Supplementary Material

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and Efficacy of Monoclonal Antibodies for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Published and Unpublished Clinical Trials

Supplementary File 1. Search strategy

1. Search strategy used for ClinicalTrials.gov (CT) and the European Clinical Trials Register (EUCT)
(Alzheimer OR Alzheimer's OR mild cognitive impairment)

2. Search strategy used for PubMed, ISI Web of Knowledge (WoK) and The Cochrane Library Databases (CLD)
(Alzheimer* OR "Mild cognitive impairment" OR MCI) AND ("monoclonal antibody" OR "monoclonal antibodies" OR "monoclonal anti-body" OR "monoclonal anti-bodies" OR aab-003 OR pf-05236812 OR abbv-8e12 OR "c2n 8e12" OR acu193 OR aducanumab OR biib037 OR al002 OR ban2401 OR lecanemab OR bapineuzumab OR aab-001 OR eln115727 OR bepranemab OR ucb0107 OR biib076 OR biib092 OR crenezumab OR mabt5102a OR ro5490245 OR donanemab OR ly3002813 OR gantenerumab OR r1450 OR gsk933776 OR jnj-63733657 OR khk6640 OR "lu af87908" OR ly2599666 OR ly3303560 OR zagotanemab OR ly3372993 OR medi1814 OR pepinemab OR ponezumab OR pf-04360365 OR ro7105705 OR semorinemab OR ro7126209 OR sar228810 OR solanezumab OR ly2062430)

Supplementary File 2. International prospective register of systematic reviews PROSPERO (CRD42021259855)

Citation

Eleonora Lacorte, Antonio Ancidoni, Valerio Zaccaria, Giulia Remoli, Leonardo Tariciotti, Ilaria Bacigalupo, Francesco Sciancalepore, Marco Canevelli, Massimo Corbo, Paola Piscopo, Nicola Vanacore. Safety and efficacy of monoclonal antibodies for Alzheimer's disease: a systematic review of published and unpublished trials and meta-analysis of available data. PROSPERO 2021 CRD42021259855 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021259855

Review question

What is the safety and efficacy of monoclonal antibodies (MAB) for Alzheimer's disease (AD)? How many trials were registered investigating MABs for AD? How many published and/or unpublished data are available from registered trials on MABs for AD?

Searches

Registered trials will be identified using two databases as sources: i) the ClinicalTrials.gov for studies registered in the US; and ii) the EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) for all interventional studies registered in the European Union (EU). The following terms will be used: (Alzheimer OR Alzheimer's OR mild cognitive impairment). No restrictions will be applied for recruitment phase/status, study design, and study phase, date of publication, or language.

Based on the results yielded from ClinicalTrials.gov and clinicaltrialsregister.eu, a systematic literature search will be conducted in the following biomedical databases: PubMed, ISI Web of Knowledge and The Cochrane Library. The following terms will be used: (Alzheimer* OR "Mild cognitive impairment" OR MCI) AND ("monoclonal antibody" OR "monoclonal antibodies" OR "monoclonal anti-body" OR "monoclonal anti-bodies" OR aab-003 OR aducanumab OR biib037 OR ban2401 OR bapineuzumab OR aab-001 OR "donanemab" OR eln115727 OR biib076 or "c2n 8e12" OR abbv-8e12 OR crenezumab OR mabt5102a OR gantenerumab OR r1450 OR gsk933776 OR khk6640 OR "lecanemab" OR ly2599666 OR ly3002813 OR ly3303560 OR ponezumab OR pf-04360365 OR ro7105705 OR sar228810 OR solanezumab OR ly2062430 OR ustekinumab). No restrictions will be applied for date of publication, study design or language.

Types of study to be included

Included:

RCTs, clinical trials, and observational studies either published or unpublished

Excluded:

case reports, case series, abstracts, posters, reviews, qualitative studies, editorials, letters, comments

Condition or domain being studied

Alzheimer's disease

Participants/population

adults >18

Intervention(s), exposure(s)

any type of monoclonal antibody under investigation for the treatment of AD, excluding potential repurposed agents of the same class

Comparator(s)/control

any type of comparison

Main outcome(s)
Safety, mainly in terms of risk of amyloid-related imaging abnormalities and serious adverse events.

Any type of clinical efficacy measure, if reported by the included literature.

Percentage of availability of information from registered trials.

Additional outcome(s)
none

Data extraction (selection and coding)
Studies will be initially selected based on their pertinence with and relevance to the topic of the review. Selected studies will be analyzed in full text and applied the inclusion and exclusion criteria.

Data will be extracted using standardized forms. Recorded information will include year of publication, characteristics of the included population (including diagnostic criteria), type of intervention investigated (type of drug, dosage, timing), type of comparison considered (e.g. placebo, other treatment), type of outcome considered (e.g. frequency of adverse reactions/effects/events), and results for each included review.

For each clinical study, we aim to provide all data sources referable to the trial identification number (posted results, published studies). All data sources resulting from the same clinical trial will be compared to identify possible discrepancies. In case of discrepancy, we will consider the most recent data source to be the most reliable. In addition, secondary studies will be screened and analyzed to identify whether outcomes of interest for our review were investigated (e.g. post hoc analysis on safety or efficacy data), and therefore, if they could be useful to correct or supplement data from the primary studies or results sheets.

Risk of bias (quality) assessment
Trials meeting the inclusion criteria will be qualitatively assessed using the Cochrane Risk of Bias tool and reported in a graphic form using the RevMan software. Only published RCTs will be applied the RoB tool, as too much methodological information is missing from the documents available on the registration platforms.

Observational studies will be qualitatively assessed using the The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

Strategy for data synthesis
Data will be summarized in a narrative form (considering both quantitative and qualitative results, and results from the quality assessment).

Meta-analyses will be performed using the software Review Manager version 5.3.

Analysis of subgroups or subsets
Safety data will be stratified per MAB and data for ARIA-E and ARIA-H will be analyzed separately. Further sensitivity analyses will be performed according to the expected differences in the definition of ARIA.

Data on efficacy, if present, will be stratified according to MAB.

Contact details for further information
Eleonora Lacorte
eleonora.lacorte@iss.it

Organisational affiliation of the review
Istituto Superiore di Sanità

Review team members and their organisational affiliations
Dr Eleonora Lacorte. Istituto Superiore di Sanità
Dr Antonio Ancidoni. Istituto Superiore di Sanità
Valerio Zaccaria. Università La Sapienza Roma

Giulia Remoli. Istituto Superiore di Sanità
Leonardo Taricciotti. Università di Milano
Ilaria Bacigalupo. Istituto Superiore di Sanità
Francesco Sciancalepore. Istituto Superiore di Sanità
Marco Canevelli. Istituto Superiore di Sanità
Massimo Corbo. Department of Neurorehabilitation Sciences, Casa Cura Policlinico (CCP), Milano
Paola Piscopo. Istituto Superiore di Sanità
Nicola Vanacore. Istituto Superiore di Sanità

Type and method of review
Intervention, Systematic review

Anticipated or actual start date
01 February 2021

Anticipated completion date
27 July 2021

Funding sources/sponsors
no funding were received nor will be received for this review

Conflicts of interest

Language
English

Country
Italy

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
09 July 2021

Date of first submission
08 June 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

09 July 2021
09 July 2021

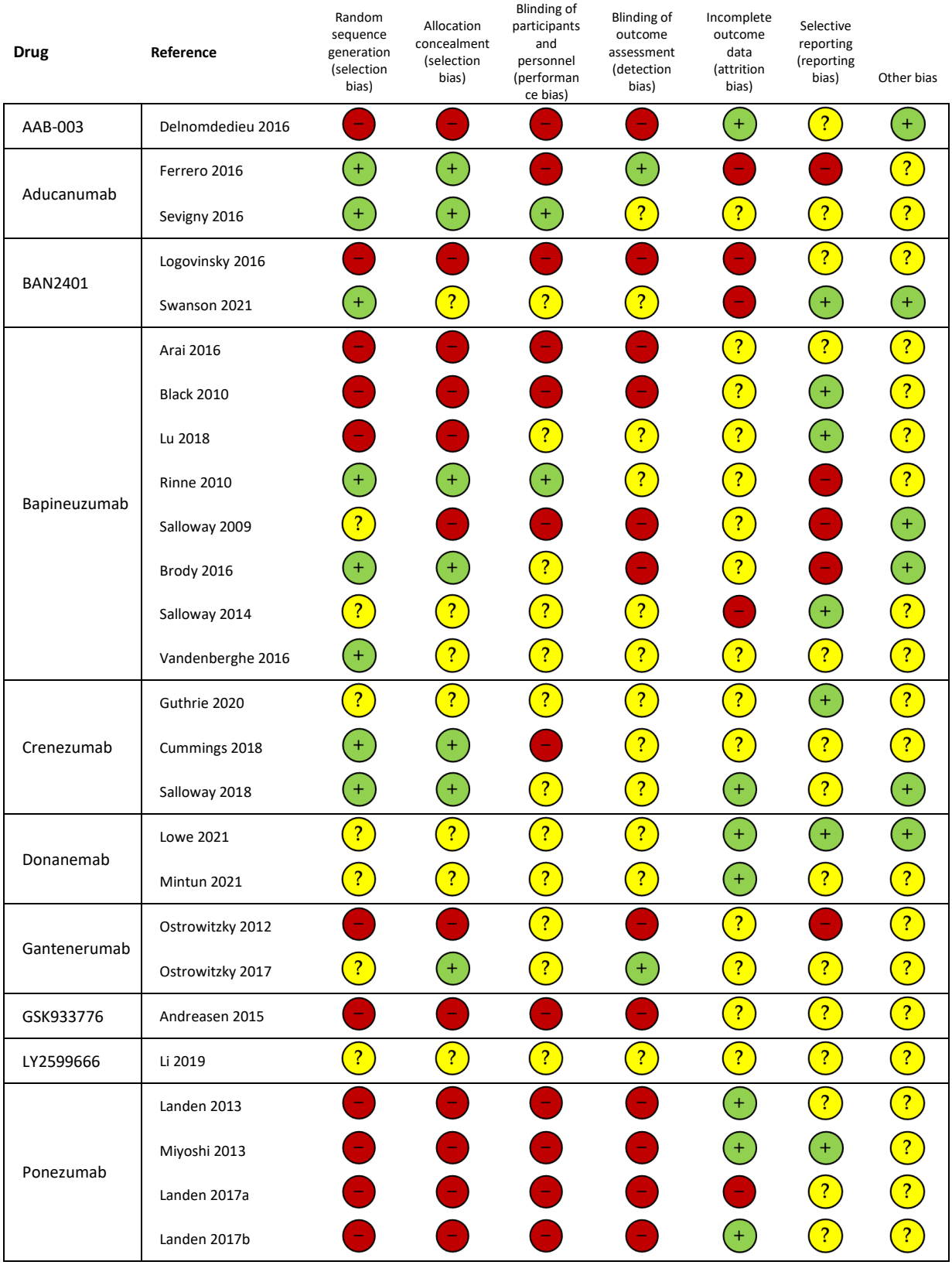
Supplementary Table 2. List of registered trials and available sources of data.

				SOURCE		
1.	**NCT01193608**	completed	Phase 1 **RCT**	CT.gov data		Delnomdedieu 2016
2	**NCT01369225**	completed	Phase 1 **OLE**	CT.gov data		Delnomdedieu 2016
3	**NCT02880956**	ongoing	Phase 2 **RCT**			-
4	**NCT03712787**	ongoing	Phase 2 **OLE**			-
5	**NCT04931459**	ongoing	Phase 1 **RCT**			-
6	**NCT01397539**	completed	Phase 1 **RCT**			Ferrero 2016
7	**NCT01677572**	terminated	Phase 1 **RCT**			Sevigny 2016
8	**NCT02434718**	completed	Phase 1 **RCT**			-
9	**NCT03639987**	terminated	Phase 2 **RCT**			results submitted
10	**NCT02477800**	terminated	Phase 3 **RCT+OLE**		EudraCT data	
11	**NCT02484547**	terminated	Phase 3 **RCT+OLE**		EudraCT data	
12	**NCT04241068**	ongoing	Phase 3 **OLE**			-
13	**NCT03635047**	completed	Phase 1 **RCT**			-
14	**NCT04592874**	ongoing	Phase 2 **RCT**			-
15	**NCT01230853**	completed	Phase 1 **RCT**			Logovinsky 2016
16	**NCT02094729**	completed	Phase 1 **RCT**			-
17	**NCT01767311**	ongoing	Phase 2b **RCT**			Swanson 2021
18	**NCT03887455**	ongoing	Phase 3 **RCT**			-
19	**NCT04468659**	ongoing	Phase 3 **RCT**			-
20	**NCT00397891**	completed	Phase 1 **RCT**	CT.gov data		Arai 2016
21	**No code reported**	completed	Phase 1 **RCT**			Black 2010
22	**No code reported**	completed	Phase 1 **RCT**			Lu 2018
23	**Eudra2004-004120-12**	completed	Phase 2 **RCT**			Rinne 2010
24	**NCT00112073**	completed	Phase 2 **RCT**			Salloway 2009
25	**NCT00174525**	unknown	Phase 2 **RCT**			-
26	**NCT00606476**	terminated	Phase 2 **OLE**			-
27	**NCT00663026**	completed	Phase 2 **RCT**	CT.gov data		
28	**NCT00916617**	terminated	Phase 2 **OLE**	CT.gov data		
29	**NCT01254773**	completed	Phase 2 **RCT**			Brody 2016
30	**NCT00574132**	completed	Phase 3 **RCT**		EudraCT data	Salloway 2014
31	**NCT00575055**	completed	Phase 3 **RCT**			Salloway 2014
32	**NCT00667810**	terminated	Phase 3 **RCT**	CT.gov data	EudraCT data	Vandenberghe 2016
33	**NCT00676143**	terminated	Phase 3 **RCT**	CT.gov data	EudraCT data	Vandenberghe 2016
34	**NCT00937352**	terminated	Phase 3 **OLE**		EudraCT data	
35	**NCT00996918**	terminated	Phase 3 **OLE**	CT.gov data	EudraCT data	Ivanoiu 2016
36	**NCT00998764**	terminated	Phase 3 **OLE**	CT.gov data	EudraCT data	Ivanoiu 2016
37	**NCT01658722**	terminated	Phase 3b **OLE**			-
38	**NCT04867616**	ongoing	Phase 2 **RCT+OLE**			-

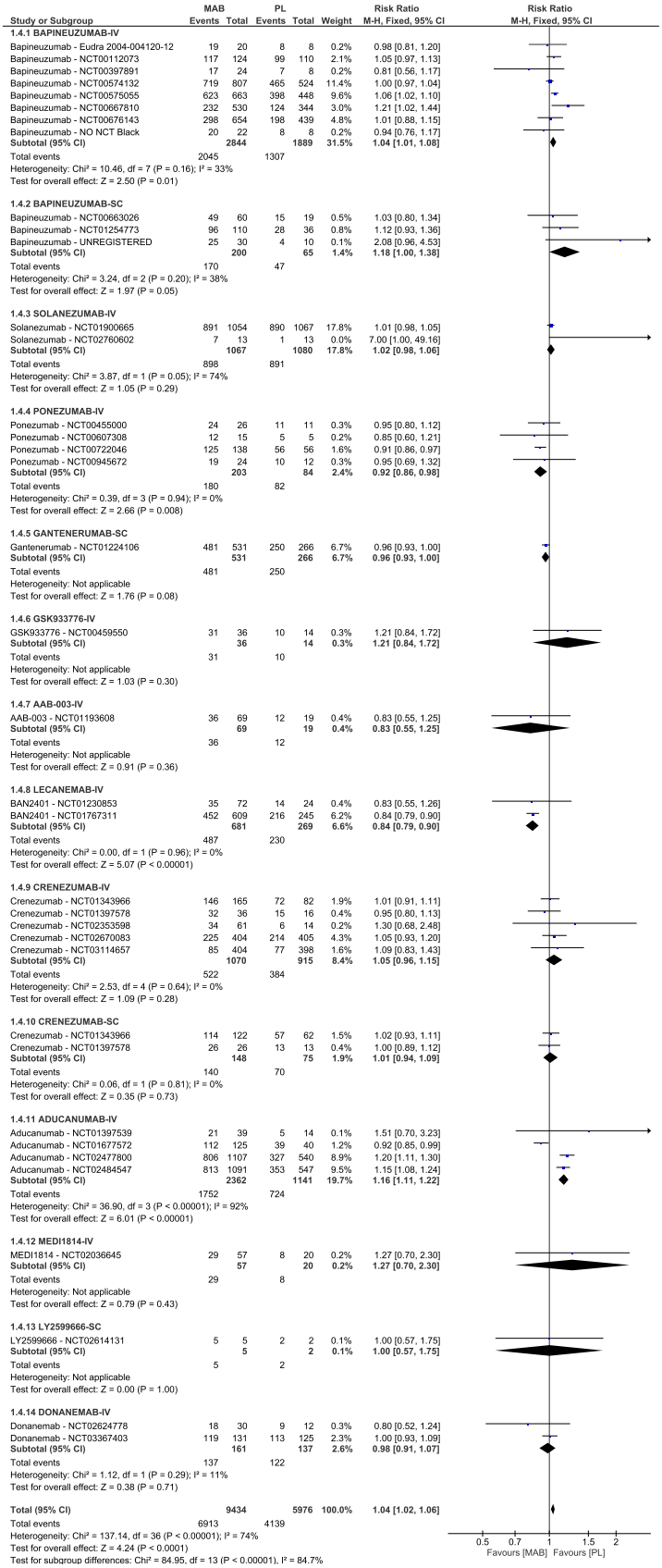
39	**NCT03056729**	completed	Phase 1 **RCT**			-
40	**NCT03352557**	ongoing	Phase 2 **RCT**			-
41	**NCT00736775**	completed	Phase 1 **RCT**			-
42	**NCT02353598**	completed	Phase 1 **RCT+OLE**			Guthrie 2020
43	**NCT01343966**	completed	Phase 2 **RCT**		EudraCT data	Cummings 2018
44	**NCT01397578**	completed	Phase 2 **RCT**		EudraCT data	Salloway 2018
45	**NCT01723826**	completed	Phase 2 **OLE**	CT.gov data	EudraCT data	
46	**NCT02670083**	terminated	Phase 3 **RCT**	CT.gov data	EudraCT data	
47	**NCT03114657**	terminated	Phase 3 **RCT**	CT.gov data	EudraCT data	
48	**NCT03491150**	terminated	Phase 3 **OLE**	CT.gov data	EudraCT data	
49	**NCT01837641**	completed	Phase 1 **RCT**			-
50	**NCT02624778**	completed	Phase 1 **RCT**			Lowe 2021
51	**NCT03367403**	ongoing	Phase 2 **RCT**			Mintun 2021
52	**NCT04640077**	ongoing	Phase 2 **OLE**			-
53	**NCT04437511**	ongoing	Phase 3 **RCT**			-
54	**NCT00531804**	completed	Phase 1 **RCT**			Ostrowitzki 2012
55	**NCT01656525**	completed	Phase 1 **RCT**			-
56	**NCT04592341**	ongoing	Phase 2 **OL**			-
57	**NCT01224106**	completed	Phase 3 **RCT**		EudraCT data	Ostrowitzki 2017
58	**NCT02051608**	completed	Phase 3 **RCT**			-
59	**NCT03444870**	ongoing	Phase 3 **RCT**			-
60	**NCT03443973**	ongoing	Phase 3 **RCT**			-
61	**NCT04339413**	ongoing	Phase 3 **OLE**			-
62	**NCT04374253**	ongoing	Phase 3 **OLE**			-
63	**NCT00459550**	completed	Phase 1 **RCT**		EudraCT data	Andreasen 2015
64	**NCT01424436**	completed	Phase 1 **OL**			Leyhe 2014
65	**NCT03375697**	completed	Phase 1 **RCT**			-
66	**NCT04619420**	ongoing	Phase 2 **RCT**			-
67	**NCT02127476**	completed	Phase 1 **RCT**			-
68	**NCT02377713**	completed	Phase 1 **RCT**			-
69	**NCT03093519**	completed	Phase 1 **RCT**			-
70	**NCT04149860**	ongoing	Phase 1 **RCT**			-
71	**NCT02614131**	terminated	Phase 1 **RCT**	CT.gov data		Li 2019
72	**NCT02754830**	completed	Phase 1 **RCT**			-
73	**NCT03019536**	completed	Phase 1 **RCT**			-
74	**NCT03518073**	ongoing	Phase 2 **RCT**			-
75	**NCT03720548**	completed	Phase 1 **RCT**			-
76	**NCT04451408**	ongoing	Phase 1 **RCT**			-
77	**NCT02036645**	completed	Phase 1 **RCT**	CT.gov data		
78	**NCT04381468**	ongoing	Phase 1/2**RCT**			-

79	**NCT00455000**	completed	Phase 1 **RCT**			Landen 2013
80	**NCT00607308**	completed	Phase 1 **RCT**			Miyoshi 2013
81	**NCT00733642**	completed	Phase 1 **OL**			-
82	**NCT01005862**	completed	Phase 1 **RCT**			-
83	**NCT01125631**	completed	Phase 1 **RCT**			-
84	**NCT00722046**	completed	Phase 2 **RCT**		EudraCT data	Landen 2017a
85	**NCT00945672**	completed	Phase 2 **RCT**		EudraCT data	Landen 2017b
86	**NCT02820896**	completed	Phase 1 **RCT**			-
87	**NCT03289143**	completed	Phase 2 **RCT**			-
88	**NCT03828747**	ongoing	Phase 2 **RCT**			-
89	**NCT04023994**	completed	Phase 1 **RCT**	results submitted		
90	**NCT04639050**	ongoing	phase 1/2**RCT**			-
91	**NCT01485302**	completed	Phase 1 **RCT**			-
92	**No code reported**	completed	phase 1 **RCT**			Siemers 2010
93	**No code reported**	completed	phase 1 **RCT**			Uenaka 2012
94	**NCT00329082**	completed	Phase 2 **RCT**			Farlow 2012
95	**NCT00749216**	completed	Phase 2**OL**			-
96	**NCT01148498**	completed	Phase 2**OL**			-
97	**NCT00904683**	completed	Phase 3 **RCT**		EudraCT data	Doody 2014
98	**NCT00905372**	completed	Phase 3 **RCT**			Doody 2014
99	**NCT01127633**	terminated	Phase 3**OLE**	CT.gov data	EudraCT data	Liu-Seifert 2015
100	**NCT01900665**	terminated	Phase 3 **RCT+OLE**	CT.gov data	EudraCT data	Honig 2018
101	**NCT02760602**	terminated	Phase 3 **RCT**	CT.gov data	EudraCT data	
102	**NCT01998841**	ongoing	Phase 2 **RCT**			
103	**NCT03977584**	ongoing	Phase 2 **OLE**			
104	**NCT02008357**	ongoing	Phase 3 **RCT**			
105	**NCT01760005**	ongoing	Phase 2/3			
106	**NCT04623242**	completed	Phase 2/3			Salloway 2021
Total				**18**	**22**	**35**

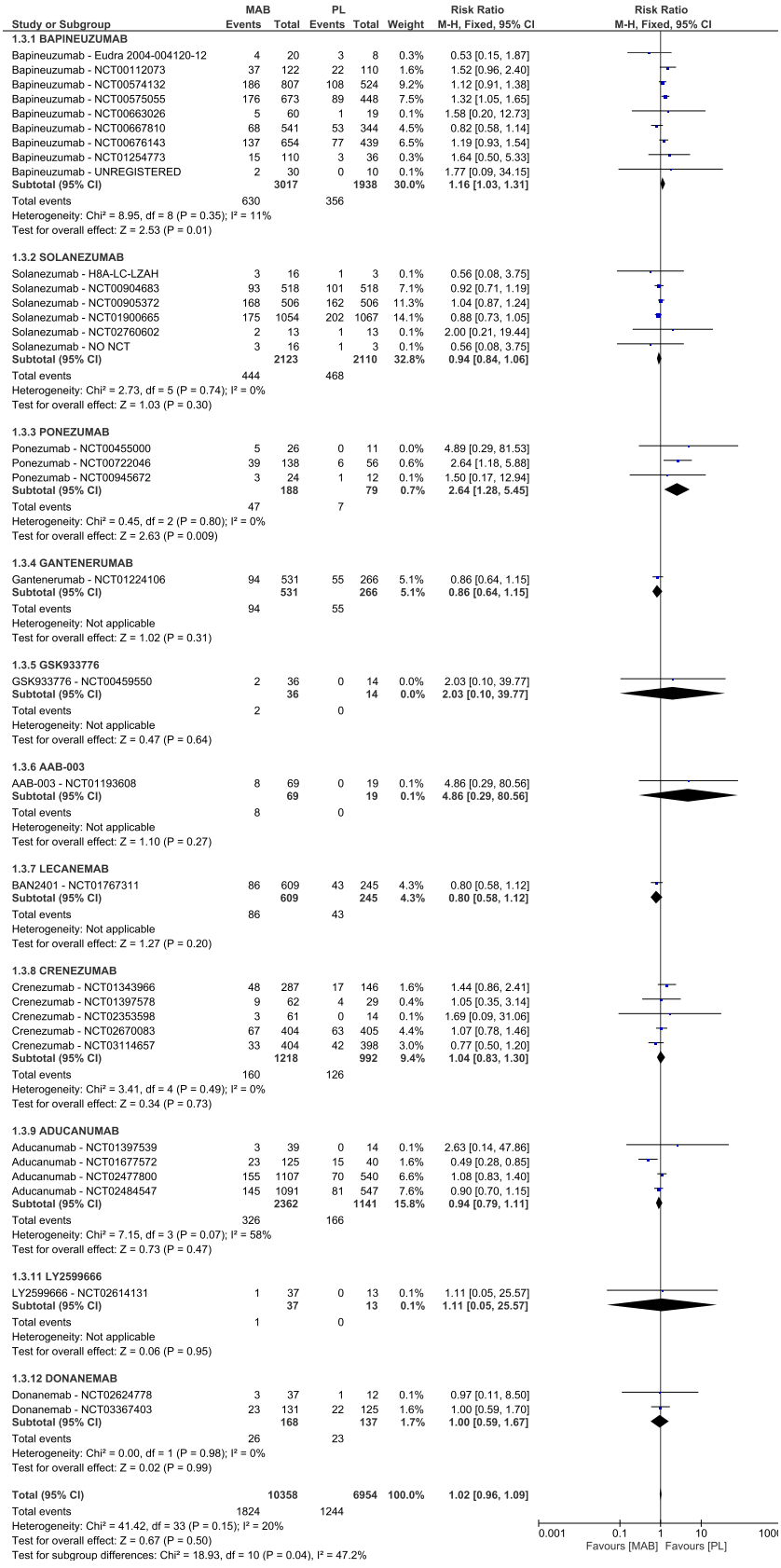
Supplementary Figure 1. Risk of bias of included published RCTs assessed using the RoB tool.



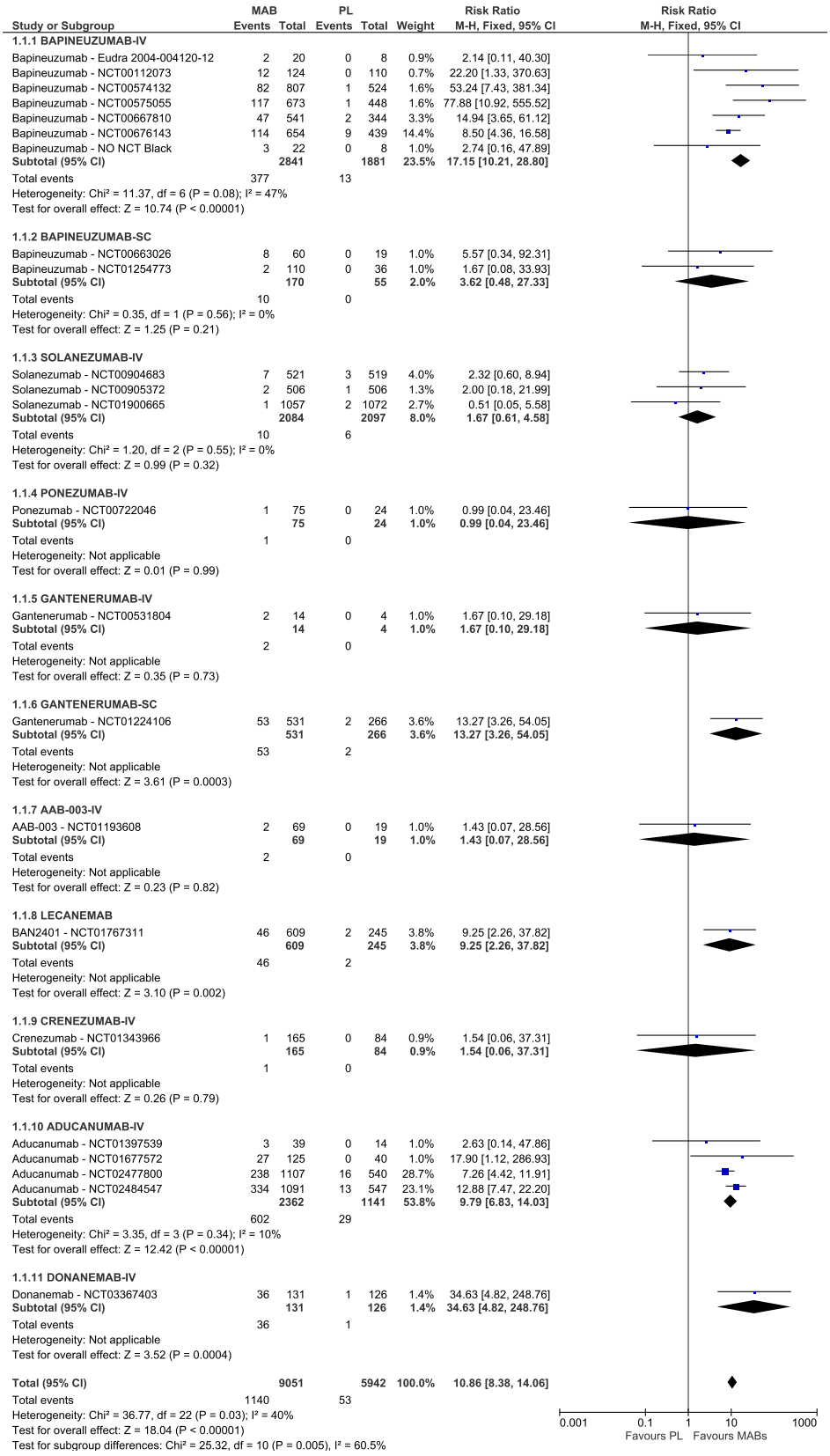
Supplementary Figure 2. Forest plot of the meta-analysis of available data on the frequency of AEs.



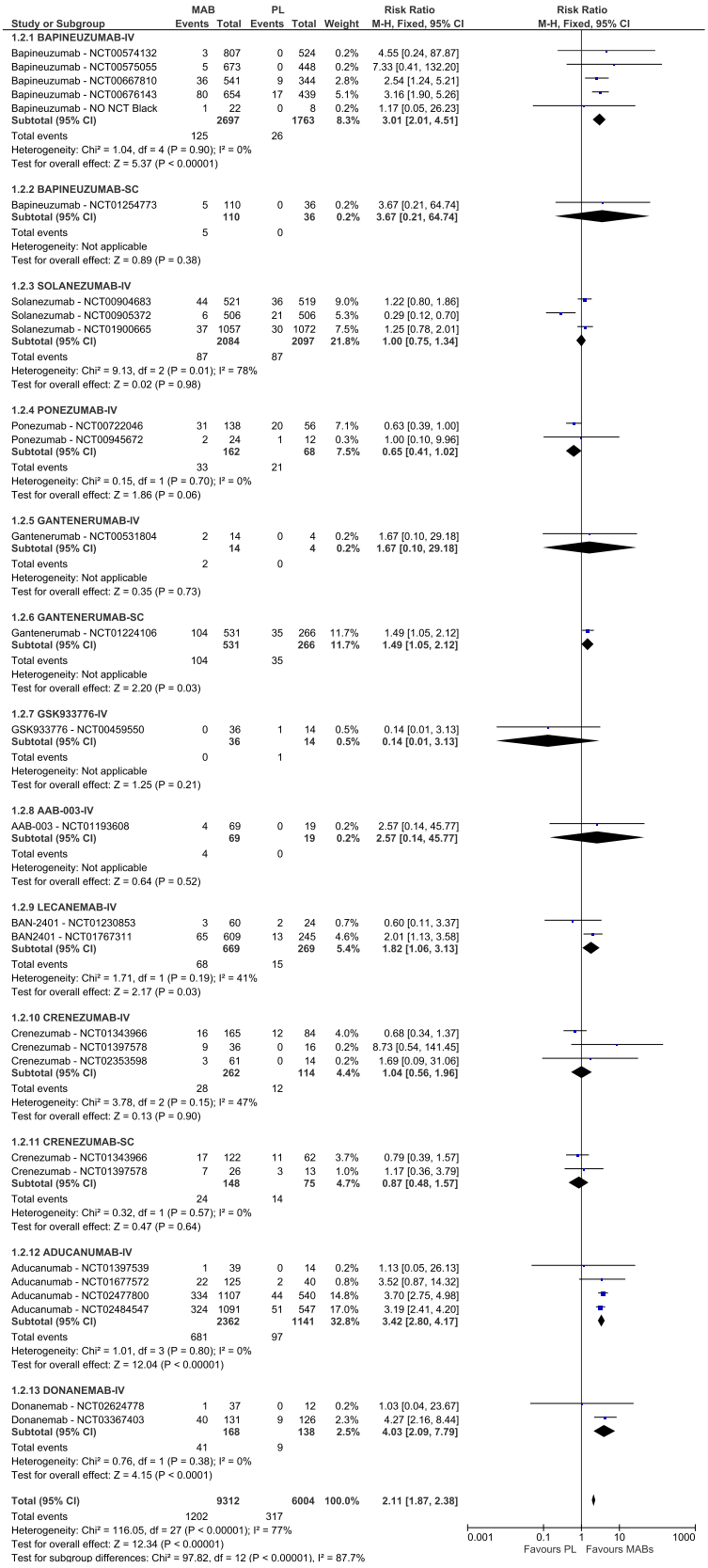
Supplementary Figure 3. Forest plot of the meta-analysis of available data on the frequency of SAEs.



Supplementary Figure 4. Forest plot of the sensitivity analysis of available data on the frequency of ARIA-E including other events such as vasogenic edemas not classified as ARIA-E within the included studies.

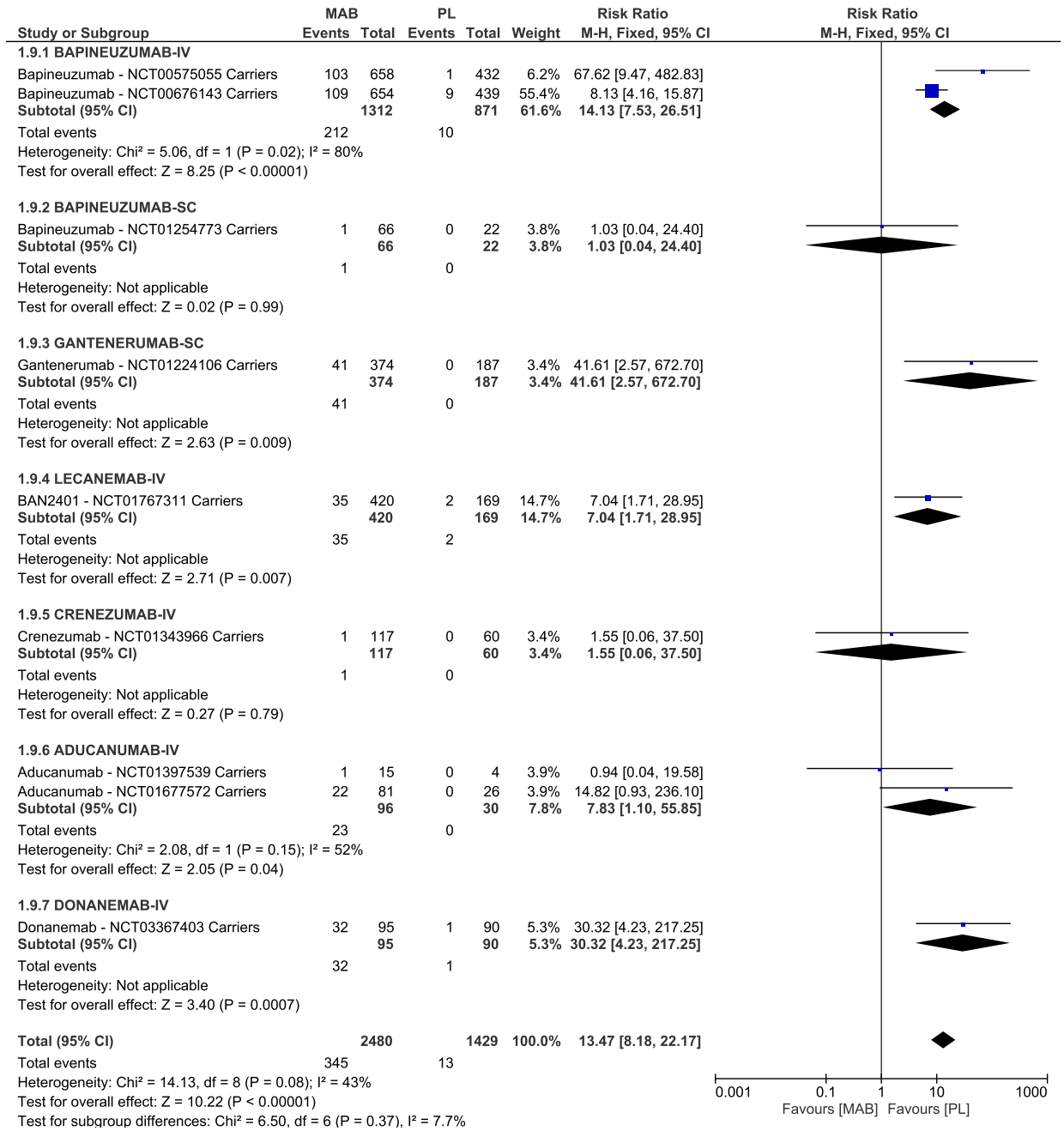


Supplementary Figure 5. Forest plot of the sensitivity analysis of available data on the frequency of ARIA-H including other events such as micro-hemorrhages not classified as ARIA-H within the included studies.

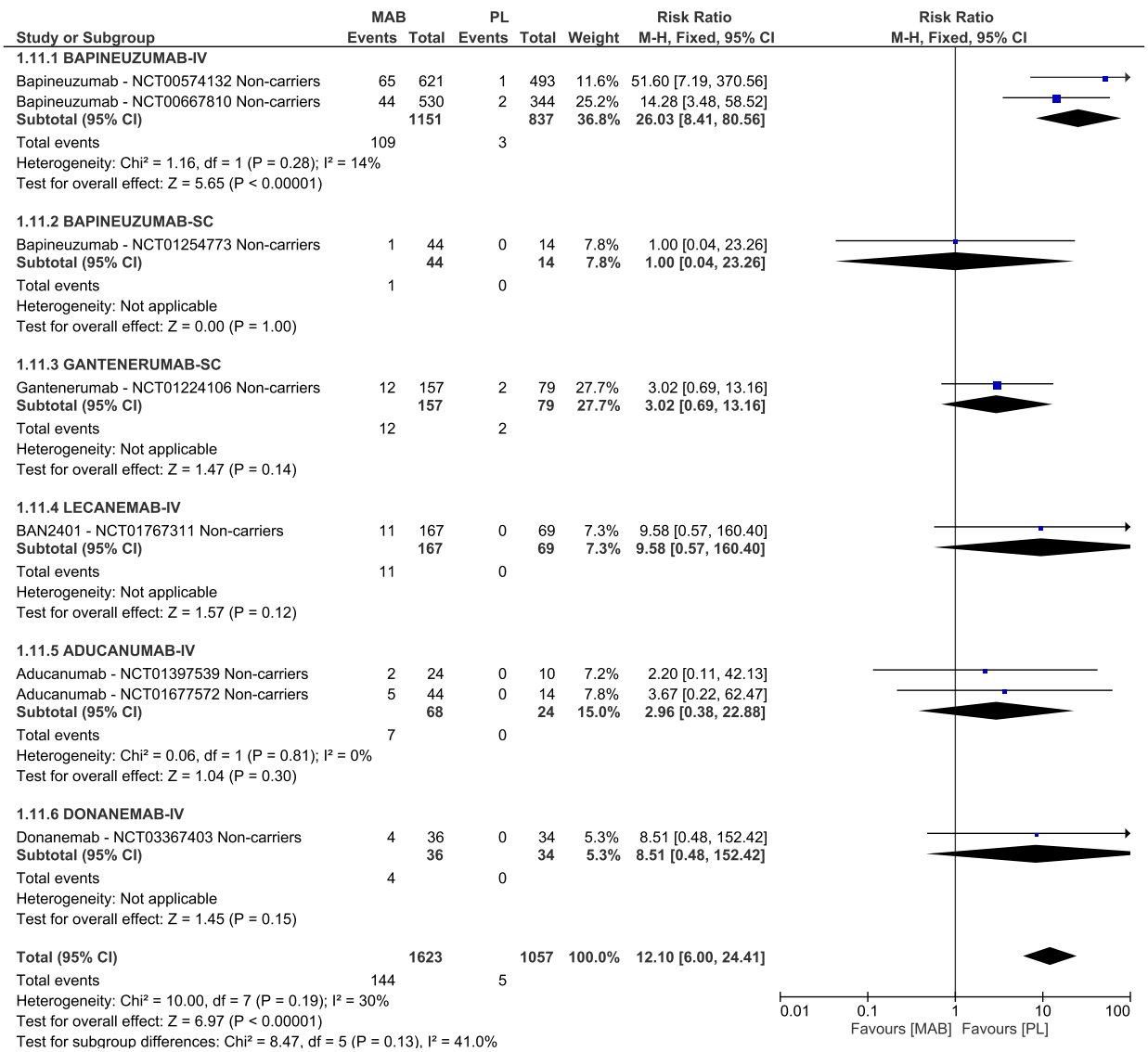


Supplementary Figure 6. Forest plot of the meta-analysis of available data on the frequency of ARIA-E according to *APOE* status. A) Meta-analysis of available data on the frequency of ARIA-E in *APOE*+ subjects. B) Meta-analysis of available data on the frequency of ARIA-E in *APOE*- subjects.

A

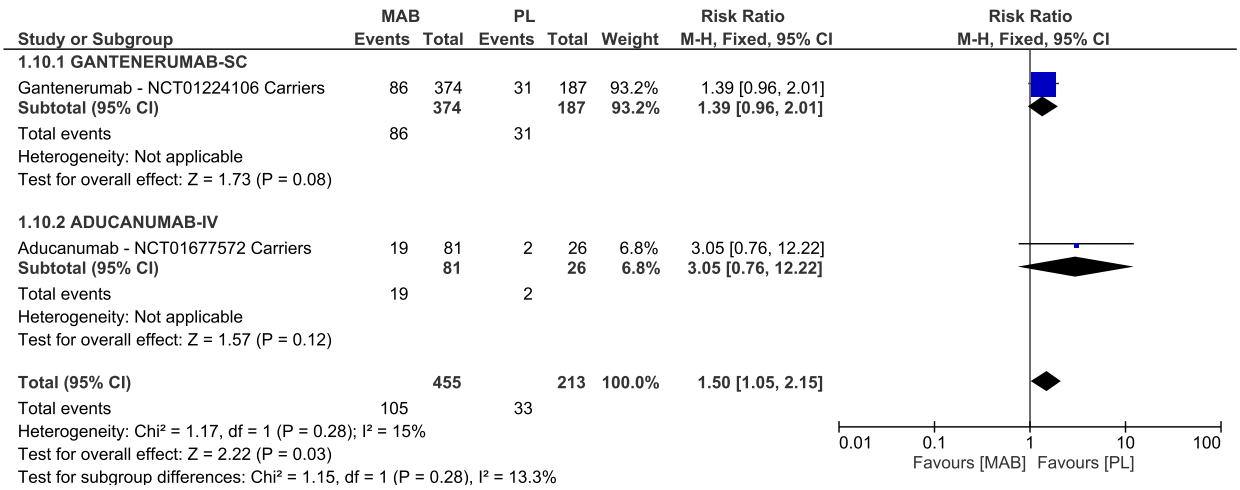


B


MAB
PL
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.11.1 BAPINEUZUMAB-IV
Bapineuzumab - NCT00574132 Non-carriers 65 621 1 493 11.6% 51.60 [7.19, 370.56]
Bapineuzumab - NCT00667810 Non-carriers 44 530 2 344 25.2% 14.28 [3.48, 58.52]
Subtotal (95% CI) 1151 837 36.8% 26.03 [8.41, 80.56]
Total events 109 3
Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 5.65 (P < 0.00001)
1.11.2 BAPINEUZUMAB-SC
Bapineuzumab - NCT01254773 Non-carriers 1 44 0 14 7.8% 1.00 [0.04, 23.26]
Subtotal (95% CI) 44 14 7.8% 1.00 [0.04, 23.26]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
1.11.3 GANTENERUMAB-SC
Gantenerumab - NCT01224106 Non-carriers 12 157 2 79 27.7% 3.02 [0.69, 13.16]
Subtotal (95% CI) 157 79 27.7% 3.02 [0.69, 13.16]
Total events 12 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
1.11.4 LECANEMAB-IV
BAN2401 - NCT01767311 Non-carriers 11 167 0 69 7.3% 9.58 [0.57, 160.40]
Subtotal (95% CI) 167 69 7.3% 9.58 [0.57, 160.40]
Total events 11 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
1.11.5 ADUCANUMAB-IV
Aducanumab - NCT01397539 Non-carriers 2 24 0 10 7.2% 2.20 [0.11, 42.13]
Aducanumab - NCT01677572 Non-carriers 5 44 0 14 7.8% 3.67 [0.22, 62.47]
Subtotal (95% CI) 68 24 15.0% 2.96 [0.38, 22.88]
Total events 7 0
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
1.11.6 DONANEMAB-IV
Donanemab - NCT03367403 Non-carriers 4 36 0 34 5.3% 8.51 [0.48, 152.42]
Subtotal (95% CI) 36 34 5.3% 8.51 [0.48, 152.42]
Total events 4 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
Total (95% CI) 1623 1057 100.0% 12.10 [6.00, 24.41]
Total events 144 5
Heterogeneity: Chi² = 10.00, df = 7 (P = 0.19); I² = 30%
Test for overall effect: Z = 6.97 (P < 0.00001)
Test for subgroup differences: Chi² = 8.47, df = 5 (P = 0.13), I² = 41.0%
0.01 0.1 1 10 100
Favours [MAB] Favours [PL]

Supplementary Figure 7. Forest plot of the meta-analysis of available data on the frequency of ARIA-H according to *APOE* status. A) Meta-analysis of available data on the frequency of ARIA-H in *APOE*+ subjects. B) Meta-analysis of available data on the frequency of ARIA-H in *APOE*- subjects.

A



B