Evidence Table 2. Individual Phase 3 RCTs, and meta-analyses, of monoclonal antibodies versus placebo in Alzheimer's Disease: Random effects modeling results (standardized mean difference (SMD) and 95% confidence interval, unless otherwise noted) for all outcomes, with only statistically significant results presented, and related author-attributed effect sizes, when available[a]

Monoclonal Antibody (Dose)	Trial Information (if singular)	Publication	ADAS-Cogc (Neg = Impr.)	MMSE (Pos = Impr.)	CDR-SB (Neg = Impr.)	Amyloid PET SUVR (Neg = Impr.)	CSF p-tau (Neg = Impr.)	ADCS-ADL (Pos = Impr.)	vMRI (Pos = Impr.)	CSF Aβ 1-42 (Pos = Impr.)	ARIA Pos = Adv.
BAPINEUZUMAB											
Bapineuzumab (0.5 mg/kg)	12/2007-6/2012 "Non-carrier Study (301)" NCT00574132	Salloway: 2014[b]	ns	ns	ns	ns	ns	-	ns	-	RR: 14.77 [1.99; 109.63]
Bapineuzumab (1.0 mg/kg)	12/2007-6/2012 "Non-carrier Study (301)" NCT00574132	Salloway: 2014[b]	ns	ns	ns	ns	-0.53 [-0.95; -0.11]	-	ns	-	RR: 17.52 [4.29; 71.60]
Bapineuzumab (.5 mg/kg)	12/2007-4/2012 "Carrier Study (302)" NCT00575055	Salloway: 2014[b]	ns	ns	ns	-0.58 [-0.97; -0.19]	-0.40 [-0.68; -0.12]	-	ns	-	RR: 19.04 [7.87; 46.07]
Bapineuzumab (0.5 mg/kg)	6/2008-10/2012 "Non-carrier Study 3000)" NCT00667810	Vandenberghe: 2016[b]	ns	-	ns	ns	ns	-	ns	-	RR: 8.62 [1.14; 65.29] Lg. ES
Bapineuzumab (1.0 mg/kg)	6/2008-10/2012 "Non-carrier Study 3000)" NCT00667810	Vandenberghe: 2016[b]	ns	-	ns	ns	ns	-	ns	-	RR: 20.86 [2.87; 151.44]
Bapineuzumab (0.5 mg/kg)	1/2008-10/2012 "Carrier Study (3001)" NCT00676143	Vandenberghe: 2016[b]	ns	-	ns	ns	ns	-	ns	-	RR: 8.13 [4.16; 15.87]
2017 Meta-analysis of: bapineuzumab		Abushouk: 2017[j]	ns	ns	ns	-	−5.04 [−8; −2.09]				RR: 40.88, [11.94; 135.95]
2019 Meta-analysis of bapineuzumab (1 mg/kg) across 2 Phase III Studies		Foroutan: 2019	ns	-	-	-	-	-	-	-	-
2019 Meta-analysis of bapineuzumab (0.5 mg/kg) across 3 Phase II studies		Foroutan: 2019	ns	-	-	-	-	-	-	-	-
2021 Meta-analysis of bapineuzumab across 6 Phase III studies		Avgerinos: 2021[l]	ns	ns	ns	ns	-0.29 [-0.48; -0.10] Sm. ES	-	ns	-	12.47 [7.80; 19.93] Lg. ES
SOLANEZUMAB											
Solanezumab (400 mg)	5/2009-4/2012 "EXPEDITION 1" NCT00905372	Doody: 2014[b]	ns	ns	ns	-	-	ns	-	ns	RR: 0.97 [0.68; 1.37]
Solanezumab (400 mg)	5/2009-4/2012 "EXPEDITION 2" NCT00904683	Doody: 2014[b]	ns	ns	ns	-	-	ns	-	0.53 [0.07; 1.00]	RR: 0.97 [0.68; 1.37]
Solanezumab	7/2013-10/2016		ns	0.10	ns	ns	-	0.11	ns	1.68	RR: 0.51

(400 mg)	"EXPEDITION 3" NCT01900665	Honig: 2018[b]		[0.01; 0.18]				[0.02; 0.19]		[1.40; 1.97]	[0.05; 5.57]
2019 Meta-analysis of solanezumab across 3 Phase II or III studies		Foroutan: 2019[p]	-1.44 [-1.51; -1.37]	-	-	-	-	-	-	-	-
2021 Meta-analysis of solanezumab across 3 Phase III studies		Avgerinos: 2021[o]	-0.07 [-0.13; -0.01] Sm. S	0.08 [0.02; 0.15] Sm. ES	ns	ns	-	ns	ns	ns	0.94 [0.21; 4.32] Sm. ES
GANTENERUMAB											
Gantenerumab (105 mg)	1/2010-9/2020 "Scarlet Road" NCT01224106	Ostrowitzki: 2017[b]	ns	ns	ns	ns	-1.60 [-2.06; -1.15]	-	-	ns	RR: 2.18 [1.37; 3.48]
Gantenerumab (225 mg)	1/2010-9/2020 "Scarlet Road" NCT01224106	Ostrowitzki: 2017[b]	ns	ns	ns	ns	-2.50 [-3.04; -1.16]	-	-	0.70 [0.28; 1.11]	RR: 2.07 [1.31; 3.27]
2021 Meta-analysis of gantenerumab across 2 Phase III studies		Avgerinos: 2021[n]	ns	ns	ns	ns	-2.04 [-2.93; -1.16] Lg. ES	-	-	ns	2.13 [1.54; 2.94] Lg. ES
ADUCANUMAB											
Aducanumab (1-6 mg/kg)	8/2015-8/2019 "EMERGE" (Study 302) NCT02484547	Haeberlein: 2020[b]	ns	ns	ns	-2.35 [-2.84; -1.85]	-0.86 [-1.58; -0.13]	ns	-	-	RR: 3.18 [2.20; 4.61]
Aducanumab (1-10 mg/kg)	8/2015-8/2019 "EMERGE" (Study 302) NCT02484547	Haeberlein: 2020[b]	-0.16 [-0.30; -0.01]	0.14 [0.00; 0.29]	-0.17 [-0.31; -0.02]	-3.41 [-3.99; -2.84]	-1.61 [-2.51; -0.71]	0.23 [0.08; 0.37]	-	-	RR: 4.00 [2.78; 5.77]
Aducanumab (1-6 mg/kg)	8/2015-8/2019 "ENGAGE"(Study 301) NCT02477800	Haeberlein: 2020[b]	ns	ns	ns	-1.66 [-2.03; -1.29]	-1.11 [-1.98; -0.24]	ns	-	-	RR: 3.14 [2.13; 4.62]
Aducanumab (1-10 mg/kg)	8/2015-8/2019 "ENGAGE" (Study 301) NCT02477800	Haeberlein: 2020[b]	ns	ns	ns	-2.59 [-3.03; -2.14]	ns	ns	-	-	RR: 4.13 [2.83; 6.04]
2021 Meta-analysis of aducanumab across 4 Phase III studies		Avgerinos: 2021[k]	-0.10 [-0.17; -0.03] Sm. ES	ns	ns	-2.48 [-3.18; -1.78] Lg. ES	-1.06 [-1.47; -0.65] Lg. ES	0.13 [0.06; 0.20] Sm. ES	-	-	RR: 3.59 [2.85; 4.53] Lg. ES
CRENEZUMAB											
Crenezumab (60 mg/kg)	2020 "CREAD1" NCT02670083	Results on Clinicaltrials.gov [b]	ns	ns	ns	-	-	ns	ns	-	-
Crenezumab (100 mg/kg)	2020 "CREAD2" NCT03114657	Results on Clinicaltrials.gov [b]	ns	ns	0.79 [-1.58; 0.00]	-	-	ns	ns	-	-
2021 Meta-analysis of crenezumab across 2 Phase III studies		Avgerinos: 2021[m]	ns	ns	ns	-	-	ns	ns	-	-
MULTI-mAb META-ANALYSES											
2021 Meta-analysis of:		Avgerinos: 2021[f]	-0.06	0.05	ns	-1.02	-0.87	0.09	0.08	ns	RR: 4.30

aducanumab (4), bapineuzumab (6), crenezumab (2), gantenerumab (2), solanezumab (3) across 17 total Phase III studies			[-0.10; -0.02] Sm. ES	[0.01; 0.09] Sm. ES		[-1.70; -0.34] Lg. S	[-1.32; -0.43] Lg. ES	[0.03; 0.14] Sm. ES	[0.00; 0.17] Sm. ES		[2.39; 7.77] Lg. ES
2019 Meta-analysis of: bapineuzumab, solanezumab, semagacestat, IVIG, AN1792, ACC-001 +/-QS-21, tramiprosate (3APS) across 10 total Phase II and III studies		Foroutan: 2019[g]	-0.39 [-0.42; -0.35] Sm. ES	0.04 [0.02; 0.05][d]	0.11 [0.10; 0.12]	-	-	-	-	-	RR: 9.3 [3.56; 24.35]
2019 Meta-analysis (non-pooled, comparative) of Aducanumab, AN1792 + QS21, Bapineuzumab, CAD106, Solanezumab were retrieved across 9 studies		Mo: 2017[h]	ns	-	-	-	-	-	-	-	e
2017 Meta-analysis of: AN1792, CAD106, bapineuzumab, solanezumab, ponezumab, gantenerumab, and aducanumab across 14 Phase III studies		Penninkilampi: 2017[i]	ns[q]	0.44 [0.07; 0.81][q]	ns[q]	-	-	-	-	-	OR: 4.79, [1.24; 18.55]

a Abbreviations: Pos=positive; Neg=negative; Impr.=improved; Adv.=adverse; Sm. ES (Small effect size); Lg. ES (Large effect size); ns: not statistically significant; "-": not studied"

b All results for individual mAb drugs are as reported in the meta-analysis conducted by the National Institute on Aging (Avgerinos 2021) [ii],

c A four-point difference is required for meaningful clinical significance, per Foroutan et al. (2019)

d Studies in this pooled analysis included only the following five: AN1792, bapineuzumab 0.5 mg/kg, bapineuzumab 1 mg/kg, solanezumab 400 mg, and semagacestat

e Authors concluded: "In terms of ARIA, bapineuzumab and aducanumab are significantly worse than placebo (OR: 60.88 95% CI: 15.07–245.94 and 6.54 1.49–28.65). Aducanumab is significantly worse than CAD106 and solanezumab (30.07 1.21–748.79 and 6.79 1.48–31.12). Also, bapineuzumab is significantly worse than solanezumab (63.20 14.91–267.86)."

f "Robust data syntheses of all included studies (12,585 participants) showed statistical improvements for monoclonal antibodies on cognitive outcomes (ADAS-Cog and MMSE) and a trend towards improvement on CDR-SB, a measure that assesses both cognition and function. The statistically significant cognitive benefits of monoclonal antibodies revealed in this meta- analysis were particularly noteworthy considering that the majority of original studies did not reach significance for ADAS-Cog and MMSE. Additional meta-analyses also showed that monoclonal antibodies statistically improved a functional measure (AD Cooperative Study- Activities of Daily Living), reduced amyloid burden (amyloid PET SUVR) and a tau biomarker (CSF p181-tau), preserved brain volume (vMRI), but also increased the risk of the hallmark adverse event for this drug class, ARIA." (Avgerinos 2021[iii])

g "In terms of safety, the rate of ARIA-E was significantly higher with monoclonal antibodies. Solanezumab and AN1792 (vaccine) were the drugs of choice both from efficacy and safety perspectives. Conclusion: In terms of efficacy, the review showed a statistically, but not clinically significant, improvement in favor of immunotherapy versus placebo." (Foroutan, 2019[iv])

h "Optimal intervention was ranked by benefit-risk ratio based on the surface under the cumulative ranking curve. Eleven eligible RCTs from 9 literatures, including 5141 patients and 5 interventions were included. The quality of evidence was rated low in comparisons. For efficacy, in terms of Mini-Mental State Examination, aducanumab and solanezumab are significantly effective than placebo. For safety, in terms of Amyloid-Related Imaging Abnormalities (ARIA), bapineuzumab and aducanumab are significantly worse than placebo. There were no significant differences in outcomes of Alzheimer's disease Assessment Scale-Cognitive subscale, Disability Assessment for Dementia, Adverse Events, and mortality. Given the clinical therapeutic effects of anti-Aβ immunotherapies for AD, aducanumab and solanezumab improve the cognitive function, while aducanumab and bapineuzumab may increase the risks of ARIA." (Mo, 2019[v])

i "Upon pooling of data, there was no increased risk of any adverse event, serious adverse events, or death with the exception of a near fivefold increase in amyloid-related imaging abnormalities (ARIA; OR 4.79, 95% CI 1.24–18.55; p = 0.02). Of the cognitive indicators, the Mini-Mental State Examination (MMSE) showed a small statistically significant improvement (diff in means =0.44; p = 0.02), while

the others (ADAS-cog, ADCS-ADL, and CDR-sb) showed no change. Therefore, immunotherapeutic agents have been relatively well tolerated, with some promise for cognitive improvements if the occurrence of ARIA can be mitigated." (Penninkilampi, 2017[vi])
j "Considering the lack of clinical efficacy, combined with the significant association with serious adverse events, bapineuzumab should not be used to treat patients with mild to moderate AD." (Abushouk, 2017[vii])
k "Aducanumab statistically improved ADAS-Cog, and it was the only drug that statistically improved CDR-SB and "AD Cooperative Study-Activities of Daily Living" … therefore potentially benefiting both cognition and function. The effect sizes for these improvements were small (effect sizes <0.2 correspond to clinically minor score changes on the ADAS-Cog, CDR-SB and "AD Cooperative Study-Activities of Daily Living" scales) … Aducanumab decreased brain Aβ burden and CSF p-tau by large effect sizes (ideal Number Needed to Treat) ... The combination of statistical improvements in multiple clinical outcomes and strong target engagement/disease-modifying properties identify Aducanumab as the most promising candidate in this drug class that has reached Phase III trials" (Avgerinos, 2021[viii])
l "Generally, there were no statistically significant differences between groups, on efficacy outcomes, except CSF p-tau, however Sm. ESs." (Avgerinos, 2021[ix])
m "Based on results of an interim analysis, CREAD 1 and 2 were discontinued because Crenezumab was unlikely to meet the primary endpoint." (Avgerinos, 2021[x])
n "Futility based on interim analysis" (Avgerinos, 2021[xi])
o "It is worth noting that Solanezumab produced some statistically significant effects on clinical outcomes (ADAS-Cog, MMSE) without increasing ARIA risk." (Avgerinos, 2021[xii])
p "The meta-analysis results showed a statistically significant change from baseline regarding ADAS-cog values (mean difference=-0.39; 95% CI -0.42, -0.35, P=0.001) in favor of immunotherapies; however, the ADAS-Cog is a detailed cognitive assessment for dementia for which a four-point difference between treatment groups is required to be considered a significant difference in the clinical practice setting which was not achieved in the present analysis … Solanezumab 400 mg is reported as the best therapeutic choice having measured cognitive outcomes of patients with the ADAS-cog scale." (Foroutan, 2019[xiii])
q Studies in this pooled analysis included only the following three: solanezumab (Doody, 2014), AN1792 (Gilman, 2005), and bapineuzumab (Salloway, 2014)