AlzMeta.2.0: A Webserver for Prediction of Risks, Benefits and Clinical Relevance of Novel Alzheimer's Drugs in Systematic Review and Network Meta-Analysis

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Abstract

Background: The risk/benefit profile and clinical relevance of anti-amyloid antibodies in Alzheimer's disease (AD) is uncertain, with no scientific basis for choosing one treatment over another.

Objective: We developed AlzMeta.app 2.0 (https://alzmetaapp.shinyapps.io/ALZMETA_APP_2/), web application that allows everyone to evaluate these drugs by pair-wise, frequentist and Bayesian network meta-analyses of phase II and III trial-level data (30/09/2024).

Methods: We followed PRISMA-NMA and GRADE guidelines for reporting and rating the certainty of evidence. Studies with < 20 sporadic AD patients and modified Jadad score < 3 were excluded. Relative risks and benefits are available with confidence, credible and prediction intervals for all outcomes.

Results: For significant results, the interventions are ranked in frequentist and Bayesian framework, and their clinical relevance can be determined by absolute risks per 1,000 people and Number-Needed-to-Treat (NNT) for expected control responses. Among seven treatments tested in 21,236 patients (26 studies with low risk of bias or with some concerns), Donanemab was the best-ranked on cognitive and functional measures, almost 2x more effective than Aducanumab and Lecanemab, and significantly more beneficial ($p < 0.05$) than other treatments on Clinical Dementia Rating Sum-of-Boxes (NNT = 10; 95% CI: 8; 16). Caution is required regarding cerebral edema and microbleeding, due to clinically relevant risks of edema for Donanemab (NNT = 8; 95% CI: 5; 16), Aducanumab (NNT = 10; 95% CI: 6; 17), and Lecanemab (NNT = 14; 95% CI: 7; 31).

Conclusions: AlzMeta.app 2.0 allows predictions of absolute risks and benefits of treatments based on clinical trial results, different prior choices, and assumptions of baseline risks of decline and adverse events. Our results show that Donanemab is more effective, yet with safety profile similar to Aducanumab and Lecanemab.?

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KEYWORDS: Alzheimer's; Antibodies; Donanemab; Aducanumab; Lecanemab

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest. The protocol for this study was not previously registered. Author disclosures are available in the Supporting Information.

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ABSTRACT

Background: The risk/benefit profile and clinical relevance of anti-amyloid antibodies in Alzheimer's disease (AD) is uncertain, with no scientific basis for choosing one treatment over another.

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Conclusions: AlzMeta.app 2.0 allows predictions of absolute risks and benefits of treatments based on clinical trial results, different prior choices, and assumptions of baseline risks of decline and adverse events. Our results show that Donanemab is more effective, yet with safety profile similar to Aducanumab and Lecanemab.

1. INTRODUCTION

Until lately, the only available therapies for Alzheimer's disease (AD) were symptomatic, and that situation remains in most countries. Regulatory approvals of Aducanumab (2021), Lecanemab (2023) and Donanemab (2024) in the United States have marked the new era in AD treatment, as these antibodies demonstrated some potential to modify disease progression by targeting amyloid-β (Aβ), toxic peptides deemed crucial in the AD pathophysiology [1]. While Aducanumab's development has been discontinued earlier this year (January 2024) [2], Lecanemab and Donanemab are currently under review for approval in Europe and worldwide [3], and Lecanemab is already available for patients outside of the United States, including those in the United Kingdom, Japan, China, South Korea, Israel and United Arab Emirates [4-6].

Despite clear advantages of anti-Aβ antibodies, substantial doubts remain about their risk/benefit profile and clinical relevance, and they still have to demonstrate clinically meaningful effect in real life [7-10]. We have previously developed web application meta-analysis of these treatments in phase III randomized placebo-controlled clinical trials (RCTs). Our analysis included Aducanumab [11], Lecanemab [12], Bapineuzumab [13, 14], and Solanezumab [15, 16], showing that Aducanumab and Lecanemab produced the most promising cognitive and functional and biomarker results. However, these effects were achieved at the great expense of increasing adverse events (AEs), primarily amyloid-related imaging abnormalities (ARIA) in the form of vasogenic cerebral edema (ARIA-E), and microhemorrhages and superficial siderosis (ARIA-H) [17]. Our study had some limitations, as we analyzed only large phase III RCTs (> 200 patients) with the conventional (pair-wise) meta-analysis method. This did not allow us to compare the effects of the treatments and rank their performance, and we failed to include smaller studies [18, 19] and novel antibodies, including Donanemab [20, 21], Gantenerumab [22, 23] and Crenezumab [24]. Therefore, the aim of this study was to update and expand our previous application with random-effect frequentist and Bayesian network meta-analyses (NMAs) of phase II and III RCTs in order to produce more reliable estimates

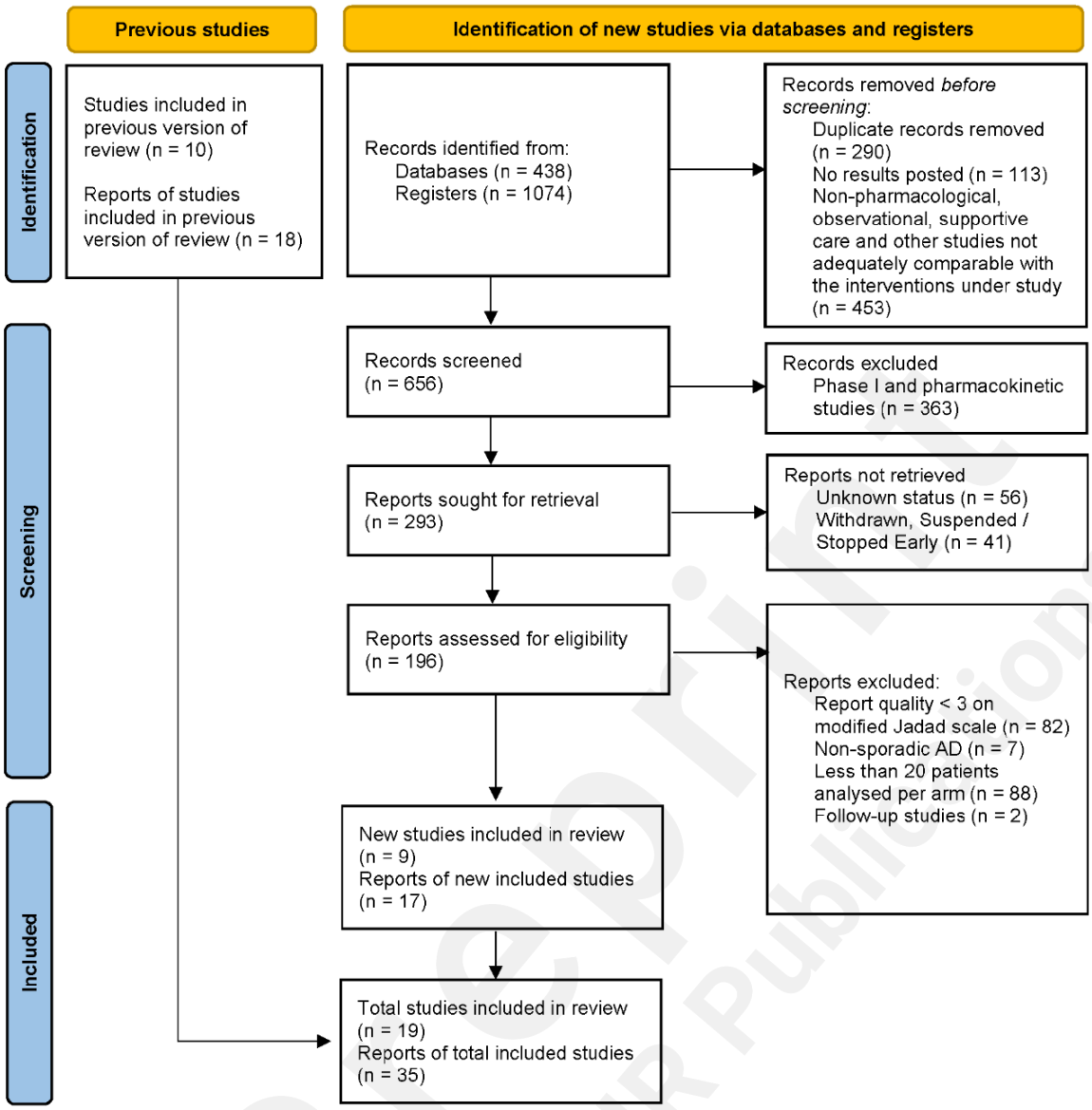
for the effects of anti-Aβ antibodies and evaluate their clinical relevance. To that extent, we provide transparent and interactive online assessment of risks and benefits for novel antibodies in sporadic AD that can be particularly useful now as the use of these antibodies becomes more widespread.

2. METHODS

We followed PRISMA-NMA [25] and GRADE guidelines [26] for reporting and rating certainty (quality) of underlying evidence. A detailed description of the methodology is provided in the Supplement.

2.1. Search strategy and inclusion criteria

The search terms included: “Alzheimer’s” , “sporadic” , “mild cognitive impairment” , “phase 3” , “phase 2” , “monoclonal antibody” , “passive immunotherapy” , “Aducanumab” , “BIIB037” , “Gantenerumab” , “Lecanemab” , “BAN-2401” , “Solanezumab” , “LY2062430” , “Crenezumab” , “Bapineuzumab” , “AAB-001” , “Donanemab” , and “LY3002813”. No age or language restrictions were applied. Study sources, report quality and risk-of-bias assessments, and statistical methods used in this study are summarized in Table S1 in the Supplement. We excluded studies that (1) tested < 20 sporadic AD patients and (2) were not phase II/III RCTs with report quality ≥ 3 on modified Jadad scale (Table S1). The search for eligible studies was done by each author independently (until September 30, 2024), and any disagreements were resolved through consensus. Excel was then used to automatically eliminate duplicate studies. The study did not include registered review protocol.



2.2. Outcomes

Primary outcomes included cognitive and functional measures from all or most studies, as mean changes from baseline on: (1) AD Assessment Scale-Cognitive Subscale (ADAS-Cog), (2) Mini Mental State Examination (MMSE), and (3) Clinical Dementia Rating scale-Sum of Boxes (CDR-SB). The results from the primary outcomes were evaluated to assess whether they achieved the minimal clinically important difference (MCID).

Secondary outcomes were biomarker and safety measures reported by all or most trials. Biomarkers included mean changes from baseline in amyloid burden on PET (centiloids), cerebrospinal fluid (CSF) biomarkers of $A\beta_{1-42}$ and p-*tau*-(Thr_{181}). Safety outcomes were serious AEs, tolerability

(treatment discontinuations due to AEs), and total events of: ARIA-E (cerebral edema and/or sulcal effusion), ARIA-H (cerebral microhemorrhages and superficial siderosis), headaches, dizziness, falls, arthralgia, diarrhea, urinary infections and nasopharyngitis.

Tertiary outcomes included AEs reported by few studies only: total events of ARIA-E in *APOE*-ε4 carriers and non-carriers, fatigue, nausea, back pain, and upper respiratory infections.

Apart from the outcome measures, we extracted inclusion criteria and baseline/participant characteristics of primary studies, including mean age (years, SD), sex/ethnicity/race, *APOE* status, baseline ADAS-Cog, MMSE and CDR-SB, dosage and administration routes.

2.3. The Certainty of Evidence

The certainty of underlying evidence at comparison-level was assessed by following GRADE approach that focuses on: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [26].

2.4. Role of funding source

The funder of the study had no role in study design, data collection, analysis, interpretation or writing of the report.

3. RESULTS

The meta-analysis included 21,236 patients with mild cognitive impairment (MCI) and early and mild-to-moderate sporadic AD in 26 studies (19 ClinicalTrials.gov registries from phase II and III RCTs, Fig. 1). Seven anti-amyloid monoclonal antibodies were evaluated: Bapineuzumab [13, 14, 19], Gantenerumab [22, 23], Aducanumab [11], Solanezumab [15, 16], Lecanemab [12, 18], Donanemab [20, 21], and Crenezumab [24, 27]. The analyzed RCTs compared the interventions with Placebo during 82.8 weeks on average (69-116 weeks), with acetylcholinesterase inhibitors and memantine allowed, alone or combined. Table 1 provides an overview of the baseline participant characteristics of the primary studies. Further baseline characteristics and inclusion/exclusion criteria

for primary studies are available in Table S2 and S3. The results of the quality of reports assessments (modified Jadad scale) and specific reasons for exclusions of each study can be found in Tables S4 and S5, respectively. Regarding the risk of bias, all studies were considered as having “low risk” or “raising some concerns” (Fig. S1-S2). For clinically relevant outcomes, Summary of Findings (SoF) Tables with rated certainty of evidence (vs. Placebo) according to GRADE approach can be found in Fig. S3-S10. Complete GRADE Table with certainty of evidence for each comparison within the NMA can be found in Table S6.

3.1. Primary outcomes

On the ADAS-Cog, five anti-amyloid antibodies were significantly more effective ($p < 0.05$) than Placebo in frequentist NMA (Table 2, Fig S3). These effect sizes were of small effect sizes (Donanemab > Gantenerumab > Lecanemab > Aducanumab > Solanezumab), with prediction intervals for Solanezumab including zero, suggesting possible non-significant difference from Placebo. Bayesian NMA validated these findings, showing strong support for the effects of Donanemab, Gantenerumab, Lecanemab and Aducanumab, and lack of strong evidence for Solanezumab.

On the MMSE, Donanemab and Solanezumab were the only treatments superior to Placebo with small effect sizes in frequentist NMA (Table 2, Fig S4). Convincing evidence in Bayesian NMA was found only for the effects of Donanemab.

On the CDR-SB, both frequentist and Bayesian NMA conclusively showed that Donanemab was significantly more effective than Placebo and all the other antibodies. While Aducanumab ($p = 0.0411$) and Lecanemab ($p = 0.0046$) demonstrated relative benefits over Placebo in frequentist NMA with small effect sizes and confidence intervals very close to zero (Table 2, Fig S5), Bayesian NMA results did not provide conclusive support for these effects. In other words, while Donanemab was superior to Placebo and other antibodies on the CDR-SB, Lecanemab and Aducanumab could be

associated with slightly higher benefits than Placebo; however, we cannot confidently rule out the possibility of no significant difference.

Heterogeneity was non-significant for primary outcomes (I^2 = 0%, p > 0.05), and inconsistency was not assessed because the networks were lacking closed loops. No evidence of publication bias was found, with Egger's test p-values of 0.554, 0.9076, and 0.7998 for the ADAS-Cog, MMSE, and CDR-SB, respectively. Funnel plots were symmetric for primary outcomes and the imputation of potentially "missing studies" did not change results. Bayesian network meta-regression revealed no impact of study characteristics (number of study sites, age of participants and baseline ADAS-Cog) on the effect size estimates for primary outcomes.

Donanemab outperformed all other antibodies according to P-scores in frequentist and SUCRA scores in Bayesian framework. SUCRA rankings were generally robust to study exclusions, with > 52% of trials not changing any rank (Table S7). High certainty (low information entropy) in ranking probabilities was found for the CDR-SB, where Donanemab produced the clinically most relevant effects (Table 2, Fig. 3).

3.2. Secondary outcomes

3.2.1. Biomarkers of Aβ and p-*tau*

Biomarker analyses (available on AlzMeta.app) revealed more promising results of the approved antibodies. Both frequentist and Bayesian NMAs of the PET data conclusively showed that four treatments significantly reduced Aβ brain burden by large effect sizes (Donanemab > Gantenerumab > Lecanemab > Aducanumab). Biomarkers of $A\beta_{1\text{-}42}$ in the cerebrospinal fluid (CSF) were improved by four antibodies in frequentist NMA (Crenezumab > Aducanumab > Lecanemab > Gantenerumab; not reported for Donanemab), however, Bayesian NMA provided strong support only for the effects of Crenezumab and Aducanumab. The results of amyloid biomarkers (CSF and PET) were not correlated with the mean changes observed in the primary outcomes.

CSF p-*tau* was significantly improved with three antibodies (Aducanumab > Gantenerumab > Lecanemab; not reported for Donanemab), however, Bayesian NMA validated only the effects of Aducanumab vs. Placebo. CSF p-*tau* measures were positively correlated with the effect sizes on the ADAS-Cog ($r = 0.77$; $p = 0.0259$) and CDR-SB ($r = 0.77$; $p = 0.0264$), with almost identical correlation coefficients and p-values. These calculations included Aducanumab, Lecanemab, Bapineuzumab, Gantenerumab and Crenezumab.

3.2.2. Safety outcomes

Anti-amyloid antibodies did not increase the risk of serious AEs. However, four interventions (Gantenerumab > Donanemab > Lecanemab > Aducanumab) were less tolerable than Placebo since they increased treatment discontinuations due to AEs by large effect sizes (Table 3, Fig S6). Crenezumab and Solanezumab were the most tolerable and the safest antibodies in terms of ARIA-E and ARIA-H. All other antibodies substantially increased the risk of total ARIA-E (Table 3, Fig S7). Heterogeneity was not significant ($p > 0.05$) for the risks of ARIA-E ($I^2 = 33.7\%$) and treatment dropouts due to AEs ($I^2 = 0\%$).

The risk of ARIA-H was significant for four antibodies (Aducanumab > Donanemab > Lecanemab > Gantenerumab) (Table 3, Fig S8), demonstrated conclusively by frequentist and Bayesian NMA. These estimates were obtained after excluding one influential study of Gantenerumab (GRADUATE II) [22] that induced heterogeneity in the full dataset analysis.

Additional safety analyses showed that anti-Aβ did not raise the risks of dizziness, arthralgia, diarrhea, nor urinary infections more than Placebo. No significant heterogeneity ($p > 0.05$) was found with all interventions analyzed, except for headaches ($I^2 = 69\%$) and urinary infections ($I^2 = 53.3\%$), and excluding influential Bapineuzumab [13] studies significantly reduced heterogeneity on both outcomes, leading to more certain estimates. This revealed that the risk of headaches was higher with Aducanumab, Lecanemab ($p < 0.05$) and Donanemab ($p < 0.05$) in the frequentist NMA (Fig 2,

3 and S9). However, Bayesian NMA did not provide conclusive evidence for these comparisons, and frequentist prediction intervals included 1 for all drugs except for Aducanumab. In addition, we found no enhanced risks of nasopharyngitis, however, these events were not reported for Donanemab and Lecanemab, antibodies tested during the COVID-19 pandemic (see 3.5 and Table S9).

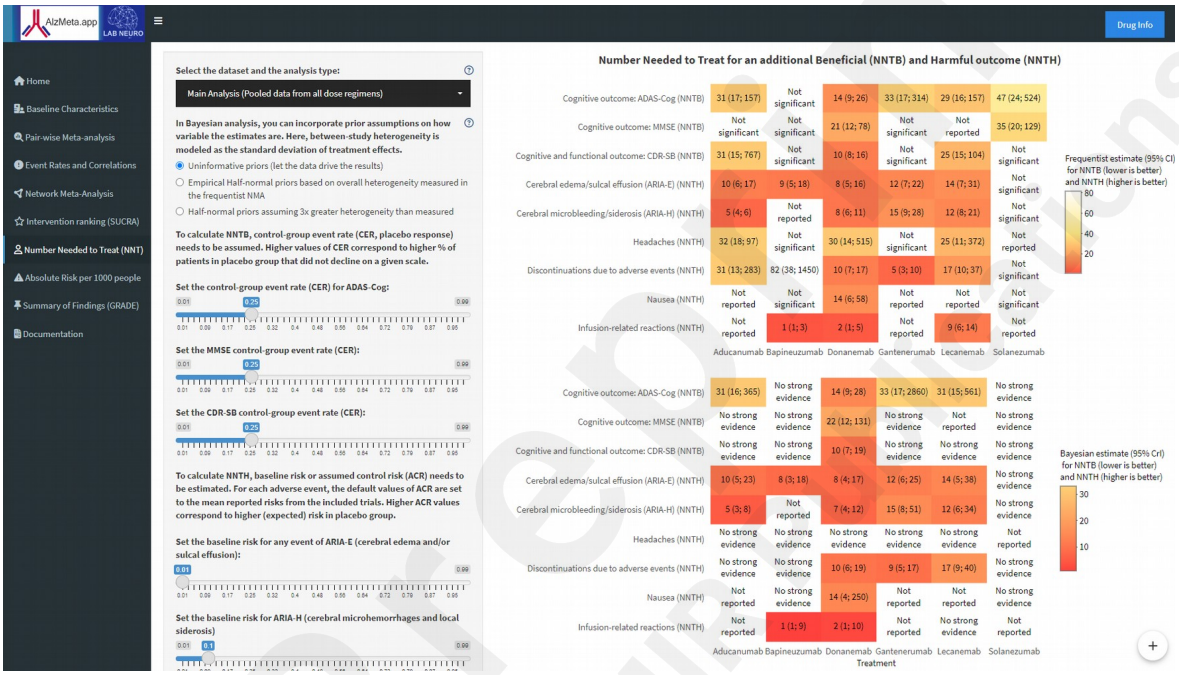
Significant positive correlations ($p \leq 0.01$) were found between the sample sizes of the intervention and control groups and the occurrences of various treatment-related AEs and potential nocebo effects. These AEs include nausea ($r > 0.96$), dizziness ($r > 0.89$), headaches ($r > 0.87$), serious AEs ($r > 0.76$) and treatment/placebo discontinuations due to AEs ($r > 0.54$). Additionally, when all interventions were analyzed, no correlation was observed between the total number of ARIA-E events and the sample size in the treatment group, while a moderate correlation was found in the control group ($r = 0.52$, $p = 0.027$). The correlations between ARIA-E events and sample sizes became significantly stronger after excluding outlying Solanezumab studies [15, 16], with $r = 0.67$ ($p = 0.004$) in the control group and $r = 0.73$ ($p = 0.002$) in the treatment group. No significant correlations were identified between the primary outcomes and safety outcomes.

The risk of ARIA-E was clinically relevant (Table 3, Fig. 2) for five antibodies (Donanemab > Bapineuzumab > Aducanumab > Gantenerumab > Lecanemab). Donanemab and Bapineuzumab were the least safe treatments based on P- and SUCRA scores (Fig. 3). For all these antibodies, except for Bapineuzumab, the risk of treatment discontinuation due to AEs was also clinically meaningful (Table 3; Fig. 2). Gantenerumab was the least tolerable, followed by Donanemab. Safety SUCRA rankings (Fig. 3) remained moderately-to-highly stable to study exclusion, with 89.5%, 50% and 81.8% of studies not affecting any rank for tolerability, ARIA-E and ARIA-H, respectively (Table S7).

3.3. Tertiary outcomes

Given the limited information about tertiary outcomes, our results indicate that Bapineuzumab,

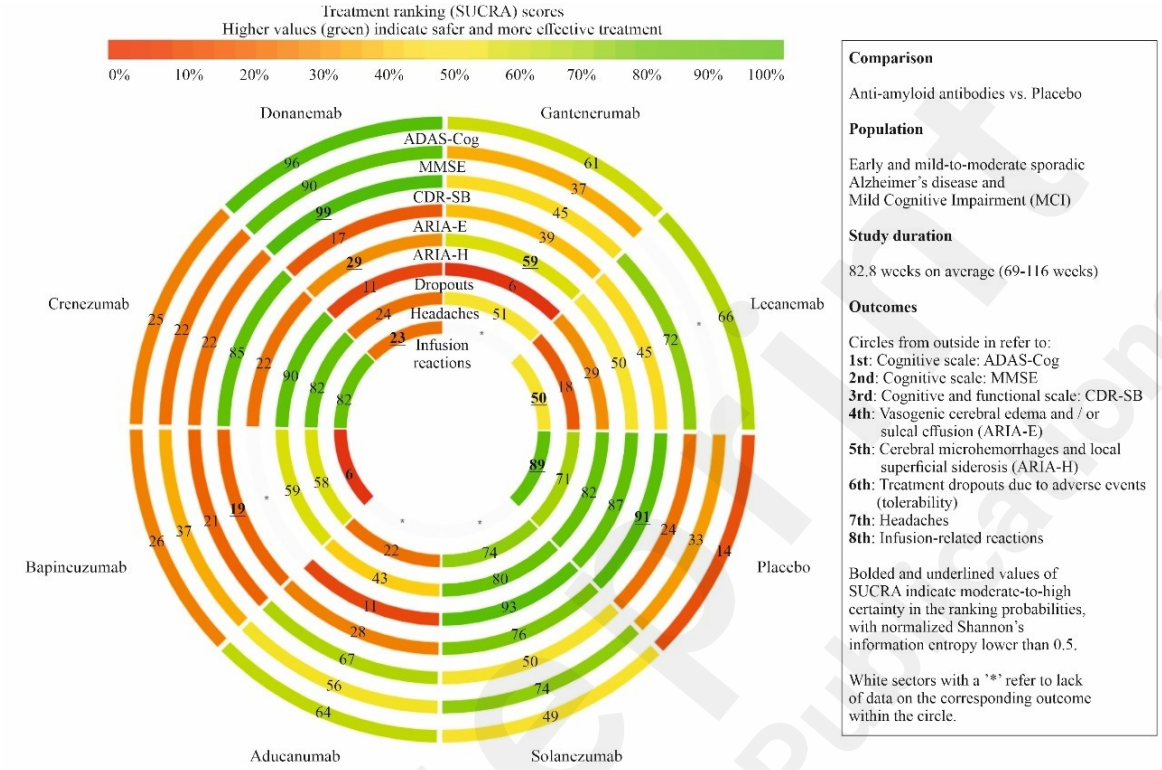
Donanemab, Lecanemab, Aducanumab, and Gantenerumab achieved clinically relevant risks of ARIA-E in both *APOE*-ε4 carriers and non-carriers (available in AlzMeta.app). The risk was higher in the carrier population, as reflected by confidence and prediction intervals and lower p-values within the frequentist NMA. The higher risk in carriers is particularly noticeable for Aducanumab and Gantenerumab (≈ 3x greater risk), and Bapineuzumab (≈ 2x greater risk), and less pronounced for Donanemab and Lecanemab, where lower number of events were reported in non-carriers, giving more uncertain estimates.



When compared to Placebo, three antibodies (Bapineuzumab > Donanemab > Lecanemab) significantly increased the risk of infusion-related reactions (Table 2, Fig. 2 and S10), which were mostly mild to moderate severity. These risks were all clinically relevant. Lecanemab was a relatively safer treatment option when compared to Donanemab and Bapineuzumab (Fig. 3), with moderate uncertainty in ranking probabilities and credible intervals including 1 in Bayesian framework. However, these estimates should be interpreted with caution, due to the small number of studies and treatments included in the comparisons, leading to the poor robustness of the SUCRA rankings (Table S7).

Donanemab increased the risk of nausea in two out of three treatment arms [20, 21]. Absolute risk

measures revealed that the risk of nausea was clinically relevant, however, with broad confidence intervals (Fig. 2), and overlapping prediction and credible intervals, suggesting considerable uncertainty in the estimates. Further analyses showed that the anti-Aβ antibodies did not increase the risks of fatigue, back pain, nor upper respiratory infections more than Placebo.



3.4. Sensitivity analyses

After excluding influential studies (Table S8), we found greater risks and benefits of high-dose Lecanemab and Aducanumab (in controversial EMERGE study [11, 28, 29]) for safety (ARIA-E, ARIA-H, headaches), cognitive/functional (ADAS-Cog, CDR-SB) and biomarker outcomes (CSF, PET). Also, the risk of ARIA-E was dose-dependent for Bapineuzumab, with greater risk with high-dose. For low-dose Aducanumab, no significant risk was found for treatment discontinuations due to AEs.

Dose-dependent efficacy of Aducanumab and Lecanemab was clinically meaningful on ADAS-Cog and CDR-SB, with greater absolute benefits of high-dose regimens. However, the intervention with Donanemab was still the best treatment option, almost 2x more effective than high-dose

Aducanumab and Lecanemab. Further sensitivity analysis showed that Donanemab had consistently greater cognitive and functional effects in patients with low/medium *tau* load than in high-*tau* population. Still, even upon removing low/medium *tau* study, Donanemab remained the best-ranked treatment, outperforming the other drugs on cognitive and functional measures.

3.5. The impact of the COVID-19

Among the studies included in this work, two Gantenerumab studies [22], one Lecanemab study [12] and three Donanemab studies [20, 21] were affected by global outbreak of coronavirus, which caused delays in study visits and assessments, possible unblinding of some participants, and other difficulties summarized in Table S9. The greatest impact was found in two phase III Donanemab studies [21], with the COVID-19 as the most commonly reported AE (≈17% in each arm). Less severe impact was found in Lecanemab phase III [12], with the COVID-19 diagnosed in ≈7% of patients in each arm. The reported impact of pandemic was minimal in other studies.

4. DISCUSSION

This study supports the efficacy of Donanemab and Lecanemab across multiple cognitive, functional and biomarker outcomes. The findings are consistent with our previous research [28] and other meta-analyses on anti-Aβ antibodies [8, 30-32], clearly indicating that Donanemab is the most effective treatment tested so far. Donanemab consistently showed greater benefits in patients with less developed *tau* pathology, suggesting more promising effect in earlier AD. At the same time, the risks of ARIA-E, ARIA-H and infusion-related reactions were substantial, indicating greater harm than benefit for all the approved antibodies. The risks for Donanemab were similar and potentially worse when compared to Lecanemab and Aducanumab. Lecanemab was a slightly safer and more tolerable option than Donanemab and Aducanumab, with lower risks of ARIA events and infusion-related reactions.

One of the main strengths of our study is its capacity to provide real-time estimates of both relative

and absolute risks and benefits of the interventions within multiple datasets and dose regimens. These calculations are done based on user-specific prior assumptions concerning heterogeneity and/or expected control responses (Fig. 2), and the intervention rankings are accompanied by measures of their robustness and uncertainty. To the best of our knowledge, this approach was not used in previous studies, and it allows researchers and clinicians to incorporate their own expectations based on clinical expertise and novel evidence, ensuring that the findings remain relevant and adaptable to various clinical scenarios. Furthermore, AlzMeta.app generates prediction intervals (PIs) for each outcome within the frequentist network meta-analysis. PIs account for uncertainty (heterogeneity) in the intervention estimates and aim to predict future individual observations. Therefore, when a new patient comes to the clinic, PIs (rather than CIs) should be used to forecast treatment effects and recommend the optimal treatment [33, 34]. Our web application (available in English and Spanish upon peer-review of this work) is very easy to use and provides extensive insight into the meta-analytic methodology, data structure and valuable information that can serve educational purposes for anyone interested in meta-analysis and/or these therapies. This approach can be easily updated and scaled up in the future, by incorporating novel treatment comparisons and other findings relevant to researchers, clinicians, and broader community.

Several limitations of this work need to be mentioned. Our study provides populational estimates based solely on the publicly available trial-level data, without integrating longitudinal findings. Potential bias might be introduced in the primary studies due to unblinding caused by the COVID-19 and frequent ARIAs. Recent simulation study estimated that 70%-100% of ARIA in trials led to some degree of therapeutic insight. Further adaptations in trial design and more detailed reporting and analysis of unblinding events are required [35]. Moreover, the patients in Donanemab phase III study [21] were stratified by their brain *tau* levels, which was not done in other trials, and direct head-to-head comparison between high-clearance antibodies has not been made yet. Therefore, our NMA only included studies where treatments were compared with Placebo. Finally, the trials done so far

lacked racial and ethnic diversity (Table S2), which prevented us from determining whether the risks and benefits of these treatments may vary across different populations. Similarly, the patients with abnormal MRI findings, brain damage, major depression, schizophrenia and other serious neuropsychiatric conditions prevalent in AD population were excluded from the primary studies (Table S3).

Low tolerance and high risks of ARIAs and infusion-related reactions loom over the approved anti-Aβ antibodies. ARIA-E is often asymptomatic and transient, but sometimes moderate or severe with symptoms such as headache, dizziness and seizures that may require interruption or discontinuation of therapy, hospitalization and enhanced monitoring (brain imaging, electroencephalography, corticosteroids and anticonvulsants) [36, 37]. ARIA events are linked to inflammation, blood-brain barrier disruption and cerebrovascular impairment, already common in elderly and patients with AD, meaning that a vast number of AD patients are potentially not eligible for the therapy [38-40], as reflected in the exclusion criteria of the clinical trials (Table S3). Risk factors for ARIA are dose-dependent and include receiving anti-Aβ immunotherapy, anticoagulant and thrombolytic medication, *APOE*-e4 carriage, and history of brain microhemorrhages or stroke [41, 42].

Based on the evidence so far, the cognitive and functional benefits of anti-Aβ antibodies are far below the minimal clinically important difference (MCID) [17, 30, 31]. Direct comparative and longitudinal studies are required to fully disclose the impact of anti-Aβ immunotherapy over longer periods of time and better assess treatment-emergent risks in different populations. Exploratory *post hoc* modeling based on phase III RCT of Donanemab [21] suggested that Aβ levels in treated patients would remain below the positivity threshold for nearly 4 years without treatment, though it is uncertain whether the MCID would be achieved in the long term on cognitive and functional outcomes.

In summary, our results demonstrate small cognitive and functional benefits and substantial biomarker effects of Donanemab and Lecanemab, and superiority of Donanemab on cognitive and

functional outcomes. Yet, these effects were achieved with significant trade-off in the form of high risks of treatment dropouts, infusion-related reactions, cerebral vasogenic edema or sulcal effusion (ARIA-E), microbleeding and local siderosis (ARIA-H). The risks may outweigh the benefits, highlighting the need for safer therapies and additional trials to better assess the risk-benefit profile and determine patient eligibility. A personalized approach that incorporates multi-target therapies together with novel vascular and inflammation biomarkers might be required to improve AD treatment [43].

AUTHORS' CONTRIBUTIONS

JDNL and LJD were responsible for the initial conceptualization, funding acquisition, supervision, and project administration; DJ was responsible for Data curation, Software development, Formal analysis, visualization and writing the original draft; JD, JDNL and LJD did the writing – review and editing. All authors read and approved the final manuscript.

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FIGURES

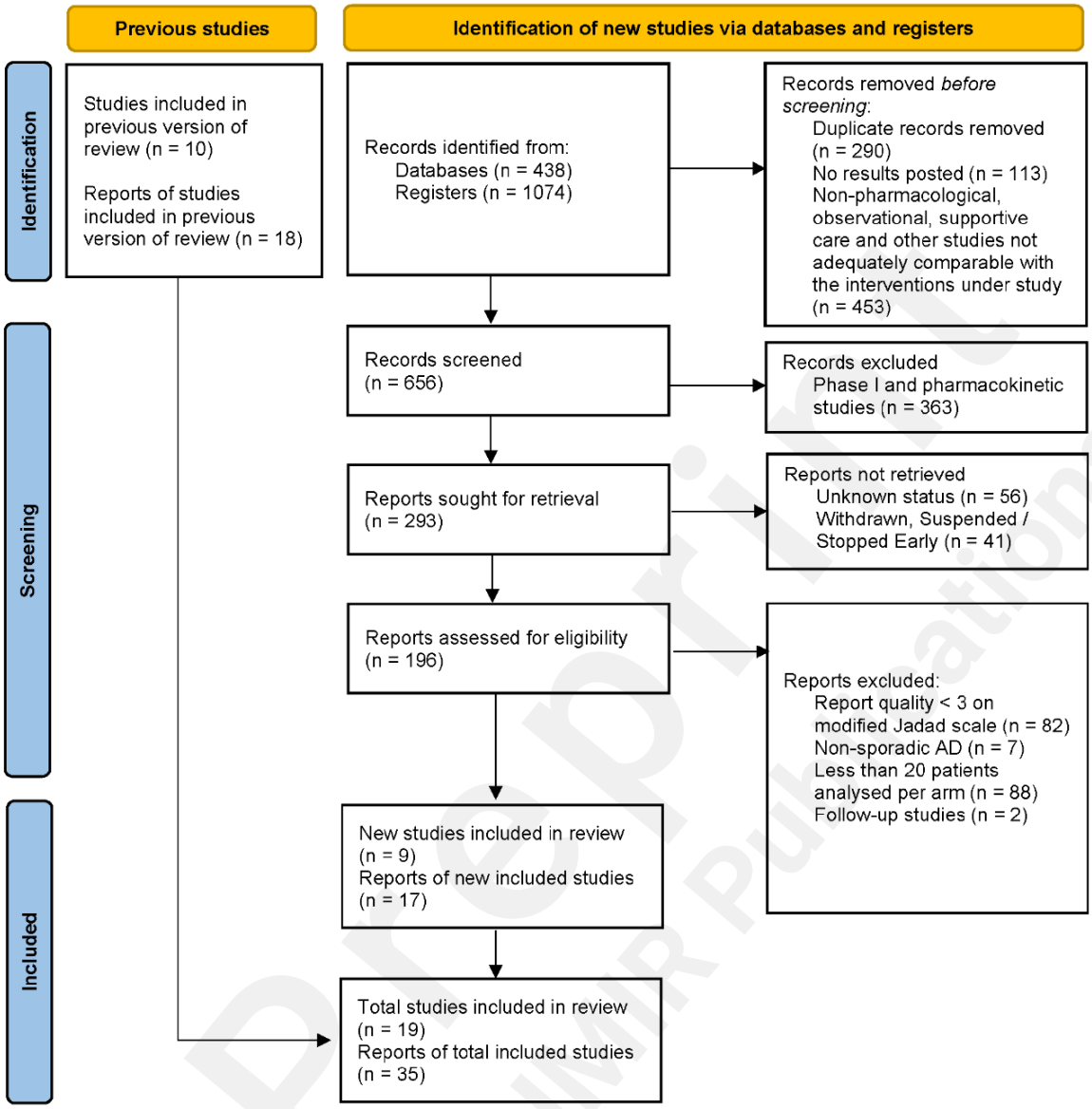


Figure 1. PRISMA Flow Diagram.

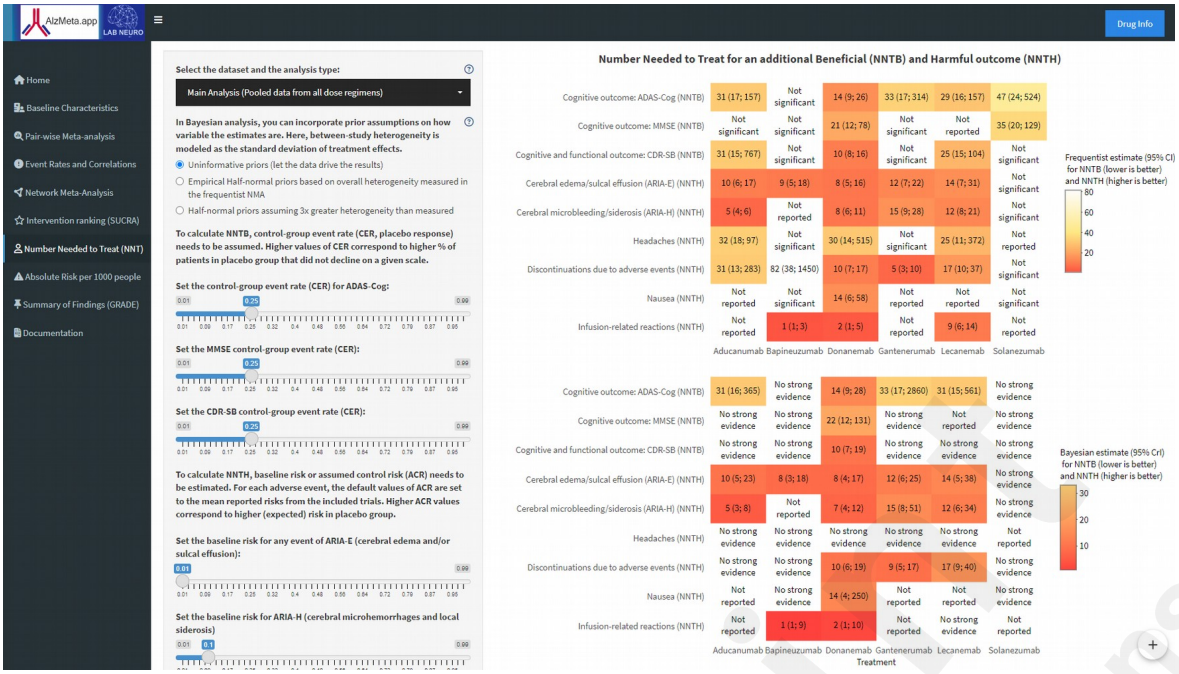


Figure 2. Number Needed to Treat (NNT) section in AlzMeta.app 2.0 showing frequentist and Bayesian estimates of NNT for an additional Beneficial (NNTB) and Harmful outcome (NNTH) for statistically significant results. The estimates can be obtained over a wide range of placebo responses, including the rates of AD progression and adverse event risks expected in the control group. Similarly, the Absolute Risks (AR) per 1000 people can be calculated based on assumed control risk. Furthermore, Bayesian NMA can be performed with different choices of heterogeneity priors (Supplementary Methods): (1) uninformative priors (with large variance), (2) half-normal priors for standard deviation, with scale factors based on overall heterogeneity measured in the frequentist NMA and (3) half-normal priors assuming three times greater heterogeneity.

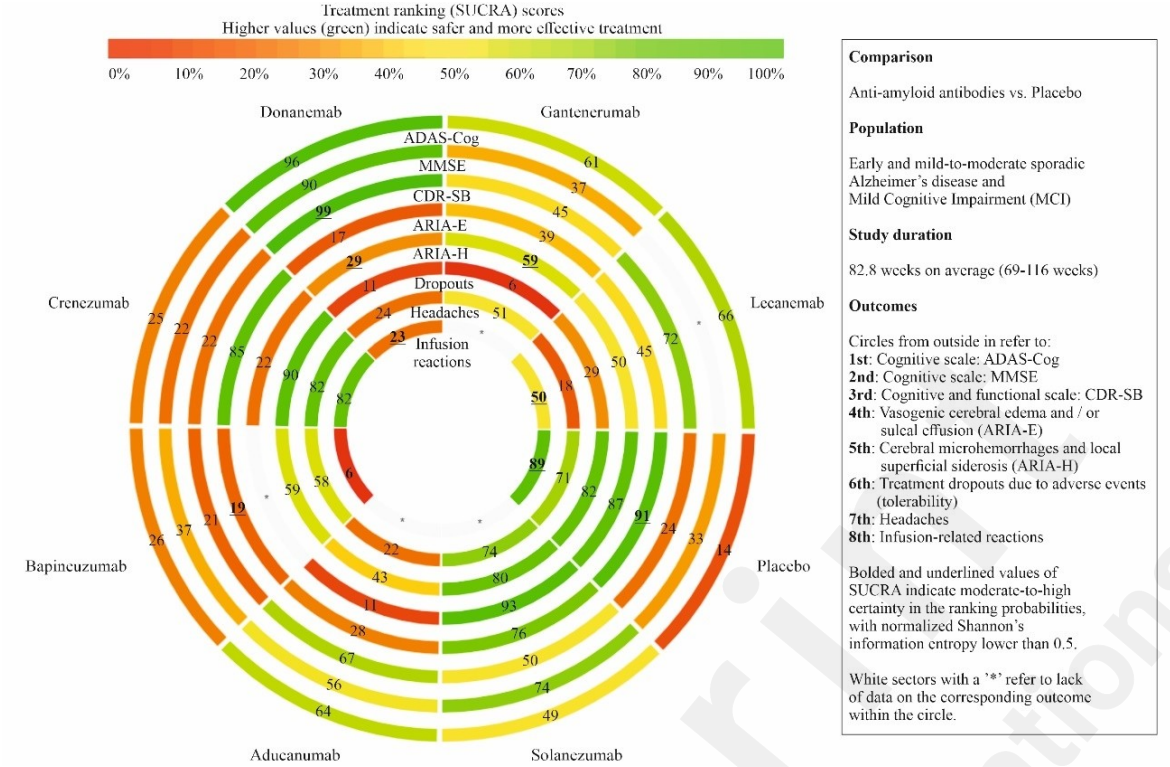


Figure 3. SUCRA Rank-Heat Plot for clinically relevant results achieved by more than one intervention.

TABLES

Table 1. Baseline participant characteristics. Abbreviations**:** MMSE – Mini-Mental State Examination; q2w – once every 2 weeks; q4w – once every 4 weeks; q13w - every 13 weeks. Additional Baseline characteristics can be found in Table S2 in the Supplement.

Study name (Year) Dose	Clinical trial ID	Phase	Study duration (weeks)	Dosage	No. of patients analyzed (Placebo vs. Intervention)	Defined AD stage and MMSE scores for inclusion
Salloway et al (2009) high dose	NCT00112073	II	78	1 mg/kg q13w for 78 weeks	22 vs. 26	Mild/moderate (16–26)
Salloway et al 1 (2014) Study 301 low dose	NCT00574132	III	78	0.5 mg/kg q13w for 78 weeks	493 vs. 314	Mild/moderate (16–26)
Salloway et al 2 (2014) Study 301 high dose	NCT00574132	III	78	1 mg/kg q13w for 78 weeks	493 vs. 307	Mild/moderate (16–26)
Salloway et al 3 (2014) Study 302 low dose	NCT00575055	III	78	0.5 mg/kg q13w for 78 weeks	432 vs. 658	Mild/moderate (16–26)
Doody et al 1 (2014) EXPEDITION 1	NCT00905372	III	78	400 mg q4w for 78 weeks.	506 vs. 506	Mild/moderate (16–26)
Doody et al 2 (2014) EXPEDITION 2	NCT00904683	III	78		519 vs. 521	Mild/moderate (16–26)
Vandenberghe et al 1 (2016) low dose	NCT00667810	III	78	0.5 mg/kg q13w for 78 weeks	328 vs. 328	Mild/moderate (16–26)
Vandenberghe et al 2 (2016) high dose	NCT00667810	III	78	0.5 mg/kg q13w for 78 weeks	328 vs. 253	Mild/moderate (16–26)
Vandenberghe et al 3 (2016) low dose	NCT00676143	III	78	1 mg/kg q13w for 78 weeks	431 vs. 650	Mild/moderate (16–26)
Honig et al (2018) EXPEDITION 3	NCT01900665	III	76	400 mg q4w for 76 weeks.	1057 vs. 1072	Mild (20–26)

Haeberlein et al (2022) EMERGE low dose	NCT02484547	III	76	3 or 6 mg/kg q4w over 76 weeks. The dose was titrated to a target dose of 3 mg/kg (*APOE* ε4+) or 6 mg/kg (*APOE* ε4-)	548 vs. 543	Early (MCI and Mild AD) (24–30)
Haeberlein et al (2022) EMERGE high dose	NCT02484547	III	76	6 mg/kg or 10 mg/kg q4w over 76 weeks. The dose was titrated to a target dose of 6 mg/kg (*APOE* ε4+) or 10 mg/kg (*APOE* ε4-) prior to protocol amendments.	548 vs. 547	Early (MCI and Mild AD) (24–30)
Haeberlein et al (2022) ENGAGE low dose	NCT02477800	III	76	3 or 6 mg/kg q4w over 76 weeks. The dose was titrated to a target dose of 3 mg/kg (*APOE* ε4+) or 6 mg/kg (*APOE* ε4-)	545 vs. 547	Early (MCI and Mild AD) (24–30)
Haeberlein et al (2022) ENGAGE high dose	NCT02477800	III	76	6 mg/kg or 10 mg/kg q4w over 76 weeks. The dose was titrated to a target dose of 6 mg/kg (*APOE* ε4+) or 10 mg/kg (*APOE* ε4-) prior to protocol amendments.	545 vs. 555	Early (MCI and Mild AD) (24–30)
van Dyck et al (2023) Clarity AD	NCT03887455	III	78	10 mg/kg every 2 weeks over 78 weeks	875 vs. 859	Early (MCI and Mild AD) (20–26)
Swanson et al.1 (2021) high dose	NCT01767311	II	78		238 vs. 152	Early (MCI and Mild AD) (22–30)
Swanson et al.2 (2021) low dose	NCT01767311	II	78	10 mg/kg every month for 78 weeks	238 vs. 246	Early (MCI and Mild AD) (22–30)

Sims et al (2023) TRAILBLAZER-ALZ 2 (pooled)	NCT04437511	III	76	700 mg for the first three doses and 1400 mg thereafter q4w over 72 weeks	876 vs. 860	Early (MCI and Mild AD) (20–28)
Mintun et al (2021) TRAILBLAZER-ALZ	NCT03367403	II	72	700 mg for the first three doses and 1400 mg thereafter q4w over 72 weeks	126 vs. 131	Early (MCI and Mild AD) (20–28)
Bateman et al (2023) GRADUATE I	NCT03448870	III	116	Participants received a minimum of 3 doses at each stage: starting at 120 mg q4w and then increasing to 255 mg q4w, then to 510 mg q4w, and finally to 510 mg q2w.	485 vs. 499	Early (MCI and Mild AD) (≥ 22)
Bateman et al (2023) GRADUATE II	NCT03443973	III	116		477 vs. 498	Early (MCI and Mild AD) (≥ 22)
Ostrowitzki et al (2022) CREAD	NCT02670083	III	105	60 mg/kg q4w for up to 100 weeks	86 vs. 80	Early (Prodromal to Mild (≥ 20)
Salloway et al (2018) BLAZE (pooled)	NCT01397578	II	69	Part 1: 300 mg subcutaneous (q2w). Part 2: 15 mg/kg intravenous crenezumab q4w.	29 vs. 62	Mild to Moderate (18-26)
Ostrowitzki et al (2017) SCarlet RoAD I	NCT01224106	III	100	105 mg by SC injection q4w (Q4W) for 104 weeks or approximately 2 years during Part 1 of the study.	133 vs. 271	Early AD (≥ 24)
Ostrowitzki et al (2017) SCarlet RoAD II	NCT01224106	III	100	225 mg by SC injection (q4w) for 104 weeks or approximately 2 years during Part 1 of the study	133 vs. 260	Early AD (≥ 24)

Table 2. Frequentist NMA-Summary of Findings: Effectiveness on cognitive and functional outcomes. Abbreviations: ADAS-Cog - Alzheimer's Disease Assessment Scale - Cognitive Subscale; CDR-SB - Clinical Dementia Rating Scale Sum of Boxes; MMSE – Mini-Mental State Examination; NNTB - Number Needed to Treat for an additional Beneficial outcome; RCT - randomized placebo-controlled clinical trial

Benefits	**Intervention** No. of RCTs; No. of patients	**Relative effect**:[*] SMD (95% CI)	**Absolute effect:**[†] NNTB (95% CI)	**Ranking:**[‡] P-score; SUCRA (Rank Uncertainty)	**Evidence certainty**	**Interpretation**
ADAS-Cog (cognitive scale; lower SMD is more favorable)	**Donanemab** 3 RCTs; 1469	SMD = -0.22 (-0.32; -0.12)	NNTB = 14 (9; 26)	0.97; 96.31% (0.81)	Low ⊕⊕⊖⊖ [1]	Probably better than Placebo
	Lecanemab 3 RCT; 2109	SMD = -0.11 (-0.19; -0.02)	NNTB = 29 (16; 157)	0.67; 66.03% (0.94)	Very low ⊕⊖⊖⊖ [2]	Probably better than Placebo
	Aducanumab 4 RCTs; 2301	SMD = -0.10 (-0.18; -0.02)	NNTB = 31 (17; 157)	0.65; 64.17 (0.95)	Very low ⊕⊖⊖⊖ [2]	Probably better than Placebo
	Gantenerumab 3 RCTs; 4172	SMD = -0.10 (-0.18; -0.01)	NNTB = 33 (17; 314)	0.62; 60.58% (0.93)	Very low ⊕⊖⊖⊖ [2]	Probably better than Placebo
	Solanezumab 3 RCTs; 4172	SMD = -0.07 (-0.13; -0.01)	NNTB = 47 (24; 524)	0.48; 48.57% (0.93)	Very low ⊕⊖⊖⊖ [3]	Possibly better, with no conclusive difference
MMSE (cognitive scale; higher SMD is more favorable)	**Donanemab** 3 RCTs; 1460	SMD = 0.14 (0.04; 0.25)	NNTB = 21 (12; 131)	0.92; 90.16% (0.53)	Very low ⊕⊖⊖⊖ [1]	Probably better than Placebo
	Solanezumab 3 RCTs; 3821	SMD = 0.09 (0.02; 0.15)	NNTB = 47 (24; 524)	0.76; 73.79% (0.74)	Very low ⊕⊖⊖⊖ [3]	Possibly better, with no conclusive difference
CDR-SB (cognitive and functional scale;	**Donanemab** 3 RCTs; 1452	SMD = -0.29 (-0.40; -0.19)	NNTB = 10 (8; 16)	1.00; 99.01% (0.27)	Low ⊕⊕⊖⊖ [1]	Probably better than Placebo
	Lecanemab	SMD = -0.12	NNTB = 25 (15;	0.75;	Very low [3]	Possibly better, with no

lower SMD is more favorable)	3 RCT; 2128	(-0.21; -0.03)	104)	72.46% (0.81)	⊕⊖⊖⊖	conclusive difference
	Aducanumab 4 RCTs; 2301	SMD = -0.10 (-0.20; -0.002)	NNTB = 31 (15; 767)	0.68; 67.48% (0.87)	Very low [3] ⊕⊖⊖⊖	Possibly better, with no conclusive difference

NMA-Summary of Findings Table definitions

* Lines in the network represent direct comparison. Line width is proportional to the number of studies.

** Relative effects are expressed as Standardized Mean Difference: SMD (95% CI). Bolded numbers indicate strong evidence of non-zero effect.

*** Absolute effects are expressed as NNTB: Number Needed to treat for an additional Beneficial outcome, with assumed control-event rate (CER) of 0.25.

**** In frequentist NMA, the treatments are ranked with a P-score that measures the mean extent of certainty that a given treatment is better than the competing treatments, ranging from 0 to 1 (higher is better). In Bayesian framework, SUCRA ranks show the average percentage of treatments that are worse than a given treatment, which can range from 0% to 100%. The closer the SUCRA score is to 100%, the more likely it is that the treatment is the best option. Rank uncertainty is measured by normalized Shannon's information entropy score of Bayesian ranking probabilities, ranging from 0 (absolute certainty) to 1 (absolute uncertainty).

GRADE Working Group grades of certainty in the evidence

High: We are very confident that the true effect size lies close to that of the estimated effect.

Moderate: We are moderately confident in the estimate. The true effect size is likely to be close to our estimate, with the possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Explanatory note:

[1] Due to small effect size, imprecision and wide prediction and credible intervals

[2] Due to small effect size, imprecision and wide prediction and credible intervals very close to zero

[3] In frequentist NMA, the Standardized Mean Differences (SMDs) were statistically significant on ADAS-Cog (p = 0.0313) and MMSE (p =

0.0068) for Solanezumab, and on CDR-SB for Lecanemab (p = 0.0073) and Aducanumab (p = 0.0464), but with the confidence and prediction intervals including zero or very close to zero and large NNTB values. This suggests that these effects are unlikely to be clinically relevant. In Bayesian framework, the interventions could be associated with a slightly higher benefit than Placebo on the respective outcomes, but with credible intervals including zero, therefore, we cannot confidently rule out the possibility of no significant difference.

Table 3. Bayesian NMA-Summary of Findings: Safety outcomes. Abbreviations: AR per 1000 – Absolute Risk expressed as number of cases per 1000 people; ARIA-E – Amyloid-Related Imaging Abnormalities in form of cerebral edema. NNTH - Number Needed to Treat for an additional Harmful outcome:

Risks (Assumed control risk, ACR) †	**Intervention** No. of RCTs; No. of patients	**Relative effect**:* SMD (95% CI)	**Absolute effect:** † NNTB; AR per 1000 (95% CI)	**Ranking:** ‡ P-score; SUCRA (Rank Uncertainty)	**Evidence certainty**	**Interpretation**
ARIA-E: Vasogenic cerebral edema and / or sulcal effusion (ACR = 0.01)	**Lecanemab** 3 RCT; 2454	RR = 8.23 (4.33; 15.64)	NNTH = 14 (7; 31) AR = 77 (42; 143)	0.46; 44.94% (0.78)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Gantenerumab 4 RCTs; 2736	RR = 9.36 (5.70; 15.37)	NNTH = 12 (7; 22) AR = 91 (56; 143)	0.40; 39.31% (0.78)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Aducanumab 4 RCTs; 3249	RR = 11.40 (6.94; 18.73)	NNTH = 10 (6; 17) AR = 112 (67; 167)	0.27; 28.38 (0.79)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Bapineuzumab 6 RCTs; 4278	RR = 12.97 (6.82; 24.65)	NNTH = 9 (5; 18) AR = 125 (67; 200)	0.19; 18.38% (0.72)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Donanemab 3 RCTs; 1981	RR = 13.60 (7.58; 24.38)	NNTH = 8 (5; 16) AR = 125 (72; 200)	0.16; 17.71% (0.71)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
ARIA-H: Cerebral microhemorrhages and local siderosis (ACR = 0.10)	**Gantenerumab** 3 RCTs; 1770	RR = 1.70 (1.36; 2.14)	NNTH = 15 (9; 28) AR = 167 (125; 200)	0.59; 58.62% (0.85)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Lecanemab 3 RCT; 2454	RR = 1.89 (1.48; 2.41)	NNTH = 12 (8; 21)	0.50; 49.56% (0.86)	Moderate [1]	Probably worse than Placebo

			AR = 167 (143; 200)		⊕⊕⊕⊖	
	Donanemab 3 RCTs; 1981	RR = 2.43 (2.00; 2.95)	NNTH = 8 (6; 11) AR = 200 (167; 250)	0.21; 28.57% (0.86)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Aducanumab 4 RCTs; 3253	RR = 3.39 (2.75; 4.18)	NNTH = 5 (4; 6) AR = 334 (250; 334)	0.10; 11.39% (0.82)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
Tolerability: Treatment Discontinuations due to Adverse Events (ACR = 0.05)	**Bapineuzumab** 7 RCTs; 4507	RR = 1.24 (1.01; 1.52)	NNTH = 82 (28; 1450) AR = 59 (50; 72)	0.59; 59.29% (0.78)	Very low [2] ⊕⊖⊖⊖	Possibly worse than Placebo, with no conclusive difference
	Aducanumab 4 RCTs; 3249	RR = 1.65 (1.07; 2.54)	NNTH = 31 (13; 283) AR = 77 (53; 125)	0.43; 43.20% (0.83)	Low [3] ⊕⊕⊖⊖	Probably worse than Placebo
	Lecanemab 3 RCT; 2454	RR = 2.18 (1.54; 3.07)	NNTH = 17 (10; 37) AR = 100 (77; 143)	0.29; 28.85% (0.74)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Donanemab 3 RCTs; 1981	RR = 3.04 (2.19; 4.23)	NNTH = 10 (7; 17) AR = 143 (100; 200)	0.11; 11.29% (0.66)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Gantenerumab 4 RCTs; 2756	RR = 3.44 (2.32; 5.10)	NNTH = 5 (3; 10) AR = 250 (143; 334)	0.05; 6.21% (0.38)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
Infusion-related reactions (ACR = 0.04)	**Lecanemab** 3 RCT; 2454	RR = 4.08 (2.87; 5.80)	NNTH = 9 (6; 14) AR = 143 (112; 200)	0.50; 49.69% (0.42)	Very low [2] ⊕⊖⊖⊖	Possibly worse than Placebo, with no conclusive difference
	Donanemab 3 RCTs; 1981	RR = 17.65 (6.71; 46.43)	NNTH = 2 (1; 5) AR = 500 (250; 1000)	0.22; 23.29% (0.47)	Moderate [1] ⊕⊕⊕⊖	Probably worse than Placebo
	Bapineuzumab 1 RCTs; 1121	RR = 68.56 (9.39; 500.85)	NNTH = 1 (1; 3) AR = 1000 (334; 1000)	0.03; 6.17% (0.38)	Very low [4] ⊕⊕⊕⊖	Probably worse than Placebo

* Relative effects are expressed as Risk Ratios: RR (95% CI).

† For safety outcomes, absolute effects are expressed as absolute risks (AR per 1000 people) and as NNTH: Number Needed to treat for an additional Beneficial outcome, with assumed control risks (ACR) equal to the average control risk for each outcome, weighted by the number of participants that received Placebo.

‡ In Bayesian framework, SUCRA ranks show the average percentage of treatments that are worse than a given treatment, which can range from 0% to 100%. The closer the SUCRA score is to 100%, the more likely it is that the treatment is the best option. Rank uncertainty is measured by normalized Shannon's information entropy score of Bayesian ranking probabilities, ranging from 0 (absolute certainty) to 1 (absolute uncertainty).

GRADE Working Group grades of certainty in the evidence

High: We are very confident that the true effect size lies close to that of the estimated effect.

Moderate: We are moderately confident in the estimate. The true effect size is likely to be close to our estimate, with the possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Explanatory note:

[1] Due to large magnitude of effect size.

[2] In frequentist NMA, statistically significant risk was found of infusion-related reactions for Lecanemab ($p < 0.0001$), and of treatment discontinuations for Bapineuzumab ($p = 0.0421$), but with prediction intervals close to 1 or including 1 (for Bapineuzumab), suggesting that these effects are unlikely to be clinically relevant. In Bayesian framework, these treatments could be associated with a slightly higher risk than Placebo on the respective outcomes, but with credible intervals including 1, thus, we cannot confidently rule out the possibility of no significant difference.

[3] Due to wide credible intervals and imprecision

[4] Due to wide credible intervals, imprecision and small number of studies

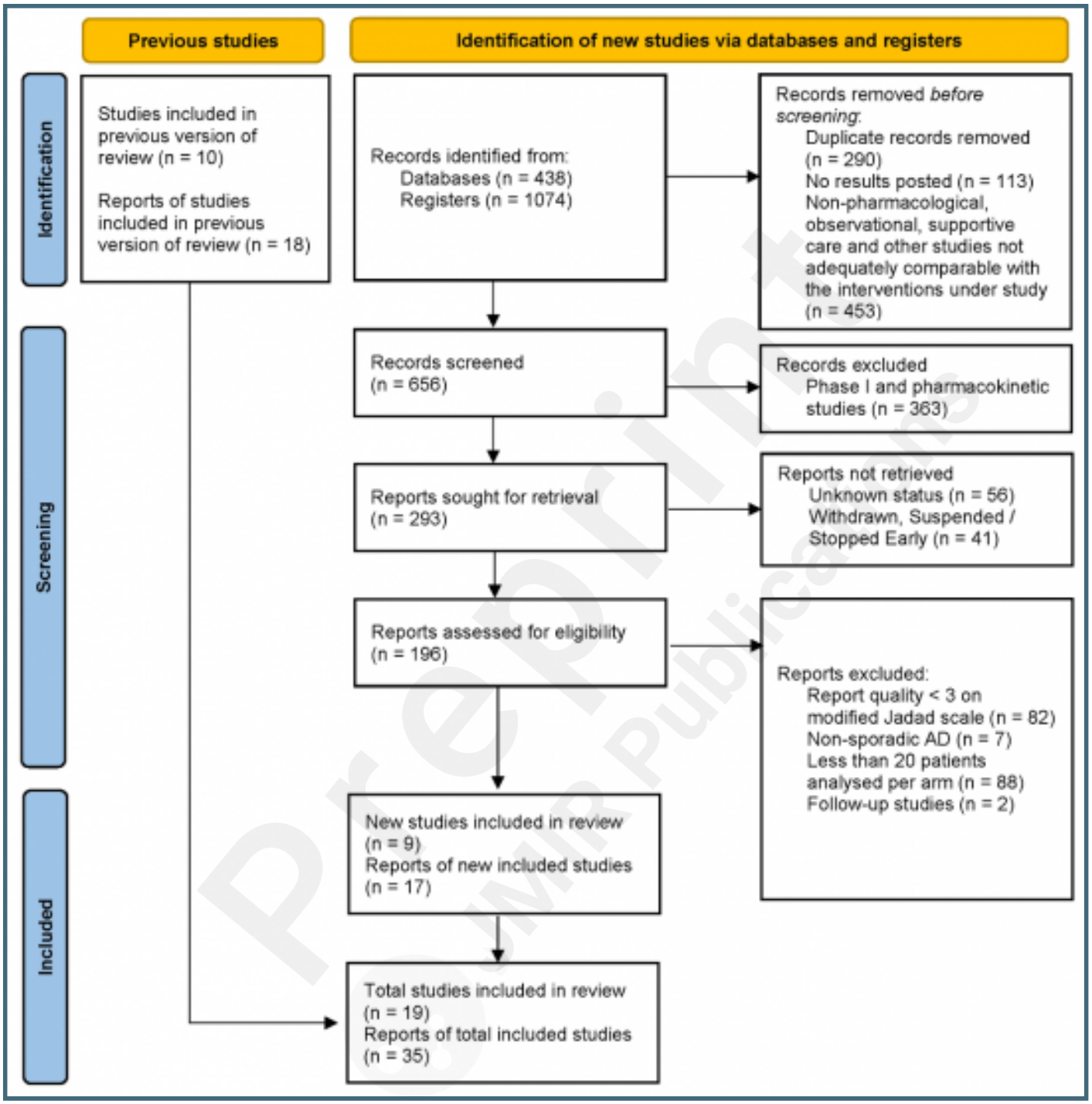
Supplementary Materials

1. PRISMA NMA Checklist
2. Supplementary Methods + Table S1
3. Supplementary Tables S2-S9
4. Supplementary Figures S1-S10

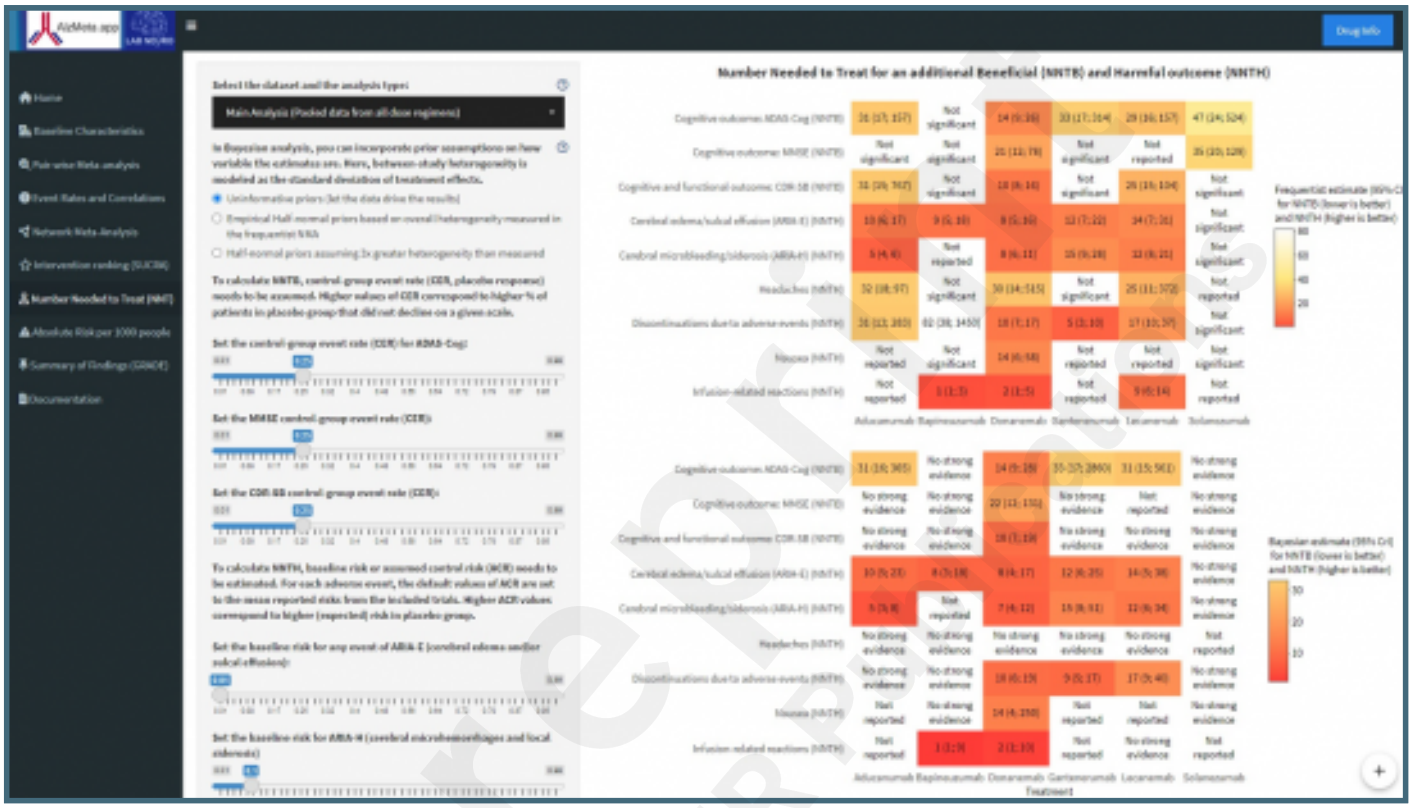
Supplementary Files

Figures

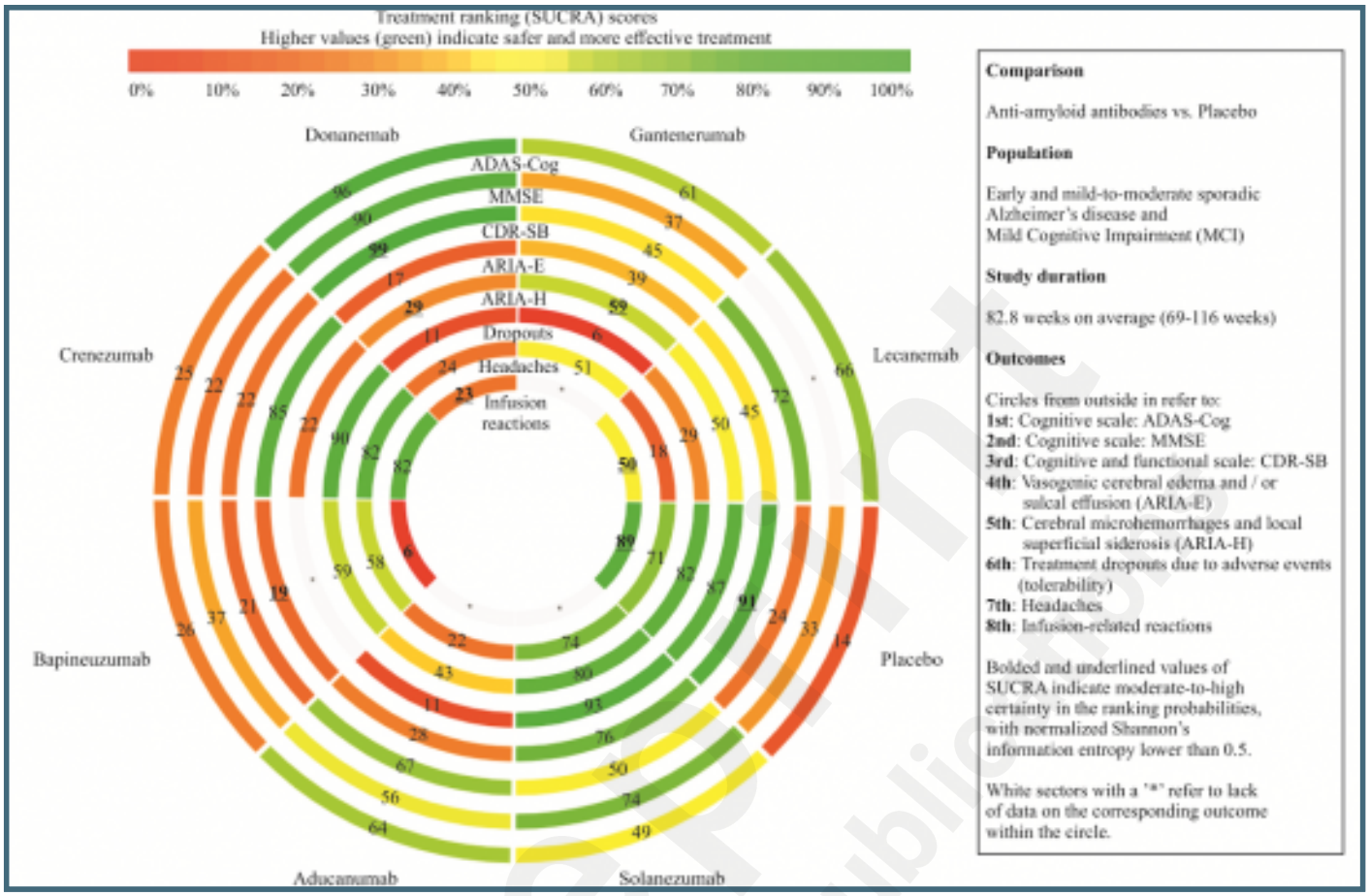
PRISMA Flow Diagram.



Number Needed to Treat (NNT) section in AlzMeta.app 2.0 showing frequentist and Bayesian estimates of NNT for an additional Beneficial (NNTB) and Harmful outcome (NNTH) for statistically significant results. The estimates can be obtained over a wide range of placebo responses, including the rates of AD progression and adverse event risks expected in the control group. Similarly, the Absolute Risks (AR) per 1000 people can be calculated based on assumed control risk. Furthermore, Bayesian NMA can be performed with different choices of heterogeneity priors (Supplementary Methods): (1) uninformative priors (with large variance), (2) half-normal priors for standard deviation, with scale factors based on overall heterogeneity measured in the frequentist NMA and (3) half-normal priors assuming three times greater heterogeneity.



SUCRA Rank-Heat Plot for clinically relevant results achieved by more than one intervention.



Multimedia Appendixes

PRISMA NMA Checklist of Items.
URL: http://asset.jmir.pub/assets/e2bf81fb89a5d8fa40fee7cf159d498b.pdf

Supplementary Methods - Table S1.
URL: http://asset.jmir.pub/assets/ea4cec89fdf3d3424d847692a1cb2921.docx

Supplementary Figures (S1-S10).
URL: http://asset.jmir.pub/assets/851f9adee66ae78453d0a18765920a25.pptx

Supplementary Tables (S2-S9).
URL: http://asset.jmir.pub/assets/acc199d42edd1861bd3f6e909b2674c5.docx