Systematic Review

Safety and Efficacy of Monoclonal Antibodies for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Published and Unpublished Clinical Trials

Eleonora Lacorte^a, Antonio Ancidoni^{a,b}, Valerio Zaccaria^c, Giulia Remoli^a, Leonardo Tariciotti^d, Guido Bellomo^a, Francesco Sciancalepore^a, Massimo Corbo^e, Flavia L. Lombardo^a, Ilaria Bacigalupo^a, Marco Canevelli^{a,c}, Paola Piscopo^f and Nicola Vanacore^{a,*}

^aNational Center for Disease Prevention and Health Promotion, Italian National Institute of Health, Rome, Italy

^bDepartment of Public Health and Infectious Diseases, Sapienza University, Rome, Italy

^cDepartment of Human Neuroscience, Sapienza University, Rome, Italy

^dNeurosurgery Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

^eDepartment of Neurorehabilitation Sciences, Casa Cura Policlinico, Milan, Italy

^fDepartment of Neuroscience, Italian National Institute of Health, Rome, Italy

Accepted 7 February 2022 Pre-press 5 March 2022

Abstract.

Background: Monoclonal antibodies (mAbs) are currently among the most investigated targets for potential diseasemodifying therapies in Alzheimer's disease (AD).

Objective: Our objectives were to identify all registered trials investigating mAbs in MCI due to AD or AD at any stage, retrieve available published and unpublished data from all registered trials, and analyze data on safety and efficacy outcomes. **Methods:** A systematic search of all registered trials on ClinicalTrials.gov and EUCT was performed. Available results were searched on both platforms and on PubMed, ISI Web of Knowledge, and The Cochrane Library.

Results: Overall, 101 studies were identified on 27 mAbs. Results were available for 50 trials investigating 12 mAbs. For 18 trials, data were available from both published and unpublished sources, for 21 trials only from published sources, and for 11 trials only from unpublished sources. Meta-analyses of amyloid-related imaging abnormalities (ARIA) events showed overall risk ratios of 10.65 for ARIA-E and of 1.75 for ARIA-H. The meta-analysis of PET-SUVR showed an overall significant effect of mAbs in reducing amyloid (SMD –0.88), but when considering clinical efficacy, data on CDR-SB showed that treated patients had a statistically significant but clinically non-relevant lower worsening (MD –0.15).

*Correspondence to: Nicola Vanacore, MD, PhD, National Center for Disease Prevention and Health Promotion, Italian National Institute of Health, Via Giano della Bella 34, 00162

Rome, Italy. Tel./Fax: +39 (0)6 49904243; E-mail: nicola.vana core@iss.it.

ISSN 1387-2877 © 2022 – The authors. Published by IOS Press. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC 4.0).

Conclusion: Our results suggest that the risk-benefit profile of mAbs remains unclear. Research should focus on clarifying the effect of amyloid on cognitive decline, providing data on treatment response rate, and accounting for minimal clinically important difference. Research on mAbs should also investigate the possible long-term impact of ARIA events, including potential factors predicting their onset.

Keywords: Alzheimer's disease, amyloid, meta-analysis, mild cognitive impairment, monoclonal antibodies, safety, systematic review, treatment outcome

INTRODUCTION

The last Alzheimer's disease (AD) drug development pipeline showed that disease-modifying therapies (DMT) are currently the most frequently investigated agents, being 82.5% of the total number of considered agents. Among the drugs considered as DMTs, 16 (15.4%) are anti-amyloid beta (anti-A β) monoclonal antibodies (mAbs), and 11 (10.6%) are anti-tau mAbs [1].

Research on anti-A β agents has been ongoing for about 15 years [2], though the lack of clinical benefits has prevented the marketing authorization except for the approval of Biogen's aducanumab so far only by the Food and Drug Administration (FDA) [3]. The main issue when considering amyloid-targeted agents is the lack of evidence supporting the association between amyloid load and cognitive outcomes, with studies reporting only an indirect link between amyloid plaques and cognitive decline [4, 5].

Another relevant issue related to the use of anti-AB mAbs in patients with AD was that a higher risk of developing vasogenic cerebral edema and cerebral micro-hemorrhages was observed in participants treated with mAbs. These abnormalities were first identified through magnetic resonance imaging (MRI) during trials testing one of the first investigated mAbs, bapineuzumab. In 2011, a working group that was specifically created to investigate these events, renamed this type of vasogenic edemas and micro-hemorrhages as amyloid-related imaging abnormalities (ARIA), and specifically ARIA-E (vasogenic edema) and ARIA-H (micro-hemorrhage) [6]. An increased risk of both ARIA-E and ARIA-H was also observed in patients treated with other anti-Aβ mAbs, even if with heterogeneous risk ratios due to some differences in the pharmacodynamics of each mAb. These differences are the result of mAbs having been produced with the objective of overcoming the safety and efficacy issues observed when testing preceding mAbs [7].

During the last few years, six systematic reviews (SR) and meta-analyses have been published investigating anti-amyloid agents, including mAbs, for the

treatment of AD or mild cognitive impairment (MCI) [8-13]. The 5 SRs included 11 to 17 randomized controlled trials (RCTs) each, published up to 2020, and all reported a statistically significant, but clinically non-relevant, improvement in cognitive and neurobiological outcomes (i.e., amyloid-positron emission tomography (PET) and cerebrospinal fluid (CSF) p181-tau), along with a significantly higher risk of ARIA events [8-13]. However, most of these SRs only included published studies [8, 9, 11] and considered widely heterogeneous molecules, such as active and passive immunization [9, 10] and all anti-amyloid agents [12]. Moreover, one SR only included phase III studies [11], and another only included phase II and III studies [10], with the latter also including only studies enrolling participants with mild to moderate AD. When reporting outcomes, most of these SRs considered only Alzheimer's Disease Assessment Scale-Cognitive Subscale and Mini-Mental State Examination as clinical outcomes, leaving out the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) which is clinically considered as the only scale reporting both cognitive and functional traits.

Therefore, considering the limitations of these SR, our objectives were to: 1) identify all registered trials investigating mAbs for the treatment of MCI due to AD or AD at any stage; 2) retrieve all available data, both published and unpublished, from registered trials; 3) cumulatively analyze all available data on both safety outcomes, focusing on ARIA-E and ARIA-H, and efficacy outcomes, specifically considering the CDR-SB score and cerebral amyloid burden measured by amyloid-PET.

METHODS

This SR was performed following the Cochrane handbook for systematic reviews [14] and reported based on the PRISMA statement [15]. We checked for the originality of our SR on PROSPERO, PubMed, ISI Web of Knowledge (WoK), and The Cochrane Library Databases (CLD). The SR protocol was registered on PROSPERO (CRD42021259855).

Search strategy and selection criteria

We initially performed a structured search (Supplementary File 1) in the two main registration databases, ClinicalTrials.gov (CT) and the European Clinical Trials Register (EUCT). No restrictions were applied for status, study design, study phase, date of publication, or language. We selected only studies that investigated any type of mAb in participants with a clinical diagnosis of AD or MCI. A list of all registered trials, and a list of all investigated mAbs were created. Available information on all the identified trials was searched both on the registration databases in the form of files with trial results and on the literature databases in the form of published studies. Based on the list of active principles obtained from CT and EUCT, a search string was defined (Supplementary File 1) and used on PubMed, ISI-WoK, and The CLD. No restrictions were applied for date of publication, study design, or language. A list of all trials with available information was defined, and details on the source of data were specified.

Study selection

Studies were initially selected based on their titles and abstracts, duplicates were removed, and full texts of all selected studies were gathered for independent assessment. Further potentially relevant articles were also retrieved from the references of identified studies. Selected studies were applied predefined eligibility criteria. All trials reporting safety and efficacy data on any type of mAbs for the treatment of subjects with a diagnosis of MCI due to AD or AD at any stage were included. Studies enrolling healthy participants or participants with any diagnosis other than MCI or AD at any stage, and all studies investigating any drug other than mAbs were excluded. In case of studies enrolling both healthy participants and patients with AD, only data on patients with AD were considered. Case reports, case series, non-systematic or narrative reviews, letters, commentaries, and editorials were also excluded. SRs were only considered to check for references and consistency of results.

Study selection, and data extraction and evaluation were performed by four independent reviewers (AA, EL, PP, VZ). Disagreements were resolved by discussion, consensus, or a third researcher. All available data up to July 7, 2021, were gathered and analyzed.

Data extraction and quality assessment

A list of all registered studies investigating mAbs for the treatment of AD or MCI was defined. For each trial, information on trial identification number, phase, and status were gathered. Trials were classified as completed, terminated, and ongoing, with ongoing defined as including any status indicating a non-completed study (e.g., active, enrolling, etc.).

For all studies for which information were available, the source of data was recorded (i.e., unpublished results retrieved from registration databases, published studies). Data were extracted using standardized forms including year of publication, characteristics of the included population, type of mAb, and results for each considered outcome. In case of information available from multiple sources, data were compared and, in case on inconsistencies, the most recent source was selected. Supplementary material and further additional reference material were also retrieved, and, in case of partial or incomplete data, the missing values, where possible, were calculated (e.g., graphs).

Published RCTs meeting inclusion criteria were qualitatively assessed using the Cochrane Risk of Bias (RoB) tool [14]. The RoB tool was used to classify the risk of bias as 'Low', 'High', or 'Unclear'. Other potential biases and/or methodological flaws were also considered. Only published studies were applied the RoB tool.

Data synthesis and analysis

Results were summarized in a narrative form. Meta-analyses of available data were performed for both safety and efficacy outcomes using the software Review Manager version 5.4.1. Data were stratified for type of mAb and organized in chronological order from the least to the most recently developed mAb, to account for heterogeneity and to identify possible evolutions over time in the safety or efficacy profile.

For safety outcomes, two meta-analyses of the frequency of adverse events (AE) and severe AEs (SAE) were performed, along with two specific metaanalyses on the reported frequency of ARIA-E and ARIA-H in all the studies for which data were available. Only events defined as ARIA within each study were included in the analyses, and data were stratified for way of administration in case of mAbs having more than 1 of them. To analyze the possible weight of potential misclassification due to the heterogeneity in the definition of ARIA across studies, we also performed a sensitivity analysis including all events classified as micro-hemorrhages, superficial siderosis, hemosiderin depositions, vasogenic edemas, etc. reported in the studies. For studies that provided data on *APOE* ε 4 status, a further subgroup analysis was performed on the frequency of ARIA events according to *APOE* carrier status.

For efficacy outcomes, data on the mean change from baseline in CDR-SB score and the PET standardized uptake value ratio (SUVR) were metaanalyzed. We considered the CDR-SB scale as a main clinical endpoint as it includes both cognitive and functional aspects, while we considered PET-SUVR as a main endpoint for its accuracy in assessing brain amyloid burden. As data on these continuous variables were provided per dose-group compared to a single placebo group, participants in the placebo group were subdivided as equally as possible, to avoid their being over-represented in the meta-analyses, leaving the group mean and SDs unchanged. This method is only partially effective in overcoming the unit-of-analysis error, but at least allowed to approximately investigate potential differences across intervention arms [14]. Meta-analyses were performed using a random effect model, and data for categorical variables were presented as risk ratios (RR) with their 95% confidence intervals (CI), while data for continuous variable were presented as standardized mean differences (SMD or mean differences (MD) with their 95% CIs.

RESULTS

Searches on CT and EUCT yielded 3,881 and 687 records respectively. After screening, 97 protocols were included referring to RCT testing mAbs in subjects with MCI or AD. Of these, 56 were registered only on CT, 1 was registered only on EUCT, while 40 were registered on both platforms.

Bibliographic searches on literature databases yielded 9,116 records. After a first screening, 58 records were selected. Of these, 25 were further excluded, as they did not meet the inclusion criteria. Overall, 34 articles were included, referring to 11 mAbs [16-49]. Four out of these 34 studies did not report any NCT/EUCT code therefore they were considered as having no trial identification code [20, 21, 44, 45]. The flow diagram of included studies is reported in Fig. 1. This led to a list of 101 trials either completed/terminated or still ongoing (97 from registration databases and 4 from literature alone), that were identified either using their NCT or EUCT code or using the "no code available" label.

A total of 75 out of 101 studies were classified as either completed (n = 56) or terminated (n = 19), investigating 22 mAbs. Considering both published and unpublished data, results were available for 50 trials, all classified as completed/terminated except for 2 studies classified as still ongoing, but with published safety and efficacy data [32, 34] (Table 1). All the unregistered studies were considered as completed. For 18 trials data were available from both published studies and registration databases [16, 19, 25–27, 29, 30, 37, 39, 42, 43, 47–49] for 21 trials data were available only from published studies [17, 18, 20–25, 28, 31–35, 38, 40, 41, 44–47], and for 11 trials data were available only from unpublished sources (Supplementary Table 1).

Overall, the 101 registered trials investigated 27 mAbs. Most of them targeted different forms of the A β peptide (n = 17), 8 targeted different forms of tau, 1 targeted the microglial receptor TREM2, and 1 targeted SEMA-4D. Data were available only on 12 anti-A β mAbs, while no data were available on the remaining 15 mAbs.

Methodological quality of published studies

Methodological quality was assessed only for studies published in journal articles (Supplementary Figure 1). The overall quality of included studies was moderate to low. The main limitation of included studies was a lack of information on the randomization process and the procedures for allocation concealment and blinding. Moreover, most of the studies were phase I with limited sample sizes, and some were structured in sub-phases, or divided participants in subgroups, thus further limiting the sample size and making the study design more complex.

Most of the included studies reported only AEs and SAEs with frequencies $\geq 5\%$, with some choosing higher cut-offs (e.g., $\geq 10\%$) or reporting only AEs or SAEs occurring in ≥ 2 participants. In these cases, we adopted a more conservative approach, considering them as being at unclear or high risk of bias for selective reporting. This approach was chosen due to some mAbs having risen safety concerns due to the occurrence of specific AEs, such as ARIA. Thus, a more complete reporting would have been expected.

Safety

Results from the meta-analysis of AEs reported a marginally but significantly higher frequency of AEs

Clinical Trial ID (S)	Status First Posted	Study Phase						Trial characte	ristics and result	s				
_			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
AAB-003 (PF- NCT 01193608	05236812) completed FP: 2010	Phase I RCT	88 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26 MRI consistent with AD	68.6±8.8 (range 51–88)	-	T: 44 (63.8) PL: F7 (36.8)	T-IV: 69 PL: 19	FU: 39 weeks Discon- tinued 14	mean change (SD) at week 39 0.5 mg: 1.00 (3.286) 1 mg: 1.75 (1.708) 2 mg: 1.00 (2.449) 4 mg: 1.86 (3.371) 8 mg: 0.79 (2.840) PL: -0.35 (1.025)	no data on amyloid PET	T: 2 on 8 mg/kg PL: 0	T: 4 (1 on 2 mg/kg; 3 on 8 mg/kg) PL: 0	CT.gov data Delnom- dedieu 2016 [16]
NCT 01369225	completed FP: 2011	Phase I OLE	52 participants from study NCT 01193608	MMSE ≥ 12	67.1 ± 9.0 (range: 52–74)	-	PL to T: 4 (44.4) T: 29 (67.4)	T-IV former T: 43 former PL: 9	FU: 52 weeks Discon- tinued 9	(1.535) mean change (SD) at week 52 0.5 mg: 0.00 (0.816) 1 mg: 0.33 (0.577) 2 mg: 2.67 (2.291) 4 mg: 2.38 (1.598) 8 mg: 1.10 (2.378) PL to T: 2.56 (2.789)	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	CT.gov data Delnom- dedieu 2016 [16]
ADUCANUM	AB (BIIB037)													
NCT 01397539	completed FP: 2011	Phase I RCT	53 mild to moderate AD (NINCDS- ADRDA)	MMSE 14–26	67.7 (range 55–84)	19 (35.8)	T: 27 (69.2) PL: 9 (64.3)	T-IV: 39 PL: 14	FU: 24 weeks	no data on CDR-SB	no data on amyloid PET	T: 3 (on 60 mg/kg) PL: 0	T: 1 (on 60 mg/kg) PL: 0	Ferrero 2016 [17]

 Table 1

 Summary of the main characteristics and results of the RCT for which data were available

Clinical Trial ID (S)	Status First Posted	Study Phase						Trial character	ristics and results					
			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
NCT 01677572 (PRIME)	terminated FP: 2012	Phase I RCT	165 prodromal or mild AD (NIA-AA)	positive amyloid PET	72.6±8.1	107 (64.8)	T: 60 (48) PL: 23 (57.5)	T-IV: 125 PL: 40	FU: 54 weeks Discon- tinued40	adj mean change $(\pm SE)$ at week 54 1 mg/kg: 1.72 \pm 0.46 3 mg/kg: 1.37 \pm 0.43 6 mg/kg: 1.11 \pm 0.44 10 mg/kg: 0.63 \pm 0.47 PL: 1.87 \pm 0.41 <i>p</i> dose- resp: < 0.05	adj mean change $(\pm SE)$ at 54 weeks 1 mg/kg: -0.055 ± 0.024 3 mg/kg: -0.135 ± 0.022 6 mg/kg: -0.210 ± 0.024 10 mg/kg: -0.268 ± 0.025 PL: 0.003 ± 0.021 p dose- resp: < 0.0001	1 mg/kg: 1/31 3 mg/kg: 2/32 6 mg/kg: 11/30 10 mg/kg: 13/32 PL: 0	1 mg/kg: 3/31 3 mg/kg: 4/32 6 mg/kg: 5/30 10 mg/kg: 10/32 PL: 2/38	Sevigny 2016 [18] ^J Aduhelm TM Product Information
NCT 02477800 (ENGAGE, 302)	terminated FP: 2015	Phase III RCT + OLE	PL period: 1,647 with MCI due to AD or mild AD OLE period: 852 participants	MCI due to AD or mild AD positive amyloid PET	PL: 69.8 \pm 7.72 T-LD: 70.4 \pm 6.96 T-HD: 70.0 \pm 7.65	-	T: 576 (52.3) PL: F287 (52.7)	T-IV: 1102 PL: 545	PL period: FU 78 weeks OLE period: FU 2 years discontinued in RCT: T 489 PL 220 discontinued in OLE: all	change (SE) at week 78 T-LD: 1.38 (± 0.108) T-HD: 1.59 (± 0.111) PL: 1.56 (± 0.108) p = 0.225 (PL versus T-LD) p = 0.833 (PL versus T-HD)	change (SE) from baseline at week 78 HD T: -0.235 (± 0.009) PL: -0.003 (± 0.008) Difference from PL: -0.232; $p < 0.0001\dagger$	T-HD: 202/558 T-LD: 36/549 PL: 16/540	T-HD: 194/558 T-LD: 140/549 PL: 44/540	EudraCT data Aduhelm™ Product Information
NCT 02484547 (EMERGE, 301)	terminated FP: 2015	Phase III RCT + OLE	PL period: 1638 OLE period: 771	MCI due to AD or mild AD positive amyloid PET	PL: 70.8 \pm 7.40 T-LD: 70.6 \pm 7.45 T-HD: 70.6 \pm 7.47	-	T: 553 (50.7) PL: 290 (52.9)	T-IV: 1090 PL: 548	PL period: FU 78 weeks OLE period: FU 2 years discontinued in RCT: T 504 PL 260 discontinued in OLE: all	change (SE) at 78 weeks (SE) T-LD: 1.47 (± 0.116) T-HD: 1.35 (± 0.115) PL: 1.74 (± 0.115) P=0.0901 (PL versus T-LD) p=0.012 (PL versus T-HD)	change (SE) from baseline at week 78 HD T: -0.264 (± 0.010) PL: -0.014 (± 0.0095) Difference from PL: -0.278; $p < 0.0001\dagger$	T-HD: 191/547 T-LD: 143/544 PL: 13/547	T-HD: 182/547 T-LD: 142/544 PL: 52/547	EudraCT data Aduhelm™ Product Information

106

BAPINEUZU	JMAB (AAB-001	1, ELN115727)												
NCT 00397891	completed FP: 2006	Phase I RCT	32 mild to moderate AD (NINCDS- ADRDA)	MMSE: 14–26 MRI consistent with AD	67.8 (range 53–85)	-	T: 10 (41.7) PL: 4 (50)	T-IV: 24 PL: 8	FU: 52 weeks Discon- tinued: 2	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data Arai 2016 [19]
No code available	completed FP: –	Phase I RCT	30 mild to moderate AD (NINCDS- ADRDA)	MMSE: 14–26 MRI consistent with AD	0.5 mg/kg: 74.7 (5.7) 1.5 mg/kg 72.3 (9.9) 5 mg/kg: 74.7 (7.4) PL: 69.9 (10.7)	-	T: 7 (31.8) PL: 7 (87.5)	T-IV: 22 PL: 8	FU: 2 years Discon- tinued: 4	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	Black 2010 [20]
No code available	completed FP: –	Phase I RCT	40 mild to moderate AD (NINCDS- ADRDA)	MMSE: 14–26	T: 71 ± 10.2 PL: 70.3 ± 12.2	19 (47.5)	T: 15 (50) PL: 4 (40)	T-SC: 30 PL: 10	FU: 16 weeks	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	Lu 2019 [21]
EudraCT 2004- 004120-12	completed FP: 2005	Phase II RCT	26 mild to moderate AD (NINCDS- ADRDA)	positive amyloid PET MRI consistent with AD	T: 67.3 ± 8.6 PL: 70.0 ± 8.8	19 (73.1)	T: 8 (42.1) PL: 4 (57.1)	T-IV: 19 PL: 7	FU: 78 weeks Discon- tinued: enrollment for 2 mg/kg was stopped due to ARIA-E	no data on CDR-SB	Mean ¹¹ C-PiB PET PL: 0.20 (0.09) T: -0.09 (0.16) obs diff: -0.29 (-0.45 to -0.13) est mean: PL: 0.15** T: -0.09^{**} est. diff: -0.24 (-0.39 to -0.09) p = 0.003	no ARIA-E observed	no ARIA-H observed	Rinne 2010 [22]
NCT 00112073	completed FP: 2005	Phase II RCT	229 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26 MRI consistent with AD	PL: 67.9 (0.85) T: 70.1 (0.82)	146 (63.8)	T: 61 (50) PL: 64 (59.8)	T-IV: 122 PL: 107	FU: 78 weeks Discon- tinued: T: 32 PL: 23	no sufficient data on CDR-SB	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	Salloway 2009 [23]
NCT 00663026	completed FP: 2008	Phase II RCT	79 mild to moderate AD (NINCDS- ADRDA)	-	5 mg: 71.3 (8.7) 10 mg: 72.42 (8.4) PL: 76.2 (8.6)	_	T: 30 (50) PL: 8 (42.1)	T-SC: 60 PL: 19	Discon- tinued: T: 10 PL: 2	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	CT.gov data

Clinical Trial ID (S)	Status First Posted	Study Phase						Trial characte	ristics and results	ŝ				
			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
NCT 00916617	terminated FP: 2009	Phase II OLE	61 participants from: NCT 663026	Mild to moderate AD (NINCDS- ADRDA)	73.9±9.1	-	PL to T 8 (47.1) AAB-001 22 (50)	T-SC: 44 PL to T: 17	FU: planned 3 years Discon- tinued: 61	no data on CDR-SB	no data on amyloid PET	5 mg/Kg: 3 PL to 5 mg/Kg: 2 PL to 10 mg/ Kg: 1	no ARIA-H observed	CT.gov data
NCT 01254773	completed FP: 2010	Phase II RCT	146 mild to moderate AD (NINCDS- ADRDA)	MMSE 18–26 MRI consistent with AD positive amyloid PET	2 mg: 73.5 (8.34) 7 mg: 74.1 (9.3) 20 mg: 70.5 (8.7) PL: 73.3 (8.8)	88 (60.3)	T: 61 (55.5) PL: 23 (63.9)	T-SC: 110 PL: 36	FU: planned 2 years Discon- tinued: 146	no data on CDR-SB	LS mean change (95%CI) 2 mg: -0.014 (-0.078, 0.050) 7 mg: -0.066 (-0.129, -0.004) 20 mg: -0.021 (-0.082, 0.040) PL: 0.000 (-0.062, 0.063)	T: 2/110 PL: 0/36	no ARIA-H observed	Brody 2016 [24]
NCT 00574132	completed FP: 2007	Phase III RCT	1,331 mITT: 1,114 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26 MRI consistent with AD	mITT PL: 71.9 ± 10.1 0.5 mg/kg: 73.1 ± 9.3 1 mg/kg: 73.5 ± 9.1	None	T: 340 (54.8) PL: 248 (50.3)	mITT: T-IV: 621 PL: 493	FU: 78 weeks Discon- tinued: T: 433 PL: 142	mean change (SE) at week 78 0.5 mg: 2.6 ± 0.2 1.0 mg: 2.8 ± 0.2 PL: 2.6 ± 0.2	LS mean change (SE) at week 71 0.5 mg: 0.039 (0.0452) 1.0 mg: -0.094 (0.0471) all BAPI: -0.025 (0.0337) PL: -0.046 (0.0443)	0.5 mg: 14/337 1.0 mg: 31/329 2 mg: 20/141 PL: 1/524	no ARIA-H observed	EudraCT data Salloway 2014 [25]

Table 1 (*Continued*)

NCT	completed	Phase III	1,121	MMSE	PL: 72.3 ± 8.4	All	T: 358 (54.4)	mITT:	FU: 78	change at	LS mean	0.5 mg/Kg:	no ARIA-H	Salloway 2014
00373033	FF: 2007	KC1	1,090 Mild to moderate AD (NINCDS- ADRDA)	MRI consistent with AD APOE \$4 allele	0.3 mg/kg: 72.0 ± 8.0		(56)	PL: 432	Discon- tinued: T: 201 PL: 106	(SE) 0.5 mg/Kg: 3.3 ± 0.1 PL: 3.0 ± 0.2	(SE) at week 71 BAPI: 0.001 (0.0207) PL: 0.102 (0.0264)	PL: 1	observed	[25]
NCT 00667810	terminated FP: 2008	Phase III RCT	885 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26 MRI consistent with AD	$\begin{array}{l} 0.5 \ \text{mg/Kg:} \\ 71.4 \pm 9.4 \\ 1 \ \text{mg/Kg:} \\ 70.8 \pm 9.7 \\ 2 \ \text{mg/Kg:} \\ 66.5 \pm 7.9 \\ \text{PL:} \\ 69.9 \pm 9.8 \end{array}$	None	T: 305 (56.4) PL: 199 (57.8)	T-IV: 541 PL: 344	FU: 78 weeks Discon- tinued T: 339 PL: 222	LS change (SE) at week 78 0.5 mg: 2.23 (0.23) 1.0 mg: 2.41 (0.23) PL: 2.59 (0.20)	LS mean change (SE) at week 71 0.5 mg: -0.04 (0.08) 1.0 mg: 0.00 (0.05) all T: -0.01 (0.04) PL: 0.02 (0.04)	0.5 mg: 13/267 1.0 mg: 32/263 PL: 2/344	no ARIA-H observed	CT.gov data EudraCT data Vandenberghe 2016 [26]
NCT 00676143	terminated FP: 2008	Phase III RCT	1,093 mild to moderate AD (NINCDS- ADRDA)	MRI consistent with AD	0.5 mg/Kg: 71 ± 7.7 PL: 70.3 ± 7.8	All	T: 421 (64.4) PL: 262 (59.7)	T-IV: 654 PL: 439	FU: 78 weeks Discon- tinued: T: 260 PL: 156	LS mean change (SE) at week 78 0.5 mg: 2.44 (0.13) PL: 2.59 (0.16)	(0.04) mean change (SD) at week 71 0.5 mg: -0.0 (0.11) PL: 0.0 (0.16)	0.5 mg/Kg: 109/654 PL: 9/439	no ARIA-H observed	CT.gov data EudraCT data Vandenberghe 2016 [26]
NCT 00937352	terminated FP: 2009	Phase III OLE	1,390 participants from studies NCT 00574132 NCT 00575055	Brain MRI scan at Visit 14/Week 71 of the parent study	<i>APOE</i> - study: PL to T: 72.2 (52-90) T to T: 73.6 (51-90) <i>APOE</i> + study: PL to T: 72.9 (53-89) T to T: 72.5 (51-90)	664 (47.8)	APOE- study PL to T: 72.2 (52-90) T to T: 73.6 (51-90). APOE+ study PL to T: 72.9 (53-89) 72.5 in the BAPI to BAPI to BAPI group (range, 51 to 90).	APOE- Study T to T: 351 PL to T: 297 APOE + Study T to T: 378 PL to T: 286	FU: 4 years Discon- tinued: 1390	no data on CDR-SB	no data on amyloid PET	APOE- Study PL to T: 16/297 T to T: 4/351 APOE + Study PL to T: 34/286 T to T: 19/378	no ARIA-H observed	EudraCT data
NCT 00996918	terminated FP: 2009	Phase III OLE	202 participants from study NCT 00667810	MMSE 16–26 MRI consistent with AD	70.4 ± 9.08 (overall)	None	T to T: 50 (42) PL to T: 27 (38)	T-IV T to T: 122 PL to T: 76	FU: 4 years, Discon- tinued: 202	no data on CDR-SB	no data on amyloid PET	T to T: 5/122 PL to T: 9/76	no ARIA-H observed	CT.gov data EudraCT data Ivanoiu 2016 [27]

Clinical Trial S ID (S) F F	Status First Posted	Study Phase					(Continued) Trial characte	ristics and results	5				
	rosteu		Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
NCT 00998764	terminated FP: 2009	Phase III OLE	490 participants from study NCT 00676143	MRI consistent with AD	PL to T: 71.4 \pm 8.1 T to T: 72.1 \pm 7.5	All	PL to T: 135 (62.8) T to T: 186 (67.6)	T-IV T to T: 275 PL to T: 215	FU: 4 years Discon- tinued: 490	no data on CDR-SB	no data on amyloid PET	T to T: 10/275 PL to T: 23/215	no ARIA-H observed	CT.gov data EudraCT data Ivanoiu 2016 [27]
CRENEZUM/ NCT 02353598	Completed FP: 2015	A, RO5490245) Phase I RCT + OLE	75 mild to moderate AD (NINCDS- ADRDA)	MMSE 18–28 positive amyloid PET	73 (51–88)	56 (74.7)	PL: 8 (57.1) T: 28 (45.9)	T-IV RCT T: 61 PL: 14 OLE 30 or 45 mg/kg: 23 60 mg/kg: 48	FU trial: 13 weeks Discon- tinued: 0 FU OLE: 133 weeks Discon- tinued: 71	no data on CDR-SB	data on amyloid PET only available in supplemen- tary graph format	no ARIA-E observed	45 mg/Kg: 2/11 60 mg/Kg: 1/21 PL: 0/14	Guthrie 2020 [28]
NCT 01343966	completed FP: 2011	Phase II RCT	433 mild to moderate AD (NINCDS- ADRDA)	MMSE 18–26	SC: PL 70.3 (7.2) T 71.2 (6.3) IV: PL 69.9 (7.1) T 70.9 (6.9)	295 (68.1)	SC PL: 30 (48.4) T: 66 (54.1) IV PL: 48 (57.1) T: 84 (50.9)	T-SC or IV T-SC: 122 PL-SC: 62 T-IV: 165 PL-IV: 84	FU: 84 weeks Discon- tinued: 110	LS mean change (SE) at week 73 T-IV: 2.49 (0.25) PL-IV: 2.57 (0.35) T-SC: 2.01 (0.26) PL-SC: 2.7 (0.35)	no data on amyloid PET	T-IV: 1/165 PL: 0 T-SC: 0 PL-SC: 0	no ARIA-H observed	EudraCT data Cummings 2018 [29]
NCT 01397578	completed FP: 2011	Phase II RCT	91 mild to moderate (NINCDS- ADRDA)	MMSE 18–26 positive amyloid PET	SC PL: 68.9 (8.3) T: 66.7 (9.5) IV PL: 69.8 (7.7) T: 71.4 (7.1)	70 (76.9)	SC PL: 8 (61.5) T: 14 (53.8) IV PL: 6 (35.3) T: 24 (68.6)	T-SC or IV T-SC: 26 PL-SC: 13 T-IV: 36 PL-IV: 16	FU: 3 years Discon- tinued: 27	CDR change from baseline at week 73# T-SC: 3.61 PL-SC: 2.20 T-IV: 3.09 PL-IV: 2.86	LS mean change from baseline at week 69 (SE) SC: -0.029 (0.038) SC-PL: -0.018 (0.059) IV: -0.02 (0.03) IV-PL: -0.071 (0.043)	no ARIA-E observed	T-SC: 4/26 PL-SC: 0 T-IV: 4/36 PL-IV: 1/16	EudraCT data Salloway 2018 [30]

NCT 01723826	completed FP: 2012	Phase II OLE	360 participants from studies NCT 01343966 NCT 01397578	MMSE 18–26	PL-SC to SC to IV 70.9 \pm 7.4 PL-IV to IV 71.9 \pm 7.5 SC to SC to IV 72.3 \pm 7.2 IV to IV 72.2 \pm 6.6	-	PL-SC to SC to IV 26 (55.3) PL-IV to IV 38 (56.7) SC to SC to IV F58 (57.4) IV to IV F77 (53.1)	T-SC or IV PL-SC to SC to IV: 47 PL-IV to IV: 67 SC to SC to IV: 101 IV to IV: 145	FU: 153 weeks discon- tinued 210	no data on CDR-SB	no data on amyloid PET	IV to IV: 1/149	PL-SC to SC to IV: 4/47 PL-IV to IV: 6/63 SC to SC to IV: 7/101 IV to IV: 10/149	CT.gov data EudraCT data
NCT 02670083	terminated FP: 2016	Phase III RCT	813 prodromal (MCI) to mild AD (NIA-AA)	positive amyloid PET or CSF	T: 71 ± 7.9 PL: 70.3 ± 8.4	-	T: 236 (58.4) PL: 247 (60.4)	T-IV: 404 PL: 409	FU: 100 weeks Discon- tinued T: 319 PL: 321	LS mean change (SE) at week 105 PL: 3.42 (±0.263) T: 3.59 (±0.264)	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data EudraCT data
NCT 03114657	terminated FP: 2017	Phase III RCT	806 prodromal (MCI) to mild AD (NIA-AA)	Positive amyloid PET or CSF	T: 70.7 ± 7.9 PL: 71.1 ± 7.5	-	T: F225/ M174 PL: F231/M176	T-IV: 407 PL: 399	FU: 100 weeks Discon- tinue: 806	LS mean change (SE) at week 77 PL: 3.19 (±0.434) T: 1.89 (±0.471)	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data EudraCT data
NCT 03491150	terminated FP: 2018	Phase III OLE	149 participants from studies NCT 02670083 NCT 03114657	Positive amyloid PET or CSF	PL to T: 73.8 \pm 7.6 T to T: 72.0 \pm 7.6	-	PL to T: F37/M39 T to T: F38/M35	T-IV PL-T-IV: 76 T-IV to T-IV: 73	FU: 54 weeks Discon- tinued: 149	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data EudraCT data
DONANEMA	AB (LY3002813)													
NCT 02624778	completed FP: 2015	Phase I RCT	63 evidence of memory impairment (FCSRT)	MMSE 16–30 positive PET	69.7 (16.4) (6 healthy volunteers, age 18–40)	-	T: 26 (51) PL: 7 (58.3)	T-IV: 37 PL: 12 T-SC 3 mg/kg: 8 (single dose) T-IV (HV) 1 mg/kg: 6	SAD: FU 12 weeks MAD: 1 dose per month up to 4 doses followed by FU 12 week	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	T-SC: 1/8 T-IV: 1/37	Lowe 2021 [31]

							Table 1							
Clinical Trial ID (S)	Status First Posted	Study Phase					(Continued)) Trial characte	ristics and results					
			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
NCT 03367403	ongoing FP: 2017	Phase II RCT	272 prodromal (MCI) or mild AD	Positive amyloid or tau PET	T: 75.0±5.6 PL: 75.4±5.4	197 (72.4)	T: F68/M63 PL: F65/M61	T-IV: 131 PL: 125	FU: 76 weeks Discon- tinued T: 37 PL: 32	LS mean change (SE) at week 76 T: 1.22 (0.176) PL: 1.58 (0.178) LS mean change difference -0.36 (95%CI, -0.83, 0.12)	mean change (SE) at week 76 T: -0.367 (0.015) PL: 0.004 (0.0112) †	T: 36/131 PL: 1/125	T: 40/131 PL: 9/125	Mintun 2021 [32]
LECANEMA NCT 01230853	3 (BAN2401) completed FP: 2010	Phase I RCT	SAD cohort 48 MAD cohort 32 Mild to moderate AD (NINCDS- ADRDA)	MMSE: 16–28	SAD: 70.9 (±10) MAD: 70.0 (±9.97)	_	SAD: T: 18 (50) PL: 5 (41.7) MAD: PL: 2 (25) T: 13 (54.2)	SAD cohort T-IV:36 PL: 12 MAD cohort T-IV: 24 PL: 12	FU: 40 weeks Discon- tinued SAD: 2 MAD: 4	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	SAD: T: 2 (1 on 0.3 mg/kg, 1 on 1 mg/kg) PL: 0 MAD: T: 1	Logovinsky 2016 [33]
NCT 01767311	ongoing FP: 2013	Phase IIb RCT	856 MCI due to AD or Mild AD	positive amyloid PET or CSF MMSE ≥ 22 (amended to 22–28 in EU)	median age T: 72 (50–90) PL: 72 (50–89)	589 (68.8)	T: 272 (46.3) PL: 137 (57.6)	T-IV: 609 PL: 245	FU: 52 weeks Discon- tinued: BAN2401: 219 PL: 58	LS mean change (SE) at 79 weeks 2.5 mgB: 1.227 (0.338) 5 mgM: 1.713 (0.334) 5 mgB: 1.463 (0.250) 10 mgM: 1.248 (0.169) 10 mgB: 1.102 (0.213) PL: 1.499 (0.16)	LS mean change (SE) at 18 months 2.5 mg: -0.094 (0.021) 5 mgM: -0.131 (0.021) 5 mgB: -0.197 (0.021) 10 mgB: -0.225 (0.0125) 10 mgB: -0.306 (0.019) PL: 0.004 (0.0125) †	T: 46/609 PL: 2/245	PL: 2 T: 65/609 PL: 13/245	Swanson 2021 [34]

GANTENER	UMAB (R1450)													
NCT 00531804	completed FP: 2007	Phase I RCT	18 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26 MRI consistent with AD	$\begin{array}{l} 60 \text{ mg:} \\ 70.9 \pm 8.1 \\ 200 \text{ mg:} \\ 66.5 \pm 9.4 \\ \text{PL:} \\ 62.8 \pm 3.5 \end{array}$	13 (72.2)	T: 5 (35.7) PL: 3 (75)	T-IV: 14 PL: 4	FU: 28 weeks	no data on CDR-SB	mean changes (SD) at week 4 PL: 0.24 (0.15) 60 mg: 0.03 (0.24) 200 mg: -0.27 (0.45)	200 mg: 2/14 PL: 0	no data on ARIA-H	Ostrowitzki 2012 [35]
NCT 01224106	completed FP: 2010	Phase III RCT	797 prodromal AD (IWG criteria)	MRI consistent with AD positive CSF	105 mg: 70.3 \pm 7.0 225 mg: 71.3 \pm 7.1 PL: 69.5 \pm 7.5	561 (70.4)	T: 304 (57.3) PL: 149 (56)	T-SC: 531 PL: 266	FU: 2 years discontinued 481	LS mean change at week 104 PL: 1.60 (1.28, 1.91) 105 mg: 1.69 (1.37, 2.01) 225 mg: 1.73 (1.42, 2.04)	(a. b) mean change (SD) at week 100 PL: -0.02 (0.13) 105 mg: 0.00 (0.20) 225 mg: -0.09 (0.14)	105 mg: 18/271 225 mg: 35/260 PL: 2/266	105 mg: 62/271 225 mg: 42/260 PL: 35/266	Ostrowitzki 2017 [36]
GSK933776 NCT	completed	Phase I	50 MCL or	MMSE	60.3 ± 6.81	34 (68)	T: 22 (61.1)	T-IV	FU: 12	no data on	no data on	no ARIA E	T: 0	FudraCT data
00459550	FP: 2007	RCT	mild AD	18–26 positive CSF	(overall)	54 (00)	PL: 9 (64.3)	Part A: 12 Part B: 24 PL: 14	months discon- tinued 2	CDR-SB	amyloid PET	observed	PL: 1/14	Andreasen 2015 [37]
NCT 01424436	completed FP: 2011	Phase I OL	18 MCI or mild AD	positive CSF	1 mg/kg: 69 (61–79) 3 mg/kg: 68.3 (57–79) 6 mg/kg: 66 (58–77)	14 (77.8)	10 (55.6)	T-IV: 18	FU: 3 months	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	Leyhe 2014 [38]
LY2599666					(30 11)									
NCT 02614131	terminated FP: 2015	Phase I RCT	7 MCI or mild to moderate AD	-	range: 58–76		4 (57.1)	T-SC: 5 PL:2	FU: 16 weeks discon- tinued 1	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data Li 2019 [39]
MEDI1814									unded 1					
NCT 02036645	completed FP: 2014	Phase I RCT	77 mild to moderate AD	-	68.5±6.55 (overall)	-	T: 37 (56.9) PL: 7 (58.3)	T-IV - SC SAD T: 33 PL: 12 MAD T: 24 PL: 8	FU: SAD cohort: 4 months MAD cohort: 7 months Discon- tinued 2	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	CT.gov data

							(Continued	()						
Clinical Trial ID (S)	Status First Posted	Study Phase						Trial characte	ristics and resul	ts				
_			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)
PONEZUMA	B (PF-04360365	6)												
NCT 00455000	completed FP: 2007	Phase I RCT	37 mild to moderate AD (NINCDS- ADRDA)	MMSE 16–26	T: 70.0 ± 8.2 PL: 71.8 ± 7.0	10 (27)	T: 11 (42.3) PL: 3 (27.3)	T-IV: 26 PL: 11	FU: 1 year	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	Landen 2013 [40]
NCT 00607308	completed FP: 2008	Phase I RCT	20 mild to moderate (NINCDS- ADRDA)	MMSE 16–26	0.1 mg/Kg: 66.5 (SD 6.4) 0.5 mg/Kg: 67.7 (8.1) 1 mg/Kg: 67 (10.1) 5 mg/Kg: 68.3 (5.1) 10 mg/Kg: 71.7 (7.2) PL: 72.2 (7.1)	11 (55)	T: 8 (53.3) PL: 3 (60)	T-IV: 15 PL: 5	FU: 1 year	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	Miyoshi 2013 [41]
NCT 00722046	completed FP: 2008	Phase II RCT	194 mild to moderate AD (NINCDS- ADRDA)	MMSE 16-26	(1.1) (0.1 mg/Kg: 70.8 (SD 8.2) 0.5 mg/Kg: 71.9 (9.4) 1 mg/Kg: 72.2 (8.4) PLA: 70.0 (7.8) 3 mg/Kg: 70.5 (8.9) 8.5 mg/Kg: 71.8 (7.3) PLB: 70.4 (10.3)	129 (66.5)	T: 75 (54.3) PL: 30 (53.6)	T-IV Part A T: 75 PL: 24 Part B T: 63 PL: 32	FU: 24 months Discon- tinued48	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	EudraCT data Landen 2017a [42]

Table 1
(Continued)

NCT 00945672	completed FP: 2009	Phase II RCT	36 mild to moderate AD (NINCDS- ADRDA)	MMSE 16-26	T-IV cohort Q T: 65.1 (7.4) PL: 71.3 (8.5) cohort M T: 69.8 (7.5) PL: 65.8 (8.3)	29 (80.6)	T: 7 (29.2) PL: 8 (66.7)	T-IV cohort Q T: 12 PL: 6 cohort M T: 12 PL: 6	FU: 18 months Discon- tinued 2	no data on CDR-SB	LS Mean (SE) from baseline at Month 13 (90%CI) T: -2.48 (0.024) (-6.47, 1.68) PL: -1.07 (0.034) (-6.76, 4.97)	no data on ARIA-E	cohort Q T: 1/12 PL: 0 cohort M T: 1/12 PL: 1/6	EudraCT data Landen 2017b [43]
SOLANEZU No code	MAB (LY206243 completed	50) phase I	19 mild to	MMSE	PI · 70 3 (5 5)	15 (78.9)	T: 5 (31 3)	T-IV: 12	FU: 1 year	no data on	no data on	no ARIA-F	no ARIA-H	Siemers 2010
available	FP: –	RCT	AD (NINCDS- ADRDA)	MMSE 14–26 MRI or CT consistent with AD	PL: 70.3 (3.3) 0.5 mg: 61.0 (6.2) 1.5 mg: 71.5 (12.3) 4 mg: 67.5 (7.6) 10 mg: 75.3 (3.9)	13 (78.9)	PL: 3 (100)	PL: 3	Discon- tinued2	CDR-SB	amyloid PET	observed	ilo ARIA-n observed	[44]
No code available	completed FP: –	phase I RCT	39 mild to moderate AD (NINCDS- ADRDA	MMSE 10-26 MRI or CT consistent with AD	0.5 mg: 70.5 (9.9) 1.5 mg: 77.0 (9.0) 4 mg: 72.8 (13.7) 10 mg: 75.8 (7.3) PL: 68.3 (12.1)	-	T: 9 (56.3) PL: 3 (75)	T-IV 16J; 16W PL: 4J; 3W	FU: 112 days Discon- tinued: 19	no data on CDR-SB	no data on amyloid PET	no ARIA-E observed	no ARIA-H observed	Uenaka 2012 [45]
NCT 00329082	completed FP: 2006	Phase II RCT	52 mild to moderate AD	MMSE 15–26	71.2±9.2 (overall)	25 (48.1)	28 (53.8)	T-IV: 42 PL:10	FU: 1 year Discon- tinued: 2	no data on CDR-SB	no data on amyloid PET	no data on ARIA-E	no data on ARIA-H	Farlow 2012 [46]

Clinical Trial ID (S)	Status First Posted	tus Study st Phase sted	study Trial characteristics and results rst Phase													
			Randomized Participants	Main inclusion criteria	mean age	APOE+ (%)	Gender, F (%)	Intervention	Attrition	Clinical Outcome: change in CDR-SB	Amyloid PET (SUVR change)	Safety Outcome: ARIA-E [§]	Safety Outcome: ARIA-H [§]	Source(s)		
NCT 00904683 (EXPEDI- TION 2)	completed FP: 2009	Phase III RCT	1040 mild to moderate AD (NINCDS- ADRDA)	MMSE 16-26	T: 72.5 ± 8.0 PL: 72.4 ± 7.8	544 (52.3)	T: F283 (54.3) PL: 286 (55.1)	T-IV: 521 PL: 519	FU: 80 weeks Discon- tinued T: 115 PL: 119	mean change at week 80 (95%CI) PL: 1.9 (1.4 to 2.4) T: 1.6 (1.2 to 2.1) mean difference -0.3 (-0.7 to 0.2) LS mean change at week 80 (SE) T: 2.33 (0.172) PL: 2.70 (0.174)	no data on amyloid PET*	T: 7/521 PL: 3/519	T: 44/521 PL: 36/519	EudraCT data Doody 2014 [47]		
NCT 00905372 (EXPEDI- TION 1)	completed FP: 2009	Phase III RCT	1012 mild to moderate AD (NINCDS- ADRDA)	MMSE 16-26	T: 75.0 ± 7.9 PL: 74.4 ± 8.0	554 (54.7)	T: 299 (59.1) PL: 287 (56.7)	T-IV: 506 PL: 506	FU: 80 weeks Discon- tinued T: 136 PL: 136	mean change at week 80 (95%CI) PL: 1.8 (1.3 to 2.3) T: 2.0 (1.5 to 2.4) mean difference (95%CI): 0.1 (-0.3 to 0.6)	no data on amyloid PET*	T: 2/506 PL: 1/506	T: 6/506 PL: 21/506	Doody 2014 [47]		
NCT 01127633 (EXPEDITION EXT)	terminated FP: 2010 I-	Phase III OLE	975 participants from studies NCT 00904683 NCT 00905372	MMSE 16–26	T: 72.96 ± 7.8 PL: 73.10 ± 8.0	_	T: F415/M319 PL: F406/M317	T-IV T to T: 484 PL to T: 491	FU: 2 years Discon- tinued T: 673 PL: 653	LS mean change (SE) at 104-week PL to T: 5.59 (0.174) T to T: 5.27 (0.169)	LS mean change (SE) at 104-week PL to T: 0.00 (0.131) T to T: -0.01 (0.222)	no data on ARIA-E	no data on ARIA-H	CT.gov data EudraCT data Liu-Seifert 2015 [48]		

Table 1 (*Continued*)

NCT	terminated	Phase III	2129 mild AD	MRI or CT	$T: 72.7 \pm 7.8$	1397 (65.6)	T: 600 (56.8)	T-IV: 1057	FU: 80 weeks	LS mean	placebo mean	T: 1/1057	T: 37/1057	CT.gov data
01900665	FP: 2013	RCT+OLE	(NINCDS-	consistent	PL:		PL: 631	PL: 1072	208 weeks	Change at	SUVr	PL: 2/1072	PL:	EudraCT
			ADRDA)	with AD	73.3 ± 8.0		(58.9)	OLE	of OLE we RCT Dis- (SE	week 80	change:0.020 ±	change:0.020 ± 0.002; 30/1072 solanezumab mean SUVr	30/1072	data
				positive				T to T: 881		(SE)	solanezumab			Honig 2018
				amyloid				PL to T:	continued	PL:	mean SUVr			[49]
				PET or CSF				859	T: 143	2.21 ± 0.11	change:			
									PL: 164	T:	0.016 ± 0.002			
									OLE dis-	1.87 ± 0.10	p = 0.131			
									continued	l est.				
									T: 881	difference				
									PL: 859	at week 80				
										-0.34				
										(-0.57 to				
										-0.11)				
										Arithmetic				
										mean at				
										week 80				
										PL:				
										2.23 ± 2.692				
										T:				
										1.91 ± 2.442				
NCT	terminated	Phase III	26 prodromal	positive	T: 73.46 ± 6.0	-	T: F4/M9	T-IV: 13	FU: 2	no data on	no data on	no data on	no data on	CT.gov data
02760602	FP: 2016	RCT	AD (IWG)	amyloid	PL:		PL: F6/M7	PL: 13	years	CDR-SB	amyloid	ARIA-E	ARIA-H	EudraCT
			or MCI due	PET or CSF	75.62 ± 4.9				Discon-		PET			data
			to AD						tinued					
			(NIA-AA)						T: 13					
									PL: 13					

AD, Alzheimer's disease; *APOE*, apolipoprotein E, ARIA-E, amyloid-related imaging abnormalities-vasogenic edema; ARIA-H, amyloid-related imaging abnormalities-micro-hemorrhage; BAPI, Bapineuzumab; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; CREN, Crenezumab; CSF, cerebrospinal fluid, CT, computerized tomography; EU, European Union; FCSRT, Free and Cued Selective Reminding Test; FP, first posted; FU, follow up; IV, intravenous; IWG, International Working Group; LS, least squares; MAD, multiple ascending dose; MCI, mild cognitive impairment; mITT, modified intention-to-treat; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; OLE, open label extension; PET, positron emission tomography; PL, placebo; PLA, placebo part A; PLB, placebo part B; RCT, randomized controlled trial; SAD, single ascending dose; SC, subcutaneous; SD, standard deviation; SE, standard error; SUVR, standardized uptake value ratio; T, treatment; T-HD, treatment-high dose; T-IV, treatment-intravenous; T-LD, treatment-low dose; T-SC, treatment-subcutaneous; W, White; J, Japanese. †data partially calculated based on available graphs; [§]Only data on events defined as ARIA within each study are included in the table, data on all events not classified as ARIA are included in the sensitivity analyses; ^fAduhelm product information was not considered as "unpublished source" as it was not provided by the registration databases; however, some data were retrieved from this source to carry out meta-analyses; ***p*<0.05 for the change from baseline within treatment group; *In the EXPEDITION 1 and EXPEDITION 2, the study reported that the composite SUVr did not change significantly in the solanezumab or the placebo groups in both studies; [#]No measure of dispersion available.



Fig. 1. Flow diagram of identified published and unpublished studies.

in treated participants compared to placebo, with a RR of 1.04 (95% CI 1.02–1.06, I^2 74%). However, data from the meta-analysis of SAEs did not show significant differences between groups (RR 1.02, 95%CI 0.96–1.09, I^2 20%) (Supplementary Figures 2 and 3).

When considering ARIA events, a significant heterogeneity in the definition and reporting of ARIA was observed across studies. In some studies (n = 14),

the information on the overall frequency of ARIA was missing, while 6 RCTs reported that no events of ARIA occurred during the study. In some cases, the criteria adopted for discriminating between what was considered as ARIA and what was considered as micro-hemorrhages, vasogenic edemas, etc. was unclear. This heterogeneity could be due to the evolution over time of the definition of ARIA as research

	mAb		PL	_		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	
Bapineuzumab - NCT00574132	65	807	1	524	1.7%	42.21 [5.87, 303.22]		
Bapineuzumab - NCT00575055	103	673	1	448	1.7%	68.56 [9.60, 489.61]		
Bapineuzumab - NCT00667810	47	541	2	344	3.4%	14.94 [3.65, 61.12]		
Bapineuzumab - NCT00676143 Subtotal (95% CI)	114	654 2675	9	439	14.9%	8.50 [4.36, 16.58]		
Total events	329	2010	13	1700	21.770	10.14 [0.00, 20.04]	•	
Heterogeneity: Chi ² = 6.80, df = 3	3 (P = 0.08)); l² = 56	3%					
Test for overall effect: Z = 10.03	(P < 0.0000	01)						
1.1.2 BAPINEUZUMAB-SC								
Bapineuzumab - NCT01254773	2	110	0	36	1.0%	1.67 [0.08, 33.93]	<u> </u>	
Subtotal (95% CI)		110		36	1.0%	1.67 [0.08, 33.93]		
Total events	2		0					
Test for overall effect: 7 = 0.33 (F	P = 0.74							
	0.14)							
1.1.3 SOLANEZUMAB-IV								
Solanezumab - NCT00904683	7	521	3	519	4.2%	2.32 [0.60, 8.94]		
Solanezumab - NCT01900665	1	1057	2	1072	2.8%	0.51 [0.05, 5.58]		
Subtotal (95% CI)		2084		2097	8.3%	1.67 [0.61, 4.58]	*	
Total events	10		6					
Heterogeneity: $Chi^2 = 1.20$, $df = 2$ Test for overall effect: $Z = 0.99$ (F	2 (P = 0.55) P = 0.32)); I ² = 09	%					
or overall effect. 2 - 0.55 (r	0.02)							
1.1.4 PONEZUMAB-IV				_				
Ponezumab - NCT00722046 Subtotal (95% CI)	1	75 75	0	24 24	1.0%	0.99 [0.04, 23.46]		
Total events	1	15	n	24	1.0 /6	0.00 [0.04, 20.40]		
Heterogeneity: Not applicable			5					
Test for overall effect: Z = 0.01 (F	P = 0.99)							
1.1.5 GANTENERUMAB-IV								
Gantenerumab - NCT00531804	2	14	0	4	1.0%	1.67 [0.10, 29.18]	<u> </u>	
Subtotal (95% CI)		14		4	1.0%	1.67 [0.10, 29.18]		
Total events	2		0					
Heterogeneity: Not applicable	2 - 0 72)							
rest for overall effect. Z = 0.35 (r	0.73)							
1.1.6 GANTENERUMAB-SC								
Gantenerumab - NCT01224106	53	531	2	266	3.7%	13.27 [3.26, 54.05]		
Total events	53	23.1	2	200	3.1%	13.27 [3.26, 54.05]		
Heterogeneity: Not applicable			2					
Test for overall effect: Z = 3.61 (F	P = 0.0003))						
1 1 7 AAB-003-IV								
AAB-003 - NCT01193608	2	69	0	19	1.1%	1.43 [0.07, 28,56]		
Subtotal (95% CI)	-	69		19	1.1%	1.43 [0.07, 28.56]		
Total events	2		0					
Heterogeneity: Not applicable Test for overall effect: 7 = 0.23 (F	P = 0.82)							
rest for overall effect. Z = 0.25 (r	0.02)							
1.1.8 LECANEMAB-IV								
BAN2401 - NCT01767311	46	609	2	245	4.0%	9.25 [2.26, 37.82]		
Total events	46	009	2	245	4.0 %	9.25 [2.20, 57.02]		
Heterogeneity: Not applicable	10		-					
Test for overall effect: Z = 3.10 (F	P = 0.002)							
1 1 9 CRENEZUMAB-IV								
Crenezumab - NCT01343966	1	165	0	84	0.9%	1.54 [0.06, 37.31]	<u> </u>	
Subtotal (95% CI)		165		84	0.9%	1.54 [0.06, 37.31]		
Total events	1		0					
Test for overall effect: 7 = 0.26 (F	P = 0.79)							
1.1.10 ADUCANUMAB-IV	-	~~				0.0010.11.17		
Aducanumab - NCT01397539 Aducanumab - NCT01677572	3	39	0	14	1.0%	2.63 [0.14, 47.86]		
Aducanumab - NCT02477800	238	1107	16	40 540	29.8%	7.26 [4.42, 11.91]		
Aducanumab - NCT02484547	334	1091	13	547	24.0%	12.88 [7.47, 22.20]		
Subtotal (95% CI)	000	2362		1141	55.9%	9.79 [6.83, 14.03]	•	
Heterogeneity: Chi ² = 3.35 df = 1	602 3 (P = 0.34)): 2 = 10	29)%					
Test for overall effect: Z = 12.42	(P < 0.0000	,, . = .c 01)						
Donanemab - NCT03367402	36	121	4	106	1 / 0/	34 63 [4 83 348 761		
Subtotal (95% CI)	30	131	1	120	1.4%	34.63 [4.82, 248.76]		•
Total events	36		1					
Heterogeneity: Not applicable								
l est for overall effect: Z = 3.52 (F	- = 0.0004))						
Total (95% CI)		8825		5797	100.0%	10.65 [8.18, 13.87]	•	
Total events	1084		53					
Heterogeneity: Chi ² = 32.63, df =	18 (P = 0.0	02); l ² =	45%				0.001 0.1 1 10	1000
Test for subgroup differences: Cl	ni² = 24.80.	df = 10	(P = 0.0	06), l² :	= 59.7%		Favours [mAb] Favours [PL]	

Fig. 2. Forest plot of the meta-analysis of available data on the frequency of ARIA-E.

on mAbs progressively increased [6]. To account for heterogeneity and over-time variations, data were stratified per mAb and presented in a chronological order. Moreover, a sensitivity analysis including events that were not defined as ARIA was also performed.

The meta-analysis of data on ARIA-E showed an overall 10.65 RR of ARIA-E for any mAb (Fig. 2), that slightly increased to 10.86 (95% CI 8.38-14.06) when performing the sensitivity analysis (Supplementary Figure 4). Ten RCTs reported that no events of ARIA-E occurred during the study period and therefore were not included in the forest plot. The meta-analysis of data on ARIA-H showed an overall RR of 1.75 (Fig. 3), that increased to 2.11 (95%CI 1.87–2.38) when performing the sensitivity analysis, which also allowed to include data for intravenous (IV) bapineuzumab (3.01, 95%CI 2.01-4.51) that were missing in the previous analysis, as in studies on bapineuzumab micro-hemorrhages and siderosis were not yet clearly identified and diagnosed, nor defined as ARIA-H (Supplementary Figure 5). Ten RCTs reported that no ARIA-H events were observed during the study period.

No evolutions over time in the frequency of both ARIA-E and ARIA-H were observed, with the most recent mAb, donanemab, showing the highest risk of both ARIA E (RR 34.63, 95% CI 4.82–248.76) and ARIA-H (RR 4.03, 95%CI 2.09–7.79), and two less recent mAbs, ponezumab and GSK933776, reporting the lowest risks of ARIA-E (RR 0.99, 95% CI 0.04–23.46) and ARIA-H (RR 0.14, 95%CI 0.01–3.13) respectively.

When considering mAbs by different ways of administration, no differences were observed in the frequency of ARIA-H between IV and subcutaneous (SC) crenezumab, while significantly less ARIA-E were observed in SC compared to IV bapineuzumab, and significantly more ARIA-E were observed in SC compared to IV gantenerumab. However, results on SC bapineuzumab were based only on 1 single relatively small phase II study, and results on IV gantenerumab only on 1 small phase I study.

When considering the potential effect of *APOE* status on the risk of ARIA, some differences were observed between carriers (*APOE*+) (ARIA-E RR 13.47, 95%CI 8.18–22.17, I^2 43%; ARIA-H RR 1.50, 95%CI 1.05–2.15, I^2 15%) and non-carriers (*APOE*-) (ARIA-E RR 12.10, 95%CI 6.00–24.41, I^2 30%; ARIA-H RR 2.18, 95%CI 0.85–5.56, I^2 0%). Data stratified per type of mAb showed a higher risk of ARIA-E in *APOE*+participants for aducanumab

(*APOE*+: RR 7.83, 95%CI 1.10–55.85; *APOE*- RR 2.96, 95%CI 0.38–22.88), donanemab (*APOE*+: RR 30.32, 95%CI 4.23–217.25; *APOE*- RR 8.51, 95%CI 0.48–152.42), and SC gantenerumab (*APOE*+: RR 41.61, 95%CI 2.57–672.70; *APOE*- RR 3.02, 95%CI 0.69–13.16) (Supplementary Figure 6), and a higher risk of ARIA-H in *APOE*+participants for aducanumab (*APOE*+: RR 3.05, 95%CI 0.76–12.22; *APOE*- RR 1.85, 95%CI 0.22–15.35) (Supplementary Figure 7).

Efficacy

Data on change from baseline of PET-SUVR were available from 14 studies on 7 mAbs, while data on CDR-SB scores were available from 16 studies on 8 mAbs.

The meta-analysis of PET-SUVR levels showed an overall significant effect of mAbs compared to placebo in reducing the amyloid burden, with an SMD of -0.88 (95%CI -1.30 to -0.47; I² 95%). A reduction in the amyloid burden was observed in all treated groups compared to placebo, except in the group treated with IV crenezumab, who showed a lower decrease in the amyloid burden (SMD 0.36, 95%CI -0.40 to 1.12). A statistically significant difference between groups in the reduction of amyloid burden was observed for 4 mAbs, with the highest difference reported for donanemab (SMD of -2.56, 95%CI -2.91 to -2.21) (Fig. 4).

When considering clinical efficacy, almost half of the studies included in the meta-analysis were classified as terminated due to futility, and the CDR-SB scale was often considered as a secondary endpoint across all considered studies (Fig. 5). None of the included studies reported an improvement from baseline in the CDR-SB score, except for 1 small phase I study on AAB-003 that reported a very small improvement from baseline in the placebo group (-0.35, SD 1.935). Results from the meta-analysis of CDR-SB scores showed that patients treated with mAbs had a statistically significant lower worsening, with a MD -0.15 (95%CI -0.26 to -0.04); I2 2%. However, considering 1-2 points in the CDR-SB scale as a minimal clinically important difference [50], the observed differences between groups were not clinically relevant. No analyses per responder were reported.

When considering potential evolutions over time, as for PET-SUVR levels, the most recently developed mAbs seem to be more effective in decreasing the amyloid burden. Specifically, lecanemab,

Study or Subgroup	mAb Events Total	PL Events	Total	Weight	Risk Ratio	Risk Ratio
1.2.1 BAPINEUZUMAB-SC	Events rotar	LVCIII	Total	Weight	1111, 1 1Xeu, 3371 0	
Bapineuzumab - NCT01254773 Subtotal (95% CI)	1 110 110	0	36 36	0.2% 0.2%	1.00 [0.04, 24.02] 1.00 [0.04, 24.02]	
Total events	1	0				
reterogeneity: Not applicable fest for overall effect: Z = 0.00 (P	9 = 1.00)					
1.2.2 SOLANEZUMAB-IV						
Solanezumab - NCT00904683 Solanezumab - NCT00905372	44 521 6 506	36 21	519 506	11.6% 6.7%	1.22 [0.80, 1.86]	†
Solanezumab - NCT01900665	37 1057	30	1072	9.5%	1.25 [0.78, 2.01]	+
Subtotal (95% CI) Fotal events	2084 87	87	2097	27.8%	1.00 [0.75, 1.34]	•
leterogeneity: Chi ² = 9.13, df = 2	(P = 0.01); l ² = 7	8%				
Fest for overall effect: Z = 0.02 (P	9 = 0.98)					
I.2.3 PONEZUMAB-IV Ponezumab - NCT00722046	12 138	9	56	4 1%	0 54 [0 24 1 21]	_
Ponezumab - NCT00945672	2 24	1	12	0.4%	1.00 [0.10, 9.96]	
oubtotal (95% CI) otal events	162 14	10	68	4.5%	0.58 [0.27, 1.25]	
leterogeneity: Chi ² = 0.24, df = 1	(P = 0.62); I ² = 0	%				
est tor overall effect: Z = 1.39 (P	r = 0.16)					
.2.4 GANTENERUMAB-SC Cantenerumab - NCT01224106	104 531	35	266	14,9%	1.49 [1 05 2 12]	-
Subtotal (95% CI)	531	30	266	14.9%	1.49 [1.05, 2.12]	♦
otal events leterogeneity: Not applicable	104	35				
est for overall effect: Z = 2.20 (P	9 = 0.03)					
.2.5 GSK933776-IV						
GSK933776 - NCT00459550 Subtotal (95% CI)	0 36 36	1	14 14	0.7% 0.7%	0.14 [0.01, 3.13] 0.14 [0.01, 3.13]	
otal events	0	1			,	
leterogeneity: Not applicable est for overall effect: Z = 1.25 (P	9 = 0.21)					
.2.6 AAB-003-IV						
AB-003 - NCT01193608	4 69	0	19	0.2%	2.57 [0.14, 45.77]	
ouprotal (95% CI) otal events	69 4	0	19	0.2%	2.57 [0.14, 45.77]	
leterogeneity: Not applicable		v				
est for overall effect: Z = 0.64 (P	r = 0.52)					
.2.7 LECANEMAB-IV AN2401 - NCT01230853	3 60	2	24	0.9%	0.60 [0 11 3 37]	
AN2401 - NCT01767311	65 609	13	245	5.9%	2.01 [1.13, 3.58]	T
otal (95% CI) otal events	669 68	15	269	6.9%	1.82 [1.06, 3.13]	
leterogeneity: Chi ² = 1.71, df = 1	(P = 0.19); I ² = 4	1%				
est for overall effect: Z = 2.17 (P	r = 0.03)					
.2.8 CRENEZUMAB-IV Crenezumab - NCT01343966	15 165	11	84	4.7%	0.69 [0 33 1 44]	4
Crenezumab - NCT01397578	5 36	1	16	0.4%	2.22 [0.28, 17.52]	
Crenezumab - NCT02353598 Subtotal (95% CI)	3 61 262	0	14 114	0.3% 5.4%	1.69 [0.09, 31.06] 0.87 [0.45, 1.68]	•
otal events	23	12			,]
ieterogeneity: Chi ² = 1.36, df = 2 est for overall effect: Z = 0.42 (P	: (P = 0.51); l ² = 0 = 0.68)	%				
.2.9 CRENEZUMAB-SC						
Crenezumab - NCT01343966	16 122	10	62	4.2%	0.81 [0.39, 1.68]	-+-
Crenezumab - NCT01397578 Subtotal (95% CI)	4 26 148	0	13 75	0.2% 4.5%	4.67 [0.27, 80.64] 1.00 [0.50, 1.99]	•
otal events	20	10				Ţ
ieterogeneity: Chi ^z = 1.43, df = 1 est for overall effect: Z = 0.01 (P	(P = 0.23); l ² = 3 = 0.99)	U%				
.2.10 ADUCANUMAB-IV						
ducanumab - NCT01397539	1 39	0	14	0.2%	1.13 [0.05, 26.13]	
Aducanumab - NC101677572 Aducanumab - NCT02477800	22 125 193 1107	2 34	40 540	1.0% 14.6%	3.52 [U.87, 14.32] 2.77 [1.95, 3.93]	-
ducanumab - NCT02484547	198 1091	37	547 1141	15.8%	2.68 [1.92, 3.75]	
otal events	414	73		51.0%	2.14 [2.10, 3.47]	*
eterogeneity: Chi ² = 0.45, df = 3 est for overall effect: Z = 8.29 /P	$(P = 0.93); I^2 = 0$ < 0.00001)	%				
2 11 DONANEMAR IV	0.00001)					
.2.11 DONANEWAB-IV Donanemab - NCT02624778	1 37	0	12	0.2%	1.03 [0.04, 23.67]	
Donanemab - NCT03367403	40 131	9	126	2.9%	4.27 [2.16, 8.44]	
oubtotal (95% CI) Total events	168 41	9	138	3.2%	4.03 [2.09, 7.79]	
leterogeneity: Chi ² = 0.76, df = 1	(P = 0.38); I ² = 0	-				
est for overall effect: Z = 4.15 (P	< 0.0001)					
otal (95% CI) otal events	6601 776	252	4237	100.0%	1.75 [1.52, 2.01]	•
leterogeneity: Chi ² = 65.44, df =	21 (P < 0.00001);	I ² = 68%				
est for overall effect: Z = 7.92 (P est for subgroup differences: Ch	e < 0.00001) ii² = 51.71, df = 10) (P < 0.00	0001), I	² = 80.7%		Favours [mAb] Favours [PL]

Fig. 3. Forest plot of the meta-analysis of available data on the frequency of ARIA-H.

$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			mAb	_		PL	_		Std. Mean Difference	Std. Mean Difference
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Beneralization - NCT0271122 Impg ² 0.046 6127 12 0.046 6129 12 0.046 6129 12 0.046 6129 12 0.0476 42 0 0.0179 42 0 0.0179 42 0 0.0179 42 0 0.0179 42 0 0.0179 42 0 0.0179 42 0 0.01 12 0.01 0.01 0.01 0.01 0.01 0.0	Bapineuzumab - NCT00574132-0.5mg/kg	0.039	0.1566	12	-0.046	0.1172	7	3.3%	0.56 [-0.39, 1.52]	
Babeleaunantie - LCT0570555. Babeleau - Babeleauna - LCT0570555. Babeleau - B	Bapineuzumab - NCT00574132-1mg/kg	-0.094	0.1632	12	-0.046	0.1253	8	3.4%	-0.31 [-1.21, 0.59]	
Bagenerame. NC1000005104-00000000 Bagenerame. NC10000050 Bagenerame. NC1000050 Bagenerame. NC1000005 Bagenerame. NC1000005 Bagenerame. NC1000050 Bagenerame. NC10000050 Bagenerame. NC10000050 Bagenerame. NC10000500 Bagenerame. NC10000500 Bagenerame. NC10000050 Bagenerame. NC10000050 Bagenerame. NC10000050 Bagenerame. NC10000050 Bagenerame. NC10000050 Bagenerame. NC1000000 Bagenerame. NC1000000 B	Bapineuzumab - NCT00575055-0.5mg/kg	0.001	0.1793	75	0.102	0.1716	40	3.9%	-0.57 [-0.96, -0.18]	
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	Bapineuzumab NCT00667810-0.5mg/kg	-0.04	0.196	6 11	0.02	0.1442	13	3.3%	-0.36 [-1.33, 0.62]	
Salitobal (95: 0) 140 163 212/6 4.35 [4.52, 0.16] Heinergenety, Tail = 0.00; Ch = 3.04, ef = 5 (P = 0.41) P = 1%. 13.3% 0.12 [4.79, 0.58] Zab Zab WHEUZUMARS-CC Biopresumme NCT01245773-20mg 0.021 [0.100] 30 0.0776 11.3.7% 0.12 [4.79, 0.58] Salisonauruho - CNT01245773-20mg 0.021 [0.100] 30 0.0776 11.3.7% 0.12 [4.79, 0.58] Salisonauruho - CNT01245773-20mg 0.01 [0.149] 0.05 0.0176 11.3.7% 0.01 [4.79, 0.58] Salisonauruho - CNT01000655 .01 [0.149] 0.05 0.0146 771 4.67 0.0172 11.0.77 Salisonauruho - CNT01000655 .01 [0.149] 0.05 0.24 0.24 0.5 2.2% .107 [2.51, 0.69] Salisonauruho - CNT01024106-105010 .00 [0.24, 0.5 2.2% .107 [2.51, 0.69] .000 .016 [2.47, 0.50] Salisonau (Hox, 2 = 1.40 (P = 0.16)) 2.2.2 (D ACT SALISON (Hox MARSALISON (Hox MARSAL	Bapineuzumab - NCT00676143-0.5mg/kg	-0.04	0.1697	32	0.02	0.1442	24	3.8%	-0.38 [-0.91, 0.15]	
Hetergraphy, Tur = 0.00, CH = 0.04, H = 0 (P = 0.41); P = 1% Tell for overall effect 2 = 0.26 (P = 0.041); P = 1% Berneturnet. NCT022477.3 mg 0.401 0.1803 35 0 0.1749 11 3.7% Berneturnet. NCT022477.3 mg 0.401 0.1803 35 0 0.1749 11 3.7% Hetergraphy, Tur = 0.00, CH = 0.41, H = 2 (P = 0.51); P = 0% Tell for overall effect 2 = 0.42 (P = 0.35); P = 0% Berneturnet. NCT012477.3 mg 0.01 0.1401 805 0 0.1749 11 3.7% Hetergraphy, Tur = 0.00, CH = 0.41, H = 2 (P = 0.51); P = 0% Tell for overall effect 2 = 0.42 (P = 0.35); P = 0% Berneturnet. NCT0124102.2103 0.02 0 0 0.22 0 0 0.140 12 2 2.06 Hetergraphy, Tur = 0.00, CH = 0.05, H = 1 (P = 0.51); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 1.41 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for overall effect 2 = 0.42 (P = 0.53); P = 0% Tell for o	Subtotal (95% CI)			148			105	21.2%	-0.36 [-0.62, -0.10]	•
22.2 EARNING MULTINE TABLE 2 (* 0.01 0.450 35 0 0.1749 11 3.75 0.07 (20.75.0.68) Bipmicsurumi - NCT01220737370 0.041 0.1683 35 0 0.1749 11 3.75 0.07 (20.75.0.68) Bipmicsurumi - NCT01220737370 0.041 0.169 35 0 0.1749 11 3.75 0.07 (20.75.0.68) Bibleoal differ Cl 1 1000085 0.01 0.149 805 0 0.1749 11 3.75 0.07 (20.75.0.68) Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1749 11 3.75 0.07 (20.75.0.68) Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1749 11 3.75 0.07 (20.75.0.68) Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 409 Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 409 Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 409 Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 409 Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 409 Bibleoal differ Cl + 0.52 (* 0.01) 1 - 0.51 19 805 0 0.1740 17 10 - 0.51 19 800 10 0.02 2 4 0.05 12 2.25 0.059 Bibleoal differ Cl + 0.62 (* 0.02) 2 4 0.02 2 1.0 13 10 3.85 0.01 11 0.27 0.04 0.124 12 0.355 0.059 Bibleoal differ Cl + 0.62 (* 0.02) 0.02 2 4 0.02 0.13 10 3.85 0.01 10.67 1.0 0.00 2.5 Converteentume - NCT0551164.00m Converteentume - NCT0551164.00m 2.5 Converteentume - NCT052120105 20m Bibleoal differ Cl + 0.62 (* 0.02) 1 - 0.51 19 8 200 Bibleoal differ Cl + 0.62 (* 0.02) 1 - 0.51 19 8 200 Bibleoal differ Cl + 0.62 (* 0.02) 1 - 0.51 19 8 200 Bibleoal differ Cl + 0.62 (* 0.02) 1 - 0.51 19 8 200 Bibleoal differ Cl + 0.62 (* 0.03) 1 - 0.50 (* 0.04 0.124 20 3.56 - 0.51 19 3.50 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 3.56 - 0.51 19 10 10 10 10 10 10 10 10 10 10 10 10 10	Heterogeneity: Tau ² = 0.00; Chi ² = 5.04, df Test for overall effect: Z = 2.69 (P = 0.007)	= 5 (P = 0	0.41); I² =	: 1%						
Bajenizzunzi. + 1072124773.0rg 0.021 0.103 98 0 0.0749 11 3.76 0.07 (0.75.0.68) Bajenizzunzi. + 1072124773.0rg 0.066 0.177 31 0 0.1749 11 3.76 0.07 (0.75.0.68) Bajenizzunzi. + 1072124773.0rg 0.066 0.177 31 0 0.1749 11 3.76 0.07 (0.75.0.68) Bajenizzunzi. + 1070124767.2 0.07 (0.76.0.68) 23 50.0.4722.00.0 (0.1 - 0.1 - 0.1 - 0.07 (0.1 - 0.07) Tat for over alloc: 2 - 0.07 (0.1 - 0.1 - 0.1 - 0.07) Hierography Tar 2 - 0.07 (0.1 - 0.1 - 0.1 - 0.07) Hierography Tar 2 - 0.07 (0.1 - 0.1 - 0.1 - 0.07) Hierography Tar 2 - 0.07 (0.1 - 0.1 - 0.1 - 0.07) Hierography Tar 2 - 0.07 (0.1 - 0.01) 23 50.0.4722.00.07 (0.1 - 0.01) Hierography Tar 2 - 0.07 (0.1 - 0.01) Hierography Tar 2 - 0.07 (0.1 - 0.01) 23 50.0.4722.00.07 (0.01) Hierography Tar 2 - 0.07 (0.1 - 0.01) 23 50.00.4722.00.07 (0.01) Subteal (05% C) Hierography Tar 2 - 0.07 (0.1 - 0.01) 23 50.00.4722.00.07 (0.01) 30 0.02 0.01 0 0.01 0 0.01 0 0.01 23 50.00.0722.00.07 (0.01) 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.01 0 0.01 0 0.01 0 0.01 0 0.01 30 0.00 0 0.00 0 0.01 30 0.00 0 0.00 0 0.00 30 0.00 0 0.00 0	2.2.2 BAPINEUZUMAB-SC									
Beinstanzamie - NCT012547737am 0 -0.014 0183 35 0 0.1740 11 3.7% -0.07 (-27.5 0.69) Meterogravity. Tarl = 0.00: Ch = 0.41, df = 2(P = 0.61); F = 0% Test for overall effect 2 = 0.20 (P = 0.61); F = 0% Test for overall effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.61); F = 0% Subtrail effect 2 = 0.20 (P = 0.65); F = 0.63; P = 0.81; F = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0% Test for overall effect 2 = 0.20 (P = 0.65); F = 0.83; P = 0	Bapineuzumab - NCT01254773-20mg	-0.021	0.1803	36	0	0.1749	11	3.7%	-0.12 [-0.79, 0.56]	_ _
Bagenaruments - IAC 1012/2477379 mg 0.066 0.177 34 0 0.1746 11 0.56 0.37 109% 0.57 (1.6.6, 0.37) 109% 0.57 (1.6.6, 0.37) 2.3 SOLAREZIMARA V Substant refs. Viol Divolation 4 2 (2.9 - 0.0); P = 0%; Test for over allefic Z = 0.62 (P = 0.8); 2.3 SOLAREZIMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Substant refs. Viol Divolation 2 (2.1 - 0.6); 2.4 AUXTYEERUMARA V Auxammark - NCTORF7731-10mg/kg 0.020 0.1572 21 0.015 0.156 11 0.56 11 0.56 10 0.5	Bapineuzumab - NCT01254773-2mg	-0.014	0.1863	35	0	0.1749	11	3.7%	-0.07 [-0.75, 0.60]	
Hearganety, Tur - 0.00; Ch ⁻¹ 0.04; d ⁻ 2 (P - 0.03); P = 0% Tel for overal lafest, 2 - 0.82 (P - 0.3) 2.13 SOLAREZIMAB-M Subscalards - NC01905086 Subscalards - NC01907071-10070g/g8 Subscalards - NC01907071-10070g/g8 Subscalards - NC01907731-10070g/g8 Subscalards - NC01907731-10070g/g8 Subscalards - NC01907731-10070g/g8 Subscalards - NC01907731-10070g/g8 Subscalards - NC01907731-10070g/g8 Subscalards - NC019077731-10070g/g8 Subscalards - NC01907773-10070g/g8 Subscalards - NC01907773-10070g/g8 Subscalards - NC01907773-10070g/g8 Subscalards - NC01907773-10070g/g8 Subscalards - NC01907772-20070g Subscalards - NC0197772-20070g Subscalards - NC01977772-0070g Subscalards - NC01977772-0070g Subscalards - NC01977772-0070g Subscalards - NC0197772-0070g Subscalards - NC01977772-0070g Subscalards - NC01977772-0070g Subscalards - NC01977772-0070g Subscalards - NC0197772-0070g Subscalards - NC01977772-0070g Subscalards - NC01977772-0070g Subscalards - NC0197772-0070g Su	Bapineuzumab - NCT01254773-7mg Subtotal (95% CI)	-0.066	0.1777	34 105	0	0.1749	11 33	3.6% 10.9%	-0.37 [-1.05, 0.32] -0.18 [-0.58, 0.21]	•
Carl Decomposition Control Control Contro	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df Test for overall effect: $Z = 0.92$ (P = 0.36)	= 2 (P = 0	0.81); l² =	0%						
advancements: NOT0500065 0.01 0.1410 605 0 0.01 0.410 605 0 0.01 0.410 605 0 0.01 0.410 605 0 0.01 0.410 605 0 0.01 0.410 605 0 0.01 0.410 605 0 0.07 0.17 0.03 0.07 <th0.07< th=""> 0.07 0.07</th0.07<>	2 2 3 SOLANEZUMAB-IV									
Subbal 19% C) $0 = 0.05$ CP 4 0% 0.07 (2.17, 0.03] Tas for ovail affect 2 = 1.4 ($P = 0.16$) 2.2 4 GANTERVERVAMA.PV Contensmunt- NCT0033198-00mg 0.07 0.45 6 0.24 0.15 2 2.4% - 1.07 [2.8, 0.69] Subbal 19% C) $0.00 = 0.05$ d = 1 ($P = 0.8$) 2.2 4 GANTERVERVAMA.PV Contensmunt- NCT0033198-00mg 0.07 0.45 6 0.24 0.15 2 2.4% - 0.07 [2.8, 0.69] Subbal 19% C) $0.00 = 0.05$ d = 1 ($P = 0.8$) 2.2 5 GANTERVERVAMA.PC Contained the 2 = 1.0 ($P = 0.0$) 2.2 5 GANTERVERVAMA.PC Contained the 2 = 0.00 ($P = 0.0$) $0.2 = 0.2 = 0.2 0.13 18 3.8% 0.11 [0.47, 0.89] Gantenemmati- NCT0122419 0.25mg 0.99 0.4 20 -0.02 0.13 17 3.7% 0.95 [1.10 0] Subbal 19% C) 0.00 = 0.14 20 -0.02 0.13 18 3.8% 0.11 [0.47, 0.89] Gantenemmati- NCT0122419 0.25mg 0.99 0.4 20 -0.02 0.13 17 3.7% 0.45 [1.42, 0.23] Subbal 19% C) 0.00 = 0.14 20 -0.02 0.13 18 3.8% 0.11 [0.47, 0.89] Subbal 19% C) 0.00 = 0.14 20 -0.02 0.13 18 3.8% 0.11 [0.47, 0.89] Subbal 19% C) 0.00 = 0.14 20 -0.02 0.13 18 3.8% 0.38 [1.42, 0.23] Subbal 19% C) 0.00 = 0.14 20 -0.04 0.124 20 3.7% -0.35 [1.42, 0.23] BAN201 NCT0177311-6mg/kgM 0.030 0.1111 20 0.004 0.124 20 3.5% -0.35 [1.42, 0.23] BAN201 NCT0177311-6mg/kgM 0.225 0.117 80 0.004 0.124 20 3.5% -0.44 [3.13, -1.5] EAX201 NCT0177311-6mg/kgM 0.225 0.1178 80 0.004 0.124 19 3.8% -0.58 [0.40, 1.12] BAN201 NCT0173731-6mg/kgM 0.030 0.128 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1862 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.1882 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.128 24 0.014 0.1102 11 3.8% 0.36 [0.40, 1.12] BAN201 NCT01307738 0.029 0.128 24 0.014 0.1102 11 3.8% 0$	Solanezumab - NCT01900665	-0.01	0.1419	805	0	0.1406	791	4.0%	-0.07 [-0.17, 0.03]	
Heterogenety: Not applicable Test for overall effect 2 = 10 4 (P = 0.6); 22.4 CMTENERUMAB-M Gentenerumab - NCT0031984-00mg 0.02 4 6 0.24 0.15 2 2.2%, -1.07 [2.83, 0.69] Gentenerumab - NCT0031984-00mg 0.03 0.24 6 0.24 0.15 2 2.4%, -0.83 [2.45, 0.29] Heterogenety: Tau" = 0.0; Ch = 0.0; d = 1 (P = 0.8); P = 0%, Tau for overall effect 2 = 1.4 (P = 0.3); P = 0%, Tau for overall effect 2 = 1.4 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.0 (P = 0.004); P = 7.4%, 2.2.6 LECAMEMAB-M BAX2d1 - NCT0172311-0 (P = 0.15); P = 52%, Tau for overall effect 2 = 0.5 (P = 0.004); P = 7.4%, 2.2.7 CENEZUMAB-4C 2.2.6 CENE	Subtotal (95% CI)			805			791	4.0%	-0.07 [-0.17, 0.03]	•
$ \frac{224 \text{ GAMTENERUMAB-V}}{\text{Gamtenerumab-NCT00538984-200mg} 0.27 0.45 6 0.24 0.15 2 2.3\% 1.07 [2.83, 0.69] \\ \text{Gamtenerumab-NCT00538984-200mg} 0.03 0.24 6 0.24 0.15 2 2.3\% 1.07 [2.83, 0.69] \\ \text{Gamtenerumab-NCT00538984-200mg} 0.03 0.24 6 0.24 0.15 2 2.4\% 1.47 [2.80, 0.89] \\ \text{Gamtenerumab-NCT00538984-200mg} 0.00 0.2 32 0.02 0.13 16 3.8\% 0.05 [0.11 [0.47, 0.69] \\ \text{Gamtenerumab-NCT01224106-22mg} 0.00 0.14 8 0 0.02 0.13 17 3.7\% 0.55 [1.10, 0.55 $	Heterogeneity: Not applicable Test for overall effect: Z = 1.41 (P = 0.16)									
Continuentues - NCT00351804-200mg 0.27 0.45 6 0.24 015 2 2.3% -1.07 (2.83, 0.89) Subbolal (9% C) 0.03 0.24 6 0.24 0.15 2 2.4% -0.03 (2.6, 0.09) Subbolal (9% C) 0.02 0.05 1 2 2.4% -0.03 (2.6, 0.09) -0.02 (2.6, 0.09) Continuentume - NCT0251804-00mg 0.02 0.2 2.0 -0.02 0.13 17 3.5% -0.01 (2.4, 0.09) Continuentume - NCT0251804-00mg 0.00 0.2 2.2 -0.02 0.13 17 3.5% -0.01 (2.4, 0.09) Subbolal (9% C) 1.01 0.04 0.124 20 3.7% -0.83 (-1.42, -0.23) CALCAMEMAEV EXAX01 - NCT07371410-6mg/kgB -0.094 0.124 20 3.6% -2.44 (3.13, -1.78) BAX201 - NCT07371410-6mg/kgB -0.094 1.24 20 3.6% -2.44 (3.13, -1.78) BAX201 - NCT07371410-6mg/kgB -0.094 1.24 20 3.6% -3.66 (-0.40, -1.12) BAX201 - NCT07371410-6mg/kgB -0.094 1.24 20 3.6% -0.06 (-0	2.2.4 GANTENERUMAB-IV									
Gardenemab - NCT0053104-60mg 0.03 0.24 6 0.24 0.15 2 2.4% 0.08 [2.50.08] 12 4 4.7% 0.30 [2.50.08] 14 Heterogenely: Tat ² = 0.00, df = 10 = 0.05; ff = 0.85; ff = 0.85 14 Heterogenely: Tat ² = 0.00, df = 10 = 0.05; ff = 0.05 Contentumb - NCT01224106-106mg 0.0 0.2 32 0.02 0.13 18 3.8% 0.11 [0.47, 0.69] Gardenemab - NCT01224106-106mg 0.0 0.2 32 0.02 0.13 17 3.7% 0.50 [-1.11, 0.10] Subtotal (8% 0) 22.6 ECAMEMAB-V Enderogenely: Tat ² = 0.10, 0ff = 2.07, df = 1 ($f = 0.15$; $f = 52\%$ Test for overall effect: 2 = 0.52 ($f = 1.6$ 0.11) 22.6 ECAMEMAB-V Enderogenely: Tat ² = 0.10, 0ff = 2.07, df = 1 ($f = 0.15$; $f = 52\%$ Test for overall effect: 2 = 0.52 ($f = 1.6$ 0.04) 0.1244 20 3.8% - 0.71 [2.38, -1.35] ENAX01 - NCT0175731-05mg/kgB - 0.094 0.1111 28 0.004 0.1244 20 3.8% - 1.91 [2.47, 0.62] ENAX01 - NCT0175731-05mg/kgB - 0.036 0.126 44 0.004 0.1244 20 3.8% - 2.41 [-3.13, -1.75] ENAX01 - NCT0175731-05mg/kgB - 0.030, 1.72 21 ENAX01 - NCT0175731-05mg/kgB - 0.030, 1.72 21 ENAX01 - NCT0175731-05mg/kgB - 0.020, 1.75 21 - 0.071 0.136 10 3.6% - 0.36 [0.40, 1.12] ENAX01 - NCT01757751 - 0.00001 22.2 CRENEZUMAB-V Crenezumab - NCT01397578 - 0.02 0.1375 21 - 0.071 0.136 10 3.6% - 0.36 [0.40, 1.12] ENAX01 - NCT0157572-05mg/kg - 0.102 0.1375 21 - 0.071 0.136 10 3.6% - 0.36 [0.40, 0.12] 22.2 CRENEZUMAB-V Crenezumab - NCT01397578 - 0.02 0.1375 21 - 0.071 0.136 10 3.6% - 0.36 [0.40, 0.12] 22.2 CRENEZUMAB-V Crenezumab - NCT01397578 - 0.020 1.122 10 3.6% - 0.36 [0.40, 0.12] 22.2 CRENEZUMAB-V Crenezumab - NCT01397578 - 0.020 1.122 10 3.6% - 0.36 [0.40, 0.12] 22.2 CRENEZUMAB-V Crenezumab - NCT01397578 - 0.02001; $r = 77\%$ Test for overall effect: 2 = 0.15 ($f = 0.30$; 0.224 24 0.018 0.1185 29 0.014 0.1102 11 3.6% - 0.25 [0.40, 0.68] 465 2.2.0% - 1.73 [2.16, -1.30] 465 2.2.0% - 1.73 [2.16, -1.30] 465 2.2.0% - 1.73 [2.16, -1.30] 465 2.2.0% - 1.73 [2.4, 0.30] 465 2.2.0% - 1.73 [2.4, 0.4] 465 2.2.0% - 1.73 [2.4,	Gantenerumab - NCT00531804-200mg	-0.27	0.45	6	0.24	0.15	2	2.3%	-1.07 [-2.83, 0.69]	
$ \begin{array}{c} \text{Latternal} & \text{Let} & \text{L} $	Gantenerumab - NCT00531804-60mg Subtotal (95% CI)	0.03	0.24	6 12	0.24	0.15	2	2.4% 4.7%	-0.80 [-2.50, 0.89]	
Treat for overall effect: $2 = 1.49 (P = 0.14)$ 2.2.5 CANTENERUMAB-SC Gentenerumab - NCT01224106-105mg 0 0.2 32 0.02 0.13 17 3.7% 0.50 [-1.11, 0.10] Set of the company is a set of the company is	Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 0.05$ df	= 1 (P = (0.83)· I² =	:0%			4	4.7 70	-0.55 [-2.15, 0.25]	
$ \frac{22.5 \text{ GATTEMETUNAB-SC}}{\text{Gathemurunb - NCT01224100-105 mg} 0.0 0.2 32 .002 0.13 17 3.7\% -0.50 [-1.11, 0.01] \\ \text{Gathemurunb - NCT01224100-105 mg} 0.0 90 4.0 111 28 0.004 0.124 20 3.7\% -0.50 [-1.11, 0.01] \\ \text{Hetrogeneity: Tar2 = 0.10, Ch2 = 2.07, d= 1 [P - 0.15]; P = 52\% \\ \text{Tast for overall effect Z = 0.52 (P = 0.54) } \\ \frac{22.5 \text{ LECANEMAB-W}}{\text{BAX201 - NCT0176731-105 mg/kgB} 0.094 0.1111 28 0.004 0.1244 20 3.7\% -0.83 [-1.42, -0.23] \\ \text{GAN201 - NCT0176731-105 mg/kgB} 0.094 0.1111 28 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.0197 0.111 (28 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.0197 0.122 0.102 44 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.036 0.1224 12 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.030 0.0124 4 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.030 0.0124 4 0.004 0.1244 20 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.030 0.0124 4 0.004 0.1244 20 3.7\% -1.19 [-2.17, -1.30] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.030 0.0124 4 0.004 0.1244 120 3.7\% -1.14 [-1.76, -0.52] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.030 0.016 1.224 0.013 0.124 19 3.8\% -1.91 [-2.17, -1.30] \\ \text{GAN201 - NCT0176731-15 mg/kgB} 0.020 0.1375 21 -0.071 0.136 10 3.6\% 0.36 [-0.40, 1.12] \\ GAN201 - NCT0167752-00005 0 -0.020 0.1862 24 -0.018 0.1066 10 3.6\% 0.36 [-0.40, 1.12] \\ \text{GAUCAUNDAB - NCT01677572-00076 gg -0.220 0.127 24 0.014 0.1102 11 3.6\% -0.57 [-1.29, 0.15] \\ \text{Aducaunumb - NCT01677572-00076 gg -0.235 0.1224 26 0.014 0.1102 11 3.6\% -0.57 [-1.20, 0.15] \\ \text{Aducaunumb - NCT01677572-00076 gg -0.235 0.1224 28 0.014 0.1102 10 3.4\% -228 [-2.1, -2.21] \\ \text{Aducaunumb - NCT01677572-00076 gg -0.235 0.1224 28 0.014 0.1102 11 3.6\% -0.55 [-2.1, -2.21] \\ \text{Aducaunumb - NCT01677572-00076 gg -0.235 0.1224 28 0.014 0.1102 11 3.6\% -0.55 [-2.24, -2.41] \\ \text{Aducaunumb - NCT01677572-00076 gg -0.235 0.1224 28 0.014 0.1102 11 3.6\% -0.55 [-2.24, -$	Test for overall effect: Z = 1.49 (P = 0.14)	. (.		•.•						
Gartenerunab - NCT0124106-226mg 0.0g 0.123 32 -0.02 0.13 17 37, -0.50 (-11.0, 0.1) Subtal (9% C)	2.2.5 GANTENERUMAB-SC									
Subtrain (unice) (1) (1) (2) (1) (2) (2) (2) (2) (2) (2) (3) (3) (2) (3) (3) (2) (3) (3) (4) (4) (4) (4) (4) (4) (4) (4) (4) (4	Gantenerumab - NCT01224106-105mg	0	0.2	32	-0.02	0.13	18	3.8%	0.11 [-0.47, 0.69]	
Heterogeneity: Tat ² = 0.10, Ch ² = 2.07, df = 1 ($p = 0.15$); $P = 52\%$. Test for overall effect: 2 = 0.62 ($p = 0.54$) 2.2.6 LECANEMAB-V BAN2401 - NCT01767311-0mg/kgB = 0.094 0.1111 28 0.004 0.1244 20 3.7% - 0.63 [-1.42, -0.23] BAN2401 - NCT01767311-0mg/kgB = 0.016 0.1264 20 3.7% - 1.14 [-1.76, 0.52] BAN2401 - NCT01767311-10mg/kgB = 0.006 0.1264 42 00 3.2% - 1.14 [-1.76, -0.52] BAN2401 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN2401 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN2401 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN2401 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN2401 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN240 - NCT01767311-10mg/kgB = 0.026 0.1264 42 00 4.1244 20 3.7% - 1.59 [-2.15, -1.5] BAN240 - NCT01767371 - 0.029 0.1375 21 - 0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] D 3.6% - 0.36 [-0.40, 1.12] D 3.6% - 0.06 [-0.80, 0.68] Test for overall effect: 2 = 0.16 ($p = 0.36$) 2.2.6 CENEZUMAB-SC Concentrumb - NCT01397778 - 0.029 0.1862 24 -0.018 0.1866 10 3.6% - 0.57 [-1.29, 0.16] Aducanumab - NCT01677772-00mg/kg - 0.265 0.1224 28 0.014 0.1102 11 3.6% - 0.57 [-1.29, 0.16] Aducanumab - NCT01677772-00mg/kg - 0.263 0.1176 24 0.014 0.1102 11 3.6% - 0.57 [-1.29, 0.16] Aducanumab - NCT01677772-00mg/kg - 0.263 0.1224 28 0.014 0.1102 10 3.4% - 1.68 [-2.77, -1.01] Aducanumab - NCT01677772-00mg/kg - 0.215 112 0.004 0.1152 112 3.6% - 2.25 [-2.1, -2.21] Aducanumab - NCT01677772-00mg/kg - 0.215 112 0.004 0.1152 112 3.9% - 2.25 [-2.1, -2.21] Aducanumab - NCT01677772-00mg/kg - 0.264 0.1239 170 0.014 0.121 11 3.6% - 2.25 [-2.1, -2.21] Aducanumab - NCT01677772-00mg/kg - 0.215 121 0.004 0.1152 112 3.9% - 2.25 [-2.1, -2.21] Aducanumab - NCT01677772-00mg/kg - 0.264 0.1239 170 0.014 0.121 11 3.8% - 2.25 [-2.1, -2.21] Aducanumab - NCT01677772-00mg/kg - 0.365 121 0.004 0.1155 112 3.9% - 2.25 [-2.1, -2.	Subtotal (95% CI)	-0.09	0.14	62	-0.02	0.15	35	7.5%	-0.19 [-0.79, 0.41]	•
178: UD VORTAIL there: 2 = 0.54 (* = 0.54) 22.6 LECANEMAE/V BAV2401 • NCT01767311-062;5mg/kgB -0.197 0.197 0.191 22 0.004 0.1244 20 3.7% -0.83 [-1.42, -0.23] BAV2401 • NCT01767311-063mg/kgB -0.197 0.191 22 0.004 0.1244 20 3.7% -1.14 [-1.76, -0.52] BAV2401 • NCT01767311-10mg/kgB -0.306 0.128 44 0.004 0.1244 20 3.6% -2.44 [-3.13, -1.75] BAV2401 • NCT01767311-10mg/kgB -0.306 0.128 44 0.004 0.1244 20 3.6% -2.44 [-3.13, -1.5] BAV2401 • NCT01767311-10mg/kgB -0.306 0.172 21 0.36 8.8% -1.59 [-2.15, -1.64] Heterogeneity: Tau" = 0.29; Ch" = 15.56, df = 4 (P = 0.004); P = 74% 10 3.6% 0.36 [-0.40, 1.12] Cenezumab - NCT01597577 -0.029 0.180 24 -0.018 0.36 [-0.40, 0.12] Z25 ADUCANUMAB-SC Cenezumab - NCT016977572-01mg/kg -0.324 20 0.144 0.102 13 3.6% -0.57 [-1.29, 0.15] -0.301 Aducanumab - NCT016977572-01mg/kg -0.254	Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 2.07$, df	= 1 (P = 0	0.15); l² =	52%						
2.2.6 LECANEMAB-V BAN2401 - NCT01767311-05mg/kgB 0.094 0.1111 28 0.004 0.124 20 3.7% -0.83 [-1.420.23] BAN2401 - NCT01767311-05mg/kgB 0.0197 0.1091 27 0.004 0.124 20 3.7% -1.71 [-2.39, 1.03] BAN2401 - NCT01767311-05mg/kgB 0.306 0.128 44 0.004 0.1244 20 3.7% -1.11 [-1.76, 0.52] BAN2401 - NCT01767311-10mg/kgB 0.306 0.128 44 0.004 0.1244 20 3.7% -1.16 [-2.7, 1.35] BAN2401 - NCT01767311-10mg/kgB 0.225 0.179 89 0.004 0.124 19 3.8% -1.91 [-2.47, 1.35] Subtal (9% C) 2.15 10.4 Heterogeneity: Not applicable Test for overall effect. 2 = 1.0.94 (P = 0.004); IP = 74% Test for vorall effect. 2 = 1.0.94 (P = 0.35) 2.2.9 ADUCANUMAB-V Aducanumb - NCT01397778 0.029 0.1862 24 0.018 0.1866 10 3.8% 0.06 [-0.80, 0.68] -1.0 3.8% -0.06 [-0.80, 0.68] -1.0 3.8% -0.07 [-1.29, 0.15] -2.2 CRENEZUMAB-V Crenezumb - NCT01397778 0.029 0.1862 24 0.018 0.1866 10 3.8% -0.07 [-1.29, 0.15] -2.2 ADUCANUMAB-V Aducanumb - NCT01397778 0.029 0.1862 24 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -2.2 ADUCANUMAB-V Aducanumb - NCT01397778 0.029 0.1862 24 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -2.2 ADUCANUMAB-V Aducanumb - NCT01397778 0.029 0.1862 124 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -4.040arumb - NCT01397778 0.028 0.1242 46 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -4.040arumb - NCT01397778 0.028 0.1242 47 40 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -4.040arumb - NCT01397782-03mg/kg 0.223 0.1247 28 0.014 0.1102 11 3.8% -0.57 [-1.29, 0.15] -4.040arumb - NCT01397782-03mg/kg 0.223 0.1245 128 0.004 0.1102 11 3.8% -0.57 [-1.29, 0.15] -4.040arumb - NCT0139776100 -0.238 0.1245 124 0.003 0.1165 22.0% -1.73 [2.16, 1.30] -4.040arumb - NCT0139776100 -0.238 0.1245 124 0.004 0.1121 112 3.9% -2.56 [2.91, -2.21] -4.040arumb - NCT01397763 0.027 0.0165 121 0.004 0.1185 112 3.9% -2.56 [2.91, -2.21] -4.040arumb - NCT013976730 0.0367 0.165 121 0.004 0.1185 112 3.9% -2.56 [2.91, -2.21] -4.040arumb - NCT013976730	Test for overall effect: $Z = 0.62$ (P = 0.54)									
$\begin{array}{c} Latter is intervalued in the second of the second$	Z.Z.b LECANEMAB-IV BAN2401 - NCT01767311-02 5mg/kgP	-0 004	0 1111	25	0.004	0 1244	20	3 7%	-0.83 [-1.42 -0.22]]
BAX201 - NCT01767311-10mg/kgM -0.131 0.111 28 0.004 0.1244 20 3.7% -1.14[1-78.0.52] BAX201 - NCT01767311-10mg/kgM -0.225 0.1179 89 0.004 0.1244 20 3.8% -2.44[3.13, -175] BAX201 - NCT01767311-10mg/kgM -0.225 0.1179 89 0.004 0.1244 19 3.8% -2.44[3.13, -175] BAX201 - NCT01767311-10mg/kgM -0.225 0.1179 89 0.004 0.1244 19 3.8% -2.44[3.13, -175] BAX201 - NCT01767311-10mg/kgM -0.225 0.1179 89 0.004 0.1244 19 3.8% -2.44[3.13, -175] BAX201 - NCT01767371 0.002 0.137 21 -0.01 0.36 [0.40, 1.12] 0.36 [0.40, 1.12] Subtotal (69% CI) 12 10 3.6% 0.36 [0.40, 1.12] 10 3.6% 0.36 [0.40, 1.12] Creanzumab - NCT01677572 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.05 [0.80, 0.68] 100.102 11 3.6% -0.25 [0.20, 0.50] 100.102 11 3.6% -0.25 [0.20, 0.50]	BAN2401 - NCT01767311-02.5mg/kgB BAN2401 - NCT01767311-05mg/kgB	-0.094	0.1091	20	0.004	0.1244	20	3.7%	-0.63 [-1.42, -0.23] -1 71 [-2 39 -1 03]	
BAN2d01 - NCT01767311-10mg/kgB - 0.266 0.126 44 0.004 0.1244 20 3.6% -2.44 [3.1, -1.75] BAN2d01 - NCT01767311-10mg/kgB - 0.225 0.179 g 80 0.004 0.124 20 3.6% -1.91 [2.47, -1.35] Subtal (6% C) - 1.27 2.23 C) - 1.55 6, df = 4 ($P = 0.004$); $P = 74\%$ Test for overall effect: $Z = 5.65$ ($P < 0.0001$) 2.7 CRENEZUMAB-W Crenezumab - NCT01397778 - 0.02 0.1375 21 -0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] Heterogeneity: Not applicable Test for overall effect: $Z = 0.34$ ($P = 0.35$) 2.8 CRENEZUMAB-SC Crenezumab - NCT01397778 - 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtal (6% C) - 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtal (6% C) - 0.050 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 10 3.4% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 28 0.014 0.1102 10 3.4% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-01mg/kg -0.255 0.124 28 0.014 0.1102 10 3.4% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-01mg/kg -0.255 0.124 183 -0.003 0.1185 294 4.0% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-01mg/kg -0.256 0.1229 170 0.014 0.1122 10 3.4% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-01mg/kg -0.256 0.1239 170 0.014 0.1126 11 3.6% -0.25 [-2.15, -1.67] Aducanumab - NCT0247572-01mg/kg -0.256 0.1239 170 0.014 0.1126 11 3.6% -2.25 [-2.16, -1.30] Heterogeneity: Not applicable 2.2 100 NONEMBA-IV Donamenda - NCT024757474 high Dose -0.264 0.1299 170 0.014 0.126 11 3.6% -2.25 [-2.16, -1.30] 4.11 112 3.9% -2.56 [-2.91, -2.21] 4.11 112 3.9% -2.56 [-2.91, -2.21] 4.11 112 3.9% -2.56 [-2.91, -2.21] 5.111 112 3.9% -2.56 [-	BAN2401 - NCT01767311-05mg/kgM	-0.131	0.1111	28	0.004	0.1244	20	3.7%	-1.14 [-1.76, -0.52]	
BAN2401 - NCT01767311-0mg/kgM -0.225 0.179 89 0.04 0.1244 19 3.8% $-1.51[2.47, -1.35]$ We to generall effect Z = 5.65 (P < 0.0001) 2.10 2.10 2.1375 21 -0.071 0.136 10 3.6% $-0.36[0.40, 1.12]$ Test for overall effect Z = 5.65 (P < 0.0001) 2.2.7 CRENEZUMAB-V Cremezumab - NCT01375778 -0.02 0.1375 21 -0.071 0.136 10 3.6% $0.36[0.40, 1.12]$ He torgeneity: Not applicable Test for overall effect Z = 0.94 (P = 0.35) 2.2.8 CRENEZUMAB-SC Cremezumab - NCT01375778 -0.029 0.1862 24 -0.018 0.1866 10 3.6% $-0.06[0.80, 0.68]$ Heterogeneity: Not applicable Test for overall effect Z = 0.15 (P = 0.88) 2.2.9 ADUCANUMAB-IV Aducanumab - NCT01377572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% $-0.57[-1.29, 0.15]$ Aducanumab - NCT01377572-01mg/kg -0.055 0.1224 28 0.014 0.1102 11 3.6% $-0.57[-1.29, 0.15]$ Aducanumab - NCT01377572-01mg/kg -0.055 0.1224 28 0.014 0.1102 11 3.6% $-0.57[-1.29, 0.15]$ Aducanumab - NCT01377572-01mg/kg -0.255 0.1224 26 0.014 0.1102 11 3.6% $-0.57[-1.29, 0.15]$ Aducanumab - NCT01377572-01mg/kg -0.255 0.1224 26 0.014 0.1102 10 3.4% $-2.28[-3.18, -1.38]$ Aducanumab - NCT01377572-01mg/kg -0.255 0.124 10.014 0.1102 10 3.4% $-2.28[-3.18, -1.38]$ Aducanumab - NCT01377572-01mg/kg -0.256 0.1247 28 0.014 0.1102 10 3.4% $-2.28[-3.18, -1.38]$ Aducanumab - NCT012477800-High Dose -0.264 0.129 170 0.014 0.126 11 59 4.0% $-1.59[-2.15, -1.67]$ Aducanumab - NCT01247800-High Dose -0.264 0.129 170 0.014 0.126 11 59 4.0% $-2.28[-2.18, -1.38]$ Aducanumab - NCT0247800-High Dose -0.264 0.129 170 0.014 0.126 11 59 4.0% $-2.28[-2.18, -1.38]$ Subtotal (65% CI) + 0.165 121 0.0000); P = 77% Test for overall effect: Z = 14.42 (P < 0.00001); T = 77% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95\% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95\% Test for overall effect: Z = 14.42 (P < 0.00001	BAN2401 - NCT01767311-10mg/kgB	-0.306	0.126	44	0.004	0.1244	20	3.6%	-2.44 [-3.13, -1.75]	
Heterogeneity: Tau ² = 0.29: Chi ² = 15.56, df = 4 (P = 0.004); P = 74% Test for overall effect: Z = 5.65 (P < 0.00001) 2.27 CRENEZUMAB-IV Crenezumab - NCT01397778 - 0.02 0.1375 21 -0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] Subtotal (95% CI) 21 10 3.6% 0.36 [-0.40, 1.12] 2.3 CRENEZUMAB-SC Crenezumab - NCT01397778 - 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtotal (95% CI) - 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: Z = 0.15 (P = 0.88) 2.2 A COLONUMAB-IV Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-03mg/kg -0.153 0.1185 29 0.014 0.1102 10 3.4% -2.28 [-2.01, -5.01] Aducanumab - NCT01677572-03mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-03mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-03mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT0247780-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.43] Aducanumab - NCT0247780-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.43] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 2.10 DONANEMAB-IV Donanemab - NCT023876703 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Tau ² = 1.0; Chi ² = 291.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001) 121 112 3.9% -2.56 [-2.91, -2.21] 4 4 5 5 5 5 5 5 5 5	BAN2401 - NCT01767311-10mg/kgM Subtotal (95% CI)	-0.225	0.1179	89 216	0.004	0.1244	19 99	3.8% 18.5%	-1.91 [-2.47, -1.35] -1.59 [-2.15, -1.04]	
Test for overall effect: $Z = 5.65 (P < 0.00001)$ 2.2.7 CRENEZUMAB-V Crenezuma - NCT01397678 -0.02 0.1375 21 -0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] Subtotal (95% CI) 21 10 3.6% 0.36 [-0.40, 1.12] Test for overall effect: $Z = 0.94 (P = 0.35)$ 2.2.8 CRENEZUMAB-SC Crenezuma - NCT01397578 -0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtotal (95% CI) 24 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: $Z = 0.15 (P = 0.88)$ 2.2.9 ADUCANUMAB-V Aducanuma - NCT01677572-06mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanuma - NCT01677572-06mg/kg -0.210 1176 40 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanuma - NCT01677572-06mg/kg -0.210 1176 40 0.014 0.1102 10 3.4% -1.28 [-2.71, -1.01] Aducanuma - NCT01677572-06mg/kg -0.235 0.1224 18 0.003 0.1185 204 4.0% -1.91 [= 21, 5.1.67] Aducanuma - NCT01247780-0.019 460 405 22.0% -1.73 [= 2.18, -1.38] Heterogeneity: Tau" = 0.19. Ch" = 21.79. df = 5 (P = 0.0006); P = 77% Test for overall effect: $Z = 7.94 (P < 0.00001)$ 2.210 DONANEMB-W Donanema - NCT03867403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 10 174 112 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 197 197 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau" = 1.10; Ch" = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: $Z = 1.4.42 (P < 0.00001)$ Test for overall effect: $Z = 14.42 (P < 0.00001)$; P = 95% Test for overall effect: $Z = 14.42 (P < 0.00001)$; P = 95% Test for overall effect: $Z = 14.42 (P < 0.00001)$; P = 95% Test for overall effect: $Z = 14.42 (P < 0.00001)$; P = 95% Test for overall effect: $Z = 14.42 (P < 0.00001)$; P = 95%	Heterogeneity: $Tau^2 = 0.29$; Chi ² = 15.56, d	f = 4 (P =	0.004); I	² = 74%						•
2.2.7 CRENEZUMAB-V Crenezumab - NCT01397578 -0.02 0.137 21 -0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] Heterogeneity: Not applicable Test for overall effect: Z = 0.94 (P = 0.35) 2.2.8 CRENEZUMAB-SC Crenezumab - NCT01397578 -0.029 0.1662 24 -0.018 0.1666 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: Z = 0.15 (P = 0.88) 2.2.9 ADUCANUMAB-V Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-01mg/kg -0.055 0.1242 28 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-01mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-01mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-10mg/kg -0.263 0.1247 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-10mg/kg -0.263 0.1247 128 0.014 0.1102 10 3.4% -2.28 [-2.49, -1.94] Aducanumab - NCT01677572-10mg/kg -0.263 0.1247 128 0.014 0.1102 10 3.4% -2.28 [-2.49, -1.94] Aducanumab - NCT01677572-10mg/kg -0.263 0.1247 128 0.014 0.1102 10 3.4% -2.28 [-2.49, -1.94] Aducanumab - NCT01677572-10mg/kg -0.264 0.129 170 0.014 0.1281 159 4.0% -2.22 [-2.49, -1.94] Aducanumab - NCT0248457-High Dose -0.264 0.129 170 0.014 0.1281 159 4.0% -2.256 [-2.91, -2.21] Heterogeneity: Tau ² = 0.19; Ch ³ = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 1.4.22 (P < 0.00001) 2.210 DONANEMAB-IV Donanemab - NCT0367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Tau ² = 1.0.19 (Ch ³ = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 1.4.42 (P < 0.00001) Total (95% CI) 174 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.19 (Ch ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95%	l est for overall effect: Z = 5.65 (P < 0.0000	1)								
Crenezuma - NC101397578 - 0.02 0.1375 21 -0.071 0.136 10 3.6% 0.36 [-0.40, 1.12] Heterogeneity: Not applicable Test for overall effect: Z = 0.94 (P = 0.36) 2.2 GRENEZUMAB-SC Crenezuma - NC101397578 - 0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtati (95% CI) - 0.055 0.1224 26 0.014 0.1102 11 3.6% -0.057 [-1.29, 0.15] Aducanuma - NC101677572-03mg/kg -0.035 0.1224 26 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanuma - NC101677572-03mg/kg -0.135 0.1185 29 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanuma - NC101677572-03mg/kg -0.235 0.1185 29 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanuma - NC101677572-03mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanuma - NC101677572-03mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.22 [-2.49, -1.40] Aducanuma - NC101677572-03mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.22 [-2.49, -1.40] Aducanuma - NC101677572-03mg/kg -0.263 0.127 28 0.014 0.1102 10 3.4% -2.22 [-2.49, -1.40] Aducanuma - NC101677572-03mg/kg -0.264 0.1239 170 0.014 0.1102 10 3.4% -2.22 [-2.49, -1.40] Subtati (95% CI) - 0.264 0.1239 170 0.014 0.1216 159 4.0% -2.22 [-2.49, -1.40] 112 3.9% -2.56 [-2.91, -2.21] 113 3.9% -2.56 [-2.91, -2.21] 114 112 3.9% -2.56 [-2.91, -2.21] 115 112 3.9% -2.56 [-2.91, -2.21] 116 112 3.9% -2.56 [-2.91, -2.21] 117 112 3.9% -2.56 [-2.91, -2.21] 118 112 3.9% -2.56 [-2.91, -2.21] 119 112 3.9% -2.56 [-2.91, -2.21] 110 112 112 112 112 3.9% -2.56 [-2.91, -2.21] 111 112 3.9% -2.56 [-2.91, -2.21] 112 112 3.9% -2.56 [-2.91, -2.21] 113 3.9% -2.56 [-2.91, -2.21] 114 112 3.9% -2.56 [-2.91, -2.21] 115 112 3.9% -2.56 [-2.91, -2.21] 116 112 112 112 112 112 112 112 112 112 11	2.2.7 CRENEZUMAB-IV	0.00	0 4075		0.074	0.400	40	0.00/	0.001.0.10.1.101	
Heterogeneity: Not applicable Test for overall effect: Z = 0.94 (P = 0.35) 2.2.8 CRENEZUMAB-SC Crenezumab - NCT01397578 -0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtotal (95% CI) 24 10 0.55 0.1224 26 0.014 0.1102 11 3.6% -0.057 [-1.29, 0.15] Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-05mg/kg -0.025 0.124 26 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-05mg/kg -0.235 0.1245 128 0.014 0.1102 10 3.4% -1.28 [-2.7, -1.01] Aducanumab - NCT01677572-05mg/kg -0.283 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.81, -1.38] Aducanumab - NCT01677572-05mg/kg -0.283 0.1217 128 0.014 0.1102 10 3.4% -2.28 [-3.81, -1.38] Aducanumab - NCT01247840-High Dose -0.284 0.1239 170 0.014 0.1210 159 4.0% -2.28 [-3.18, -1.38] Aducanumab - NCT01247840-High Dose -0.284 0.1239 170 0.014 0.1216 159 4.0% -2.28 [-3.18, -1.38] Aducanumab - NCT0247840-High Dose -0.284 0.1239 170 0.014 0.1216 159 4.0% -2.266 [-2.91, -2.21] Subtotal (95% CI) -0.264 0.129 177 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 2.2.10 DONANEMAB-IV Donanemab -NCT0357403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 0.0000 1; P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 0.0000 1; P = 0.0000 1; P = 0.00000 1; P = 0.0000 1; P =	Crenezumab - NC101397578 Subtotal (95% CI)	-0.02	0.1375	21	-0.071	0.136	10	3.6%	0.36 [-0.40, 1.12]	
Test for overall effect: $Z = 0.94$ (P = 0.35) 2.2.8 CRENEZUMAB-SC Crenezumab - NCT01397578 -0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Subtotal (95% CI) 24 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: $Z = 0.15$ (P = 0.88) 2.2.9 ADUCANUMAB-IV Aducanumab - NCT01677572-03mg/kg -0.155 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-03mg/kg -0.158 29 0.014 0.1102 11 3.6% -1.25 [-2.01, 0.50] Aducanumab - NCT01677572-03mg/kg -0.263 0.1247 28 0.014 0.1102 10 3.4% -1.89 [-2.77, -1.01] Aducanumab - NCT01677572-03mg/kg -0.263 0.1245 183 -0.003 0.1185 204 4.0% -2.28 [-3.18, -1.38] Aducanumab - NCT02477800-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.54] Aducanumab - NCT02477800-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.54] Aducanumab - NCT0247800-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.25 [-2.91, -2.21] Aducanumab - NCT02484547-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.56 [-2.91, -2.21] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.0001) 2.2.10 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.0001) Total (95% CI) 1974 1604 100.% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.0; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.0001) Total (95% CI) 10 1974 1604 100.% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.0; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.0001) Total (95% CI) 10 00 00 00 00 00 00 00 00 00 00 00 00	Heterogeneity: Not applicable							0.070	0.00 [0.10, 1112]	
2.2.8 CRENEZUMAB-SC Crenezumab NCT01397578 -0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: Z = 0.15 (P = 0.88) 24 10 3.6% -0.06 [-0.80, 0.68] 2.2.9 ADUCANUMAB-V Aducanumab - NCT01677572-01mg/kg -0.055 0.124 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-00mg/kg -0.215 0.1185 29 0.014 0.1102 10 3.4% -1.89 [-2.77, -1.01] Aducanumab - NCT01677572-00mg/kg -0.235 0.1245 183 -0.003 0.1185 204 4.0% -2.28 [-3.18, -1.38] Aducanumab - NCT02477800-High Dose -0.245 0.1245 183 -0.003 0.1185 204 4.0% -2.22 [-2.49, -1.94] Aducanumab - NCT02484547-High Dose -0.246 0.1239 170 0.014 0.1185 112 3.9% -2.56 [-2.91, -2.21] Aducanumab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21]	Test for overall effect: Z = 0.94 (P = 0.35)									
Crenezumab - NCT01397578 -0.029 0.1862 24 -0.018 0.1866 10 3.6% -0.06 [-0.80, 0.68] Heterogeneity: Not applicable Test for overall effect: $Z = 0.15 (P = 0.88)$ 2.2.9 ADUCANUMAB-IV Aducanumab - NCT01677572-03mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-03mg/kg -0.21 0.1176 24 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-03mg/kg -0.21 0.1176 24 0.014 0.1102 10 3.4% -1.28 [-2.77, -1.01] Aducanumab - NCT01677572-03mg/kg -0.235 0.1245 183 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumab - NCT0244547-High Dose -0.235 0.1245 183 -0.003 0.1185 204 4.0% -2.22 [-2.49, -1.94] Subtotal (95% Cl) - 0.0006); P = 77% Test for overall effect: $Z = 7.94 (P < 0.00001)$; P = 77% Test for overall effect: $Z = 7.94 (P < 0.00001)$ Total (95% Cl) - 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Tau ² = 1.0; ChP = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: $Z = 4.19 (P < 0.00001)$ Total (95% Cl) - 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; ChP = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: $Z = 4.19 (P < 0.00001)$	2.2.8 CRENEZUMAB-SC									
Heterogeneity: Not applicable Test for overall effect: $Z = 0.15 (P = 0.88)$ 2.2.9 ADUCANUMAB-IV Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-03mg/kg -0.21 0.1176 24 0.014 0.1102 10 3.4% -1.28 [-2.77, -1.01] Aducanumab - NCT01677572-10mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-10mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT0247450-High Dose -0.235 0.1224 51 83 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumab - NCT02484547-High Dose -0.235 0.1224 51 83 -0.003 0.1185 204 4.0% -2.22 [-2.49, -1.94] Subtotal (95% CI) Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 2.2.10 DONANEMAB-IV Donanemab - NCT0367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Tau ² = 1.0; Chi ² = 51.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 14.42 (P < 0.00001) Total (95% CI) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Total (95% CI) 10 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Total (95% CI) 10 01 00 01 00 00 01 00 00 01 00 00 00	Crenezumab - NC101397578 Subtotal (95% CI)	-0.029	0.1862	24 24	-0.018	0.1866	10 10	3.6% 3.6%	-0.06 [-0.80, 0.68] -0.06 [-0.80, 0.68]	
Test for overall effect: $Z = 0.15 (P = 0.88)$ 22.9 ADUCANUMAB-IV Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-05mg/kg -0.215 0.1176 24 0.014 0.1102 10 3.4% -1.29 [-2.7, -1.01] Aducanumab - NCT01677572-05mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT001677572-05mg/kg -0.264 0.123 170 0.0114 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT02477800-High Dose -0.235 0.1245 183 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumab - NCT02477800-High Dose -0.264 0.123 170 0.0114 0.1261 159 4.0% -2.22 [-2.49, -1.94] Subtotal (95% CI)	Heterogeneity: Not applicable							01070	0.000 [0.000, 0.000]	Ť
2.2.9 ADUCANUMAB-IV Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-05mg/kg -0.215 0.1185 29 0.014 0.1102 10 3.4% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-05mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-05mg/kg -0.263 0.1245 183 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumab - NCT02477800-High Dose -0.264 0.123 170 0.014 0.116 159 4.0% -1.91 [-2.15, -1.67] Subtotal (95% CI) 406 405 22.0% -1.73 [-2.16, -1.30] - - Peterogeneity: Tau ² = 0.19, Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% 78 -	Test for overall effect: Z = 0.15 (P = 0.88)									
Aducanumab - NCT01677572-01mg/kg -0.055 0.1224 26 0.014 0.1102 11 3.6% -0.57 [-1.29, 0.15] Aducanumab - NCT01677572-05mg/kg -0.135 0.1185 29 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-05mg/kg -0.216 0.1176 24 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT01677572-05mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT02477800-High Dose -0.235 0.1245 133 -0.003 0.1185 204 4.0% -1.91 [-2.75, -1.67] Aducanumab - NCT024784547-High Dose -0.264 0.123 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.94] Subtotal (95% Cl) -0.014 0.1261 159 -4.0% -1.73 [-2.16, -1.30] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) Z.210 DONANEMAB-IV Donanemab - NCT03457403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% Cl) -121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Nat applicable Test for overall effect: Z = 1.4.22 (P < 0.00001); P = 95% Total (95% Cl) -0.00001); P = 95% Total (95% Cl) -0.00001); P = 95% Total (95% Cl) -0.00001; P = 5(P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 0000 + 0.0000; P = 7000000; P = 70000000; P = 70000000000000000000000000000000000	2.2.9 ADUCANUMAB-IV									
Aducanumab - NCT01677572-03mg/kg -0.135 0.1185 29 0.014 0.1102 11 3.6% -1.25 [-2.01, -0.50] Aducanumab - NCT01677572-03mg/kg -0.221 0.1176 24 0.014 0.1102 10 3.4% -1.89 [-2.77, -1.01] Aducanumab - NCT01677572-10mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumab - NCT02477800-High Dose -0.235 0.1245 183 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumab - NCT02484547-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.9, -1.94] Subtotal (95% Cl) 400 -22.25 (-2.94, -1.94] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 22.10 DONANEMAB-IV Donanemab - NCT0367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% Cl) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Nat applicable Test for overall effect: Z = 1.42 (P < 0.00001); P = 95% Total (95% Cl) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001)	Aducanumab - NCT01677572-01mg/kg	-0.055	0.1224	26	0.014	0.1102	11	3.6%	-0.57 [-1.29, 0.15]	
Aducanumbo - NC 10107 / 572-00mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -1.89 [-2./7, -1.01] Aducanumbo - NCT0107 / 572-00mg/kg -0.263 0.1217 28 0.014 0.1102 10 3.4% -2.28 [-3.18, -1.38] Aducanumbo - NCT02477800-High Dose -0.235 0.1245 183 -0.003 0.1185 204 4.0% -1.91 [-2.15, -1.67] Aducanumbo - NCT0248457-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.94] Subtotal (95% Cl) - 460 - 200006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 22.10 DONANEMAB-IV Donanemabo - NCT0367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Nat applicable Test for overall effect: Z = 14.42 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 000001; P = 000001; P = 0000001; P = 000001; P = 0000001; P = 000001; P = 0000001; P = 0000001; P = 000001; P = 0000001; P = 0000001; P = 000001; P = 000001; P = 000001; P = 0000001; P = 0000001; P = 0000001; P = 000001; P = 0000001; P = 000001; P = 0000001; P = 000001; P = 0000001; P = 000001; P = 000001; P = 000001; P = 000001; P = 0000001; P = 0000001; P = 0000001; P = 0000001; P = 000001; P = 0000001; P = 0000001; P = 0000001; P = 000001; P = 000001; P = 0000001; P = 000000	Aducanumab - NCT01677572-03mg/kg	-0.135	0.1185	29	0.014	0.1102	11	3.6%	-1.25 [-2.01, -0.50]	
Advacanumab NCT0247800-High Dose -0.235 0.121 to 50 0.001 0.112 10 0.014 0.1261 159 4.0% -1.91 [2:5, 1.67] Advacanumab - NCT02484547-High Dose -0.236 0.1239 170 0.014 0.1261 159 4.0% -2.22 [2:49, -1.94] Advacanumab - NCT02484547-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [2:49, -1.94] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 2.2.10 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.00001) Total (95% CI) 1074 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Total (95% CI) - 0.001 (D = 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Total (95% CI) - 0.001 (D = 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.00001); P = 0.00001; P = 0.000001; P = 0.00001; P = 0.000001; P	Aducanumab - NCT01677572-06mg/kg Aducanumab - NCT01677572-10mg/kg	-0.21	0.11/6	24 28	0.014	0.1102	10	3.4% 3.4%	-1.89 [-2.77, -1.01] -2.28 [-3.18 -1.38]	
Aducanumab - NCT02484547-High Dose -0.264 0.1239 170 0.014 0.1261 159 4.0% -2.22 [-2.49, -1.94] Subtotal (95% CI) 460 405 22.0% -1.73 [-2.16, -1.30] Heterogeneity: Tau ² = 0.19; Ch ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 ($P < 0.00001$) 2.210 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 1.42 ($P < 0.00001$) Total (95% CI) 974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 ($P < 0.00001$); I ² = 95% Test for overall effect: Z = 4.19 ($P < 0.00001$)	Aducanumab - NCT02477800-High Dose	-0.235	0.1245	183	-0.003	0.1185	204	4.0%	-1.91 [-2.15, -1.67]	-
Subtoral (95% CI) 460 405 22.0% -1.73 [-2.16, -1.30] Heterogeneity: Tau ² = 0.19; Chi ² = 21.79, df = 5 (P = 0.0006); P = 77% Test for overall effect: Z = 7.94 (P < 0.00001) 2.2.10 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 41.42 (P < 0.00001) Total (95% CI) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.0001) Total (95% CI) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); P = 95% Test for overall effect: Z = 4.19 (P < 0.0001)	Aducanumab - NCT02484547-High Dose	-0.264	0.1239	170	0.014	0.1261	159	4.0%	-2.22 [-2.49, -1.94]	
Test for overall effect: Z = 7.94 (P < 0.00001) 2.2.10 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% Cl) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 41.42 (P < 0.00001) Total (95% Cl) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); I ² = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001)	Subtotal (95% CI)	f = 5 (D	0.0000	460	0/		405	22.0%	-1.73 [-2.16, -1.30]	-
22.210 DONANEMAB-IV Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.00001)	Test for overall effect: Z = 7.94 (P < 0.0000	1) = 5 (P =	0.0006);	r [_] ≓ //	70					
Donanemab - NCT03367403 -0.367 0.165 121 0.004 0.1185 112 3.9% -2.56 [-2.91, -2.21] Subtotal (95% CI) 121 112 3.9% -2.56 [-2.91, -2.21] Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.00001) Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); i ² = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001)	2.2.10 DONANEMAB-IV									
Subtational (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 14.42 (P < 0.00001) Total (95% CI) Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); l ² = 95% Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.19 (P < 0.00001) Test for overall effect: Z = 4.1	Donanemab - NCT03367403	-0.367	0.165	121	0.004	0.1185	112	3.9%	-2.56 [-2.91, -2.21]	$\overline{}$
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Subtotal (95% CI)			121			112	3.9%	-2.56 [-2.91, -2.21]	▼
Total (95% CI) 1974 1604 100.0% -0.88 [-1.30, -0.47] Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); l ² = 95% -4 -2 0 2 4 Test for overall effect: Z = 4.19 (P < 0.0001)	Test for overall effect: Z = 14.42 (P < 0.000	01)								
Heterogeneity: Tau ² = 1.10; Chi ² = 591.35, df = 27 (P < 0.00001); l ² = 95% Test for overall effect: Z = 4.19 (P < 0.0001) Favours [mAb]-Decrease Favours [PL]-Increase	Total (95% CI)			1974			1604	100.0%	-0.88 [-1.30, -0.47]	•
Test for overall effect: Z = 4.19 (P < 0.0001) Favours [mcb]-Decrease Favours [PL-Increase	Heterogeneity: Tau ² = 1.10; Chi ² = 591.35,	df = 27 (F	o < 0.000	01); l² =	95%					
	Test for overall effect: $Z = 4.19$ (P < 0.0001)		004: 17		,				Favours [mAb]-Decrease Favours [PL]-Increase

Fig. 4. Forest plot of the meta-analysis of available data on change from baseline in PET-SUVR.

		mAb			PL			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.1.1 BAPINEUZUMAB-IV									
Bapineuzumab - NCT00574132-0.5mg/kg	2.6	3.54	314	2.6	4.44	246	2.4%	0.00 [-0.68, 0.68]	
Bapineuzumab – NCT00574132–1mg/kg	2.8	3.5	307	2.6	4.44	247	2.5%	0.20 [-0.48, 0.88]	
Bapineuzumab – NC100575055–0.5mg/kg	3.3	2.57	658	3	4.16	432	5.8%	0.30 [-0.14, 0.74]	T
Bapineuzumab – NCT00667810-0.5mg/kg	2.23	3.67	255	2.59	3.62	164	2.2%	-0.36 [-1.07, 0.35]	T
Bapineuzumab NCT00676142 0 5mg/kg	2.41	2 2 1	200	2.59	2 2 2 2	104	6.9%	-0.16 [-0.69, 0.55]	
Subtotal (95% CI)	2.44	5.51	2437	2.39	5.52	1684	21.8%	0.00 [-0.23, 0.23]	1
Heterogeneity: $T_{2}u^2 = 0.00$: $Chi^2 = 3.88$ df	- 5 (P -	0 5 7) 1	- 0%			100.		0.000[0.115, 0.115]	Ť
Test for overall effect: $Z = 0.01$ (P = 0.99)		. 0.57), 1	- 0/0						
2.1.2 SOLANEZUMAB-IV									
Solanezumab - NCT00904683	2.3	3.93	521	2.7	3.96	519	4.8%	-0.40 [-0.88, 0.08]	
Solanezumab – NCT00905372	2	5.7247	506	1.8	5.7247	506	2.3%	0.20 [-0.51, 0.91]	- - -
Solanezumab – NCT01900665	1.87	3.25	1057	2.21	3.6	1072	12.5%	-0.34 [-0.63, -0.05]	-
Subtotal (95% CI)			2084			2097	19.7%	-0.29 [-0.54, -0.04]	•
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.17$, df	= 2 (P =	= 0.34); l'	= 8%						
Test for overall effect: $Z = 2.24$ (P = 0.03)									
2.1.3 CANTENERUMAR-SC									
Cantonorumah - NCT01224106-105mg	1.60	2.68	271	1.6	2.61	122	2.8%	0.00[-0.46_0.64]	
Cantenerumab – NCT01224106-225mg	1.09	2.00	260	1.0	2.01	133	3.8%	0.13 [-0.41, 0.67]	
Subtotal (95% CI)	1.75	2.54	531	1.0	2.01	266	7.6%	0.11 [-0.27, 0.49]	•
Heterogeneity: $Tau^2 = 0.00$: $Chi^2 = 0.01$. df	= 1 (P =	• 0.92): l ²	= 0%					- / -	ľ
Test for overall effect: $Z = 0.56$ (P = 0.57)	- •								
2.1.4 AAB-003-IV									
AAB-003 - NCT01193608-0.5mg/kg	1	3.286	6	-0.35	1.935	4	0.1%	1.35 [-1.89, 4.59]	
AAB-003 - NCT01193608-1mg/kg	1.75	1.708	6	-0.35	1.935	4	0.2%	2.10 [-0.24, 4.44]	
AAB-003 - NCT01193608-2mg/kg	1	2.449	16	-0.35	1.935	4	0.2%	1.35 [-0.89, 3.59]	
AAB-003 - NCT01193608-4mg/kg	1.86	3.371	17	-0.35	1.935	4	0.2%	2.21 [-0.27, 4.69]	
AAB-003 - NCT01193608-8mg/kg Subtotal (95% CI)	0.79	2.84	24	-0.35	1.935	19	0.2%	1.14 [-1.33, 3.61]	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.60$, df	- 4 (P -	- 0 96)· 14	- 0%			15	0.570	1.05 [0.54, 2.77]	
Test for overall effect: $Z = 2.90$ (P = 0.004)	() -	. 0.50), 1	- 070						
2.1.5 LECANEMAB-IV									
BAN2401 - NCT01767311-02.5mg/kgB	1.23	2.44	52	1.5	2.47	48	1.2%	-0.27 [-1.23, 0.69]	
BAN2401 - NCT01767311-05mg/kgB	1.46	2.36	89	1.5	2.47	48	1.6%	-0.04 [-0.89, 0.81]	
BAN2401 – NCT01767311–05mg/kgM	1.71	2.31	48	1.5	2.47	48	1.2%	0.21 [-0.75, 1.17]	_ _
BAN2401 - NCT01767311-10mg/kgB	1.1	2.63	152	1.5	2.47	48	1.7%	-0.40 [-1.21, 0.41]	
BAN2401 – NCT01767311–10mg/kgM	1.25	2.65	246	1.5	2.47	228	1.8%	-0.25 [-1.04, 0.54]	
Hotorogonoity: $T_{2}u^2 = 0.00$: $Chi^2 = 1.08$ df	- 4 (P -	. 0 00) 18	- 0%			230	7.0%	-0.17 [-0.30, 0.22]	•
Test for overall effect: $Z = 0.85$ (P = 0.39)	- + (1 -	• 0.50), 1	- 070						
2.1.6 CRENEZUMAB-IV									
Crenezumab – NCT01343966–15mgkg	2.49	3.21	165	2.57	3.21	84	1.6%	-0.08 [-0.92, 0.76]	
Crenezumab - NCT02670083-60mg/kg	3.59	2.45	86	3.42	2.47	88	2.1%	0.17 [-0.56, 0.90]	+
Crenezumab – NCT03114657–60mg/kg	1.89	1.63	12	3.19	1.68	15	0.7%	-1.30 [-2.55, -0.05]	
Subtotal (95% Cl)	2 (0	0.14)-14	203			187	4.4%	-0.26 [-1.01, 0.48]	-
Heterogeneity: $Tau^{-} = 0.22$; $Chi^{-} = 3.99$, dr Test for overall effect: $Z = 0.68$ (P = 0.49)	= 2 (P =	• 0.14); I	= 50%						
1000000000000000000000000000000000000									
2.1.7 CRENEZUMAB-SC									
Crenezumab – NCT01343966–300mg	2.01	2.87	122	2.7	2.83	62	1.5%	-0.69 [-1.56, 0.18]	
Subtotal (95% CI)			122			62	1.5%	-0.69 [-1.56, 0.18]	◆
Heterogeneity: Not applicable									
Test for overall effect: $Z = 1.56 (P = 0.12)$									
Aducanumah - NCT01677572 01ma/li-	1 70	2 50		1 07	2 50	10	0.20/	_0 15 [1 00 1 60]	
Aducanumab – NCT01677572–01mg/kg	1.72	2.50	33	1.07	2.59	10	0.5%	-0.15 [-1.99, 1.69]	
Aducanumab = $NCT01077572-05mg/kg$	1 11	2.45	30	1.07	2.39	10	0.3%	-0.30 [-2.51, 1.51]	
Aducanumab – NCT01677572–10mg/kg	0.63	2.41	32	1.87	2.55	10	0.3%	-1 24 [-3 09 0 61]	
Aducanumab – NCT02477800-High Dose	1.59	2.61	555	1.56	2.52	273	8.0%	0.03 [-0.34, 0.40]	+
Aducanumab - NCT02477800-Low Dose	1.38	2.52	547	1.56	2.52	272	8.1%	-0.18 [-0.55, 0.19]	-+
Aducanumab - NCT02484547-High Dose	1.35	2.69	547	1.74	2.69	274	7.2%	-0.39 [-0.78, 0.00]	
Aducanumab - NCT02484547-Low Dose	1.47	2.7	543	1.74	2.69	273	7.2%	-0.27 [-0.66, 0.12]	-
Subtotal (95% CI)			2317			1132	31.9%	-0.21 [-0.40, -0.03]	•
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.19$, df	= 7 (P =	= 0.76); l ²	= 0%						
Lest for overall effect: $Z = 2.27$ (P = 0.02)									
2.1.9 DONANEMAB-IV									
Donanemab - NCT03367403	1.22	2.01	131	1.58	1.99	125	4.6%	-0.36 [-0.85, 0.13]	
Subtotal (95% CI)		2.01	131		2.55	125	4.6%	-0.36 [-0.85, 0.13]	◆
Heterogeneity: Not applicable									
Test for overall effect: $Z = 1.44$ (P = 0.15)									
T							100		
I OTAI (95% CI)	(8541			5810	100.0%	-0.15 [-0.26, -0.04]	
Heterogeneity: $Iau^* = 0.00$; $Chi^* = 33.54$, d	T = 33 (I	P = 0.44)	; 1* = 2	%					-4 -2 0 2 4
Test for subgroup differences $Ch^2 = 17.20$	df. e	(P _ 0.07	2) 12	E 4 0%					Favours [mAb] Favours [PL]
rescrot subgroup afferences: Cnr = 17.39	, ui = 8	r = 0.02	o, i` =	54.0%					

Fig. 5. Forest plot of the meta-analysis of available data on change from baseline in the CDR-SB score.

aducanumab, and donanemab, that are still investigated for the treatment of people with MCI due to AD or AD, seem to be the ones with the most significant results in terms of PET-SUVR levels. However, results from the CDR-SB scale do not show a similar profile, with all mAbs having substantially similar ranges of results.

DISCUSSION

Since 2005, 101 trials have been registered investigating mAbs in patients with MCI or AD. Of these, information is available from 50 trials enrolling nearly 18,000 participants. To our knowledge, this is the first SR reporting the number of trials with published results (n = 39) and unpublished results (n = 66)and documenting the number of trials with results only available from registration databases (n=11)and those with no data available (n = 51). The rate of unpublished and unavailable results is clearly in contrast with the principles of open science and open data movement. Missing information both hinders the process of critical evaluation of acquired evidence and affects the possibility of raising hypotheses on new possible etiopathogenetic mechanisms in AD that could be investigated and tested as possible therapeutic targets [51]. Moreover, the lack of negative studies published in journal articles prevents the opportunity for a realistic discussion among the scientific community. Therefore, the US National Academy of Medicine recommended the creation of a culture of responsible sharing of data from clinical trials [52].

Our results on safety data showed an overall higher risk of both ARIA-E and ARIA-H in patients treated with mAbs compared to placebo. When analyzing data in a chronological order to account for a possible evolution of the safety profile over time, the analysis showed no variations over time. However, newer mAbs, such as donanemab, seemed to have a common profile showing an increase in the neurobiological efficacy despite an increase in the frequency of ARIA events. However, ARIA should be considered as treatment-related AEs, and, since they are extremely challenging to account for both in RCTs and in clinical practice, specific protocols should be defined, including criteria for identifying the type of subjects eligible for MRI, the timing of MRI controls, and the criteria for interrupting treatment. The accurate and timely identification of ARIA is, in fact, essential, as no data are available on their potential long-term consequences. A longitudinal study on families with dominantly inherited AD reported that the presence of either prevalent or incident cases of cerebral microhemorrhages predicted a faster decline of the CDR score [53]. This shows that, though a very small proportion of ARIA events were symptomatic, and most of them resolved within the duration of the study, the potential effect of ARIA on the natural history of the disease remains unclear. Conducting further and more targeted statistical analyses to explore whether specific variables can be useful to predict the risk of both overall and symptomatic ARIA, could also help in reducing the safety concerns related to these drugs.

To analyze the efficacy of mAbs, we considered PET-SUVR data, which are currently considered as one of the reference standard measures for assessing in vivo the cerebral amyloid burden, and the CDR-SB scale, which is currently the most widely used cognitive and functional measure in clinical practice. We chose amyloid-PET as it has been proven to have a high accuracy in detecting amyloid burden [54], with good inter-rater agreement [55], and no significant differences between tracers [56] and compared to CSF. A study investigating the diagnostic accuracy of CSF AB1-42 and amyloid-PET reported an overall 77% concordance and 23% discordance between the two measures [57], and another study investigating the accuracy of the CSF A $\beta_{1-42}/A\beta_{1-40}$ ratio and amyloid-PET reported a 65% and 88% concordance for MCI (n=48) and for AD (n=7)[58] respectively. Results from the meta-analyses of PET-SUVR data showed an overall significant effect of mAbs in reducing the amyloid burden, with the most recent mAbs having the highest effect. However, when considering results on clinical efficacy, data showed an overall statistically significant but clinically non-relevant lower worsening of the CDR-SB scores in patients treated with mAbs compared to placebo. All included studies reported results only in terms of means and standard deviations, with none of them reporting data as response rates nor providing a definition of responders accounting for the minimum clinically important difference that, when considering the CDR-SB, is 1-2 points [50, 59]. The observed lack of clinical efficacy is in line with results from a recent meta-analysis on anti-amyloid treatments in AD reporting that lowering or removing amyloid plaques led to no substantial improvement in cognition [12]. Some postmortem studies also showed that in subjects who were treated with active immunization the removal of amyloid plaques, even though

lasting for 14 years after treatment, failed to either stop or slow disease progression [60, 61]. Therefore, currently available evidence does not support a clear link between amyloid load and cognitive performance, suggesting that reducing the amyloid load might have low-to-no effect in improving cognitive performance or slowing cognitive decline [4].

On June 7, 2021, the FDA authorized the marketing of aducanumab (ADUHELM, Biogen), under accelerated approval procedure. Based on the summary of product characteristics, aducanumab "is indicated for the treatment of AD", and "treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials". The approval was based on results from a surrogate endpoint, the reduction of amyloid plaques, that was considered as "reasonably likely" to predict a clinical effect [62, 63]. Furthermore, Elli Lilly, based on results from a phase II study [32], recently announced their intention to apply to FDA for an "accelerated approval" of donanemab (https://www.drugdiscoverytrends.com/ lilly-pushing-for-accelerated-fda-approval-of-alzhe imers-drug-donanemab/). Considering the mentioned evidence questioning the relation between amyloid burden and cognitive outcomes, the approval of aducanumab has raised a large-scale debate throughout the scientific community [64, 65]. These events, in fact, seem to suggest some similarities with the approval procedures of some oncological drugs. A recent study reported that between 1992 and 2019 the FDA authorized 194 oncological drugs, all based on surrogate endpoints for a specific cancer type [67]. The study also reported that the use of surrogate endpoints increased from 2016 to 2019, underlining that, though surrogate endpoints can ease trial completion, they increase uncertainty in the actual benefit of marketed intervention. As highlighted in the study, the FDA steadily accepting surrogate endpoints that are not validated nor justified by regulatory precedents, along with its unlikeliness to demand strict confirmation of any clinical benefit after market approval might have relevant consequences. When considering AD and mAbs, though the approval procedure of aducanumab required Biogen to provide additional data on clinical efficacy in the next 9 years, such extended period further increases uncertainty, underlining that currently available data are not robust enough to show a direct impact, that could be relevant to patients over time, of removing amyloid plaques on

clinical outcomes. Moreover, the lack of data on the possible long-term effects of ARIA on brain and cognitive performances raises additional concerns on the risk-benefit profile for mAbs. On the same basis, in fact, the European Medicines Agency considered that the studies presented by Biogen "did not show that the medicine was sufficiently safe as images from brain scans of some patients showed abnormalities suggestive of swelling or bleeding, which could potentially cause harm" and that "it is not clear that the abnormalities can be properly monitored and managed in clinical practice" [67]. Furthermore, the European Medicines Agency "noted that although Aduhelm reduces amyloid beta in the brain, the link between this effect and clinical improvement had not been established", and therefore the European Medicines Agency's opinion was "that the benefits of Aduhelm did not outweigh its risks and it recommended refusing marketing authorisation" [67].

This SR aimed at systematically collecting all available information on trials on mAbs for MCI and AD, documenting the amount of published, unpublished, and unavailable data. A possible limitation to this SR is that we did not report data for all the outcome measures considered in the included trials. However, the PET-SUVR and CDR-SB scores are reported to be accurate tools to measure the amyloid load and the cognitive and functional performance of subjects with MCI or AD. Our purpose was also to attempt to provide an "historical" overview of research on this topic, thus focusing on the interpretation of data on mAbs over time rather than considering results only in a cumulative way regardless of whether mAbs were still under investigation or already discontinued. Though our SR has no regulatory purposes, our results strongly suggest that the risk-benefit profile on mAbs remains unclear.

Research on mAbs should be focused on clarifying whether removing the amyloid burden affects the progression of cognitive decline, providing data also on treatment response rate, accounting for MCID. This is extremely relevant considering that the target population is shifting towards the earlier stages of the disease in an assumption that removing plaques in a relatively still intact brain can lead to a higher clinical effect. Research on these drugs should also be focused on determining the possible longterm impact of ARIA events, investigating potential factors predicting their onset, as the treatment with mAbs is still linked, even in the most recently developed ones, to a significantly higher risk of ARIA.

DISCLOSURE STATEMENT

Authors' disclosures available online (https:// www.j-alz.com/manuscript-disclosures/22-0046r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/ 10.3233/JAD-220046.

REFERENCES

- [1] Cummings J, Lee, G, Zhong K, Fonseca J, Taghva K (2021) Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement (N Y)* **7**, e12179.
- [2] Tian Hui Kwan A, Arfaie S, Therriault J, Rosa-Neto P, Gauthier S (2020) lessons learnt from the second generation of anti-amyloid monoclonal antibodies clinical trials. *Dement Geriatr Cogn Disord* 49, 334-348
- [3] Food & Drug Administration. FDA news release. FDA Grants Accelerated Approval for Alzheimer's Drug. Available at: https://www.fda.gov/news-events/press-announ cements/fda-grants-accelerated-approval-alzheimers-drug. Last updated June 7, 2021, Accessed on February 9, 2022
- [4] Planche V, Villain N (2021) US Food and Drug Administration approval of Aducanumab-Is amyloid load a valid surrogate end point for Alzheimer disease clinical trials? *JAMA Neurol* 78, 1307-1308.
- [5] Hanseeuw BJ, Betensky RA, Jacobs HIL, Schultz AP, Sepulcre J, Becker JA, Cosio DMO, Farrell M, Quiroz YT, Mormino EC, Buckley RF, Papp KV, Amariglio RA, Dewachter I, Ivanoiu A, Huijbers W, Hedden T, Marshall GA, Chhatwal JP, Rentz DM, Sperling RA, Johnson K (2019) Association of amyloid and tau with cognition in preclinical Alzheimer disease: A longitudinal study. JAMA Neurol 76, 915-924.
- [6] Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ (2011) Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement* 7, 367-385.
- [7] Aisen PS, Cummings J, Doody R, Kramer L, Salloway S, Selkoe DJ, Sims J, Sperling RA, Vellas B (2020) The future of anti-amyloid trials. *J Prev Alzheimers Dis* 7, 146-151.
- [8] Penninkilampi R, Brothers HM, Eslick GD (2017) Safety and efficacy of anti-amyloid-β immunotherapy in Alzheimer's disease: A systematic review and metaanalysis. J Neuroimmune Pharmacol 12, 194-203.
- [9] Mo JJ, Li JY, Yang Z, Liu Z, Feng JS (2017) Efficacy and safety of anti-amyloid-β immunotherapy for Alzheimer's disease: A systematic review and network meta-analysis. *Ann Clin Transl Neurol* 4, 931-942.
- [10] Foroutan N, Hopkins R B, Tarride JE, Florez ID, Levine M (2019) Safety and efficacy of active and passive immunotherapy in mild-to-moderate Alzheimer's disease: A systematic review and network meta-analysis. *Clin Invest Med* 42, E53-E65.

- [11] Avgerinos KI, Ferrucci L, Kapogiannis D (2021) Effects of monoclonal antibodies against amyloid-β on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer's disease. Ageing Res Rev 68, 101339.
- [12] Ackley SF, Zimmerman SC, Brenowitz WD, Tchetgen Tchetgen EJ, Gold AL, Manly JJ, Mayeda ER, Filshtein TJ, Power MC, Elahi FM, Brickman AM, Glymour MM (2021) Effect of reductions in amyloid levels on cognitive change in randomized trials: Instrumental variable meta-analysis. *BMJ* **372**, n156.
- [13] Lahoz Fernandez PE, Diogo Silva G (2021) Cognitive outcomes of anti-amyloid-β monoclonal antibodies in patients with Alzheimer's disease: A systematic review and metaanalysis of randomized controlled trials. *Alzheimers Dement* **17** (Suppl 9), e057778.
- [14] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (2021) Cochrane Handbook for Systematic Reviews of Interventions, version 6.2 (updated February 2021). Cochrane. Available from www. training.cochrane.org/handbook.
- [15] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 372, n71.
- [16] Delnomdedieu M, Duvvuri S, Li DJ, Atassi N, Lu M, Brashear HR, Liu E, Ness S, Kupiec JW (2016) First-In-Human safety and long-term exposure data for AAB-003 (PF-05236812) and biomarkers after intravenous infusions of escalating doses in patients with mild to moderate Alzheimer's disease. *Alzheimers Res Ther* 8, 12.
- [17] Ferrero J, Williams L, Stella H, Leitermann K, Mikulskis A, O'Gorman J, Sevigny J (2016) First-in-human, doubleblind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease. *Alzheimers Dement (N Y)*, **2**, 169-176.
- [18] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A (2016) The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* 537, 50-56.
- [19] Arai H, Umemura K, Ichimiya Y, Iseki E, Eto K, Miyakawa K, Kirino E, Shibata N, Baba H, Tsuchiwata S (2016) Safety and pharmacokinetics of bapineuzumab in a single ascending-dose study in Japanese patients with mild to moderate Alzheimer's disease. *Geriatr Gerontol Int* 16, 644-650.
- [20] Black RS, Sperling RA, Safirstein B, Motter RN, Pallay A, Nichols A, Grundman M (2010) A single ascending dose study of bapineuzumab in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord* 24, 198-203.
- [21] Lu M, Brashear HR (2019) Pharmacokinetics, pharmacodynamics, and safety of subcutaneous bapineuzumab: A single-ascending-dose study in patients with mild to moderate Alzheimer disease. *Clin Pharmacol Drug Dev* 8, 326-335.
- [22] Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello

AA, Rodriguez Martinez de Liano S, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M (2010) 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: A phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol* **9**, 363-372.

- [23] Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M, Bapineuzumab 201 Clinical Trial Investigators (2009) A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* **73**, 2061-2070.
- [24] Brody M, Liu E, Di J, Lu M, Margolin RA, Werth JL, Booth K, Shadman A, Brashear HR, Novak G (2016) A phase II, randomized, double-blind, placebo-controlled study of safety, pharmacokinetics, and biomarker results of subcutaneous bapineuzumab in patients with mild to moderate Alzheimer's disease. J Alzheimers Dis 54, 1509-1519.
- [25] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, Reichert M, Ketter N, Nejadnik B, Guenzler V, Miloslavsky M, Wang D, Lu Y, Lull J, Tudor IC, Liu E, Grundman M, Yuen E, Black R, Brashear HR; Bapineuzumab 301 and 302 Clinical Trial Investigators (2014) Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* **370**, 322-333.
- [26] Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, Tuchman M, Gass A, Fiebach JB, Hill D, Lobello K, Li D, McRae T, Lucas P, Evans I, Booth K, Luscan G, Wyman BT, Hua L, Yang L, Brashear HR, Black RS; Bapineuzumab 3000 and 3001 Clinical Study Investigators (2016) Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimers Res Ther* 8, 18.
- [27] Ivanoiu A, Pariente J, Booth K, Lobello K, Luscan G, Hua L, Lucas P, Styren S, Yang L, Li D, Black RS, Brashear HR, McRae T (2016) Long-term safety and tolerability of bapineuzumab in patients with Alzheimer's disease in two phase 3 extension studies. *Alzheimers Res Ther* 8, 24.
- [28] Guthrie H, Honig LS, Lin H, Sink KM, Blondeau K, Quartino A, Dolton M, Carrasco-Triguero M, Lian Q, Bittner T, Clayton D, Smith J, Ostrowitzki S (2020) Safety, tolerability, and pharmacokinetics of Crenezumab in patients with mild-to-moderate Alzheimer's disease treated with escalating doses for up to 133 weeks. J Alzheimers Dis 76, 967-979.
- [29] Cummings JL, Cohen S, van Dyck CH, Brody M, Curtis C, Cho W, Ward M, Friesenhahn M, Rabe C, Brunstein F, Quartino A, Honigberg LA, Fuji RN, Clayton D, Mortensen D, Ho C, Paul R (2018) ABBY: A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease. *Neurology* **90**, e1889-e1897.
- [30] Salloway S, Honigberg LA, Cho W, Ward M, Friesenhahn M, Brunstein F, Quartino A, Clayton D, Mortensen D, Bittner T, Ho C, Rabe C, Schauer SP, Wildsmith KR, Fuji RN, Suliman S, Reiman EM, Chen K, Paul R (2018) Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). *Alzheimers Res Ther* **10**, 96.
- [31] Lowe SL, Willis BA, Hawdon A, Natanegara F, Chua L, Foster J, Shcherbinin S, Ardayfio P, Sims JR (2021) Donanemab

(LY3002813) dose-escalation study in Alzheimer's disease. *Alzheimers Dement (N Y)* **7**, e12112.

- [32] Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks J, Sims JR, Brys M, Apostolova LG, Salloway SP, Skovronsky DM (2021) Donanemab in early Alzheimer's disease. N Engl J Med 384, 1691-1704.
- [33] Logovinsky V, Satlin A, Lai R, Swanson C, Kaplow J, Osswald G, Basun H, Lannfelt L (2016) Safety and tolerability of BAN2401–a clinical study in Alzheimer's disease with a protofibril selective Aβ antibody. *Alzheimers Res Ther* 8, 14.
- [34] Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L, Berry DA, Berry S, Gordon R, Kramer LD, Cummings JL (2021) A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimers Res Ther* 13, 80.
- [35] Ostrowitzki S, Deptula D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli L (2012) Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. *Arch Neurol* 69, 198-207.
- [36] Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, Ashford E, Retout S, Hofmann C, Delmar P, Klein G, Andjelkovic M, Dubois B, Boada M, Blennow K, Santarelli L, Fontoura P; SCarlet RoAD Investigators (2017) A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther* 9, 95.
- [37] Andreasen N, Simeoni M, Ostlund H, Lisjo PI, Fladby T, Loercher AE, Byrne GJ, Murray F, Scott-Stevens PT, Wallin A, Zhang YY, Bronge LH, Zetterberg H, Nordberg AK, Yeo AJ, Khan SA, Hilpert J, Mistry PC (2015) First administration of the Fc-attenuated anti-β amyloid antibody GSK933776 to patients with mild Alzheimer's disease: A randomized, placebo-controlled study. *PloS One* 10, e0098153.
- [38] Leyhe T, Andreasen N, Simeoni M, Reich A, von Arnim CA, Tong X, Yeo A, Khan S, Loercher A, Chalker M, Hottenstein C, Zetterberg H, Hilpert J, Mistry P (2014) Modulation of β-amyloid by a single dose of GSK933776 in patients with mild Alzheimer's disease: A phase I study. *Alzheimers Res Ther* 6, 19.
- [39] Li L, Zhen EY, Decker RL, Willis BA, Waters D, Liu P, Hake AM, Demattos RB, Ayan-Oshodi M (2019) Pharmacokinetics and pharmacodynamics of LY2599666, a PEG-linked antigen binding fragment that targets soluble monomer amyloid-β. J Alzheimers Dis 68, 137-144.
- [40] Landen JW, Zhao Q, Cohen S, Borrie M, Woodward M, Billing CB Jr, Bales K, Alvey C, McCush F, Yang J, Kupiec JW, Bednar MM (2013) Safety and pharmacology of a single intravenous dose of ponezumab in subjects with mild-to-moderate Alzheimer disease: A phase I, randomized, placebo-controlled, double-blind, dose-escalation study. *Clin Neuropharmacol* 36, 14-23.
- [41] Miyoshi I, Fujimoto Y, Yamada M, Abe S, Zhao Q, Cronenberger C, Togo K, Ishibashi T, Bednar MM, Kupiec JW, Binneman B (2013) Safety and pharmacokinetics of PF-04360365 following a single-dose intravenous infusion in Japanese subjects with mild-to-moderate Alzheimer's disease: A multicenter, randomized, double-blind, placebocontrolled, dose-escalation study. *Int J Clin Pharmacol Ther* **51**, 911-923.

- [42] Landen JW, Cohen S, Billing CB Jr, Cronenberger C, Styren S, Burstein AH, Sattler C, Lee JH, Jack CR Jr, Kantarci K, Schwartz PF, Duggan WT, Zhao Q, Sprenger K, Bednar MM, Binneman B (2017) Multiple-dose ponezumab for mild-to-moderate Alzheimer's disease: Safety and efficacy. *Alzheimers Dement (N Y)*, **3**, 339-347.
- [43] Landen JW, Andreasen N, Cronenberger CL, Schwartz PF, Börjesson-Hanson A, Östlund H, Sattler CA, Binneman B, Bednar MM (2017) Ponezumab in mild-to-moderate Alzheimer's disease: Randomized phase II PET-PIB study. *Alzheimers Dement (N Y)* **3**, 393-401.
- [44] Siemers ER, Friedrich S, Dean RA, Gonzales CR, Farlow MR, Paul SM, Demattos RB (2010) Safety and changes in plasma and cerebrospinal fluid amyloid beta after a single administration of an amyloid beta monoclonal antibody in subjects with Alzheimer disease. *Clin Neuropharmacol* 33, 67-73.
- [45] Uenaka K, Nakano M, Willis BA, Friedrich S, Ferguson-Sells L, Dean RA, Ieiri I, Siemers ER (2012) Comparison of pharmacokinetics, pharmacodynamics, safety, and tolerability of the amyloid β monoclonal antibody solanezumab in Japanese and white patients with mild to moderate Alzheimer disease. *Clin Neuropharmacol* 35, 25-29.
- [46] Farlow M, Arnold SE, van Dyck CH, Aisen PS, Snider BJ, Porsteinsson AP, Friedrich S, Dean RA, Gonzales C, Sethuraman G, DeMattos RB, Mohs R, Paul SM, Siemers ER (2012) Safety and biomarker effects of solanezumab in patients with Alzheimer's disease. *Alzheimers Dement* 8, 261-271.
- [47] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R; Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* **370**, 311-321.
- [48] Liu-Seifert H, Siemers E, Holdridge KC, Andersen SW, Lipkovich I, Carlson C, Sethuraman G, Hoog S, Hayduk R, Doody R, Aisen P (2015) Delayed-start analysis: Mild Alzheimer's disease patients in solanezumab trials, 3.5 years. *Alzheimers Dement (N Y)*, **1**, 111-121.
- [49] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ, Siemers E (2018) Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med* 378, 321-330.
- [50] Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR (2019) Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement* (*N Y*) 5, 354-363.
- [51] Lo B (2015) Sharing clinical trial data: Maximizing benefits, minimizing risk. JAMA 313, 793-794.
- [52] Kadakia KT, Beckman AL, Ross JS, Krumholz HM (2021) Leveraging open science to accelerate research. N Engl J Med 384, e61.
- [53] Joseph-Mathurin N, Wang G, Kantarci K, Jack CR Jr, McDade E, Hassenstab J, Blazey TM, Gordon BA, Su Y, Chen G, Massoumzadeh P, Hornbeck RC, Allegri RF, Ances BM, Berman SB, Brickman AM, Brooks WS, Cash DM, Chhatwal JP, Chui HC, Correia S, Cruchaga C, Farlow MR, Fox NC, Fulham M, Ghetti B, Graff-Radford NR, Johnson KA, Karch CM, Laske C, Lee AKW, Levin J,

Masters CL, Noble JM, O'Connor A, Perrin RJ, Preboske GM, Ringman JM, Rowe CC, Salloway S, Saykin AJ, Schofield PR, Shimada H, Shoji M, Suzuki K, Villemagne VL, Xiong C, Yakushev I, Morris JC, Bateman RJ, Benzinger TLS; Dominantly Inherited Alzheimer Network (2021) Longitudinal accumulation of cerebral microhemorrhages in dominantly inherited Alzheimer disease. *Neurology* **96**, e1632-e1645.

- [54] Ikonomovic MD, Buckley CJ, Heurling K, Sherwin P, Jones PA, Zanette M, Mathis CA, Klunk WE, Chakrabarty A, Ironside J, Ismail A, Smith C, Thal DR, Beach TG, Farrar G, Smith AP (2016) Post-mortem histopathology underlying β-amyloid PET imaging following flutemetamol F 18 injection. Acta Neuropathol Commun 4, 130.
- [55] Bischof GN, Bartenstein P, Barthel H, van Berckel B, Doré V, van Eimeren T, Foster N, Hammes J, Lammertsma AA, Minoshima S, Rowe C, Sabri O, Seibyl J, Van Laere K, Vandenberghe R, Villemagne V, Yakushev I, Drzezga A (2021) Toward a universal readout for 18F-labeled amyloid tracers: The CAPTAINs Study. J Nucl Med 62, 999-1005.
- [56] Morris E, Chalkidou A, Hammers A, Peacock J, Summers J, Keevil S (2016) Diagnostic accuracy of (18)F amyloid PET tracers for the diagnosis of Alzheimer's disease: A systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 43, 374-385.
- [57] Jung NY, Kim ES, Kim HS, Jeon S, Lee MJ, Pak K, Lee JH, Lee YM, Lee K, Shin JH, Ko JK, Lee JM, Yoon JA, Hwang C, Choi KU, Lee EC, Seong JK, Huh GY, Kim DS, Kim EJ (2020) Comparison of diagnostic performances between cerebrospinal fluid biomarkers and amyloid PET in a clinical setting. J Alzheimers Dis 74, 473-490.
- [58] Niemantsverdriet E, Ottoy J, Somers C, De Roeck E, Struyfs H, Soetewey F, Verhaeghe J, Van den Bossche T, Van Mossevelde S, Goeman J, De Deyn PP, Mariën P, Versijpt J, Sleegers K, Van Broeckhoven C, Wyffels L, Albert A, Ceyssens S, Stroobants S, Staelens S, Bjerke M, Engelborghs S (2017) The cerebrospinal fluid Aβ1-42/Aβ1-40 ratio improves concordance with amyloid-PET for diagnosing Alzheimer's disease in a clinical setting. J Alzheimers Dis 60, 561-576.
- [59] Alexander GC, Emerson S, Kesselheim AS (2021) Evaluation of Aducanumab for Alzheimer disease: Scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA 325, 1717-1718.
- [60] Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled phase I trial. *Lancet* 372, 216-223.
- [61] Nicoll JAR, Buckland GR, Harrison CH, Page A, Harris S, Love S, Neal JW, Holmes C, Boche D (2019) Persistent neuropathological effects 14 years following amyloid-β immunization in Alzheimer's disease. *Brain* 142, 2113-2126.
- [62] Alexander GC, Knopman DS, Emerson SS, Ovbiagele B, Kryscio RJ, Perlmutter JS, Kesselheim AS (2021) Revisiting FDA Approval of Aducanumab. N Engl J Med 385, 769-771.
- [63] Dunn B, Stein P, Temple R, Cavazzoni P (2021) An appropriate use of accelerated approval - Aducanumab for Alzheimer's disease. *N Engl J Med* 385, 856-857.
- [64] Knopman DS, Perlmutter JS (2021) Prescribing Aducanumab in the face of meager efficacy and real risks. *Neurology* 97, 545-547.

- [65] Salloway S, Cummings J (2021) Aducanumab, amyloid lowering, and slowing of Alzheimer disease. *Neurology* 97, 543-544.
- [66] Chen EY, Haslam A, Prasad V (2020) FDA acceptance of surrogate end points for cancer drug approval: 1992–2019. *JAMA Intern Med* 180, 912-914.
- [67] European Medicines Agency. Aduhelm: Aducanumab. Available at: https://www.ema.europa.eu/en/medicines/hu man/summaries-opinion/Aduhelm. Last updated December 17, 2021, Accessed on February 9, 2021)