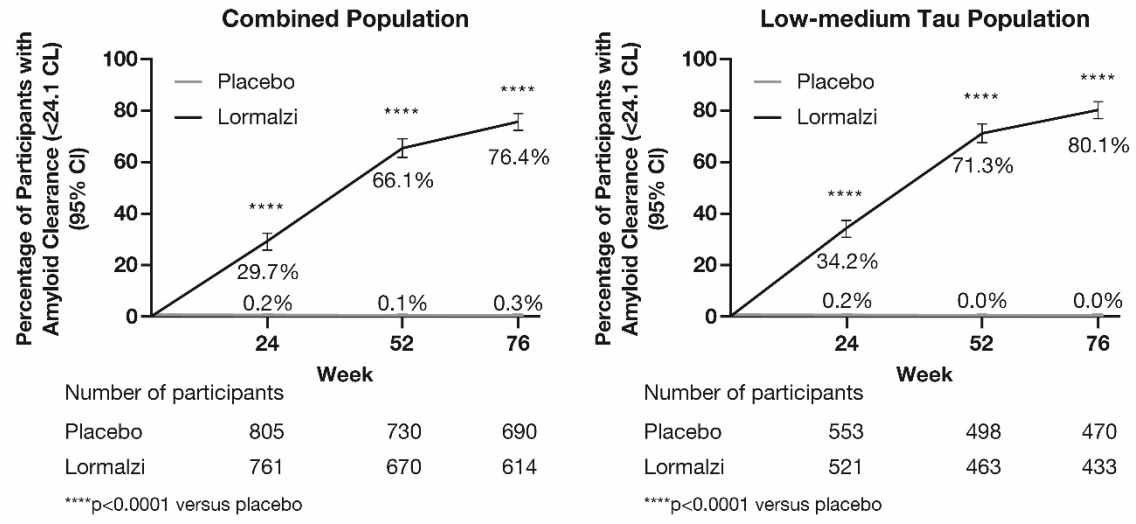
At Week 76, patients treated with donanemab had less decline in cognition than placebo-treated participants as assessed by the MMSE change from baseline values in both the low-medium tau and in the combined population.

*Biomarkers*
The percentage of donanemab treated patients with amyloid clearance (that is, less than 24.1 Centiloids (CL) or visually negative on an amyloid PET scan) in Study TRAILBLAZER-ALZ 2 is represented in Figure 2. In the intermediate tau population, LS mean change difference ± SE was -66.2 CL ± 1.40 and -88.2 CL ± 1.54 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). In the combined population, LS mean change difference ± SE was -63.0 CL ± 1.19 and -86.4 CL ± 1.28 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points).

A reduction in plasma P-tau217 was observed with donanemab compared to placebo. In the low-medium tau population, LS mean change difference ± SE was - 0.19 ± 0.011 and - 0.25 ± 0.014 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). Consistent with this, in the combined population, LS mean change difference ± SE was - 0.16 ± 0.010 and - 0.22 ± 0.012 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points).

There was no significant difference in LSM change in tau PET between donanemab and placebo in the frontal lobe at 76 weeks.

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




*High tau population*
In the high-tau population (271 patients on donanemab and 281 patients on placebo), donanemab slowed clinical decline by 6 % (1.26 ± 1.54 [$p = 0.415$]) on iADRS, and 21 % (- 0.69 ± 0.25 [$p = 0.006$]) on CDR-SB, at Week 76 compared with placebo. Efficacy in the high tau population was less than in patients with low-medium tau.

*MCI (MMSE scores ≥27) and mild AD subgroups (MMSE scores 20-26 at baseline)*
In the MCI subgroup (142 patients on donanemab and 124 patients on placebo), LS mean difference was 2.14 ± 1.72 (39.3% slowing, p=0.214) on iADRS and -0.29 ± 0.29 (30.4% slowing, p=0.326) on CDR-SB, at Week 76 compared to placebo.

In the mild AD subgroup (514 patients on donanemab and 526 patients on placebo) LS mean difference was 2.25 ± 0.89 (19.2% slowing; p=0.011) on iADRS and -0.68 ± 0.15 (32.5% slowing; p<0.001) on CDR-SB, at Week 76 compared to placebo.

*Phase II Study TRAILBLAZER-ALZ*
In this study, 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 (n=131) or placebo (n=126) for a total of up to 72 weeks. The study enrolled a low-medium tau population. 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. The study excluded patients with pre-existing ARIA-E, greater than 4 microhaemorrhages, more than 1 area of superficial siderosis, any intracerebral haemorrhage > 1 cm or severe white matter disease. Patients with significant neurological disease affecting the central nervous system other than AD that may affect cognition (such as other dementias or epilepsy), history of cancer within 5 years (unless low risk of recurrence or spread), or potentially confounding psychiatric diagnoses (including schizophrenia or chronic psychosis) were excluded. At baseline, 46 participants had MCI and 185 had mild AD. At baseline, mean age was 75 years, with a range of 61 to 86 years. 52% of patients were female and 95% where white. Patients treated with donanemab demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in iADRS compared to placebo at week 76 (3.20 [- 32%], p = 0.042). In the MCI subgroup (25 patients on donanemab and 21 patients on placebo), LS mean difference was 4.35 (95% CI -2.67, 11.37; p=0.223), and in the mild AD subgroup (91 patients on donanemab and 94 patients on placebo) was 3.99 (95% CI 0.42, 7.56; p=0.029), at Week 76 compared to 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 700/700/700mg, 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.

*Phase III, direct comparative study (TRAILBLAZER-ALZ 4)*
TRAILBLAZER-ALZ 4 was a multicentre, randomised, open-label, active-comparator Phase III study investigating donanemab vs aducanumab in 148 patients with early symptomatic Alzheimer's disease. The participants were required to have evidence of amyloid beta pathology including confirmation of amyloid burden on an amyloid PET scan. Baseline flortaucipir F18 PET scan was collected but there was no tau restriction at entry. Donanemab was superior to aducanumab on the co-primary study objectives: Percentage of patients who reached amyloid plaque clearance (less than 24.1 Centiloids) on florbetapir F18 PET scan at 6 months (donanemab 37.9 % vs aducanumab 1.6 %; p < 0.001) and percentage of patients who reached amyloid plaque clearance (less than 24.1 Centiloids) on florbetapir

F18 PET scan in the low-medium tau subpopulation at 6 months (donanemab 38.5 % vs aducanumab 3.8 %; p = 0.008). Comparable reduction in p-Tau217 and amyloid as measured by PET was observed regardless of baseline tau presence.

## 5.2 Pharmacokinetic properties

Absorption

Donanemab is for intravenous administration only.

Distribution

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.

Biotransformation

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.

Elimination

Following intravenous dosing, donanemab undergoes biphasic elimination. The half-life of donanemab is approximately 12.1 days. Donanemab clearance was 0.0255 L/h (24.9 % inter-individual variability).

Other intrinsic factors

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. No dose adjustment is necessary in patients with renal or hepatic impairments.

## 5.3 Preclinical safety data

No animal studies have been performed to test donanemab for potential of carcinogenicity, genotoxicity, or fertility impairment. As a high molecular weight protein, donanemab is not expected to interact directly with DNA or other chromosomal material.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

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

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years

## 6.4 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 to 25 °C.
Keep the vial in the outer carton in order to protect from light.
Do not freeze or shake.

Diluted solution for infusion

Use prepared dosing solution immediately.
If not used immediately, store the donanemab dosing solution under refrigeration 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 assuming dilution has taken place using aseptic techniques.
Storage times include the duration of infusion.
Do not freeze the donanemab dosing solution.

## 6.5 Nature and contents of container

Lormalzi is supplied in a type I clear glass, 20 mL, single dose vial, with a chlorobutyl elastomer stopper and an aluminium seal with a polypropylene cap.
Pack size of 1 vial.

## 6.6 Special precautions for disposal and other handling

Donanemab 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 (see Table 5), donanemab is administered as an intravenous infusion:

**Table 5: Preparation of donanemab**

| Lormalzi Dose (mg) | Lormalzi Volume (mL) | Volume of sodium chloride 9 mg/mL (0.9 %) solution for injection (mL) | Final volume of diluted solution to be infused (mL) | Final concentration of diluted solution (mg/mL)[a] |
|---|---|---|---|---|
| 350 mg | 20 mL | 15 mL to 67.5 mL | 35 mL to 87.5 mL | 350 mg/87.5 mL (4 mg/mL) to 350 mg/35 mL (10 mg/mL) |
| 700 mg | 40 mL[b] | 30 mL to 135 mL | 70 mL to 175 mL | 700 mg/175 mL (4 mg/mL) to 700 mg/70 mL (10 mg/mL) |
| 1050 mg | 60 mL[c] | 45 mL to 202.5 mL | 105 mL to 262.5 mL | 1050 mg/262.5 mL (4 mg/mL) to 1050 mg/105 mL (10 mg/mL) |
| 1 400mg | 80 mL[d] | 60 mL to 270 mL | 140 mL to 350 mL | 1 400 mg/350 mL (4 mg/mL) to 1 400 mg/140 mL (10 mg/mL) |

[a] final concentration of 4 mg/mL to 10 mg/mL
[b] 2 vials of Lormalzi
[c] 3 vials of Lormalzi
[d] 4 vials of Lormalzi

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. PRODUCT OWNER

Eli Lilly and Company, Indianapolis, Indiana 46285, USA

## 8. DATE OF REVISION OF THE TEXT

24 Feb 2025