

Efficacy, safety, and injection frequency with novel aflibercept 8 mg in neovascular age-related macular degeneration - a comparison with existing anti-VEGF regimens using a Bayesian network meta-analysis

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Supplementary Material

SUPPLEMENTARY TABLE 1. INCLUSION AND EXCLUSION CRITERIA [POPULATION, INTERVENTION, COMPARATORS, OUTCOMES, AND STUDY DESIGN (PICOS)].....	3
SUPPLEMENTARY TABLE 2. SEARCH STRATEGY – MEDLINE AND EMBASE (VIA OVID INTERFACE) (THE SEARCH WAS RUN ON 24TH OF MAY 2022).....	5
SUPPLEMENTARY TABLE 3. SEARCH STRATEGY – COCHRANE CENTRAL (THE SEARCH WAS RUN ON 26TH OF MAY 2022)	8
SUPPLEMENTARY TABLE 4. ADDITIONAL CRITERIA FOR STUDY INCLUSION IN NMA	10
SUPPLEMENTARY TABLE 5. PRIOR DISTRIBUTIONS FOR MODEL PARAMETERS USED FOR ANALYSIS IN A BAYESIAN FRAMEWORK.	11
SUPPLEMENTARY TABLE 6. INPUT DATA FOR CHANGE FROM BASELINE IN BCVA, BASE CASE ANALYSIS.	12
SUPPLEMENTARY TABLE 7. INPUT DATA FOR PROPORTION OF PATIENTS WHO GAINED/LOST 15 ETDRS LETTERS, BASE CASE ANALYSIS	14
SUPPLEMENTARY TABLE 8. INPUT DATA FOR CRT/CST CHANGE FROM BASELINE, BASE CASE ANALYSIS.....	16
SUPPLEMENTARY TABLE 9. RANKINGS FOR BCVA CHANGE FROM BASELINE – RANDOM EFFECTS MODEL (BASE CASE ANALYSIS).....	18
SUPPLEMENTARY TABLE 10. RANKINGS FOR CRT/CST CHANGE FROM BASELINE – RANDOMS EFFECT MODEL (BASE CASE ANALYSIS).....	19
SUPPLEMENTARY TABLE 11. INPUT DATA FOR PROPORTION OF PATIENTS WITH OCULAR ADVERSE EVENTS, BASE CASE ANALYSIS	20
SUPPLEMENTARY TABLE 12. INPUT DATA FOR PROPORTION OF PATIENTS WITH NON-OCULAR ADVERSE EVENTS, BASE CASE ANALYSIS	21
SUPPLEMENTARY TABLE 13. RANKINGS FOR PROPORTION OF PATIENTS WITH OCULAR ADVERSE EVENTS – RANDOM EFFECTS MODEL, BASE CASE ANALYSIS.....	22
SUPPLEMENTARY TABLE 14. RANKINGS FOR PROPORTION OF PATIENTS WITH NON-OCULAR ADVERSE EVENTS – RANDOM EFFECTS MODEL (BASE CASE ANALYSIS)	23
SUPPLEMENTARY FIGURE 1. PRISMA DIAGRAM OF SEARCH RESULTS IN SCENARIO INCLUDING BEVACIZUMAB AND BROLUCIZUMAB	25
SUPPLEMENTARY FIGURE 2. NETWORK OF EVIDENCE FOR PROPORTION OF PATIENTS WHO GAINED/LOST $\geq$ 15 ETDRS LETTERS (BASE CASE ANALYSIS)	26
SUPPLEMENTARY FIGURE 3. NETWORK OF EVIDENCE FOR CRT/CST CHANGE FROM BASELINE (BASE CASE ANALYSIS)	27
SUPPLEMENTARY FIGURE 4. NETWORK OF EVIDENCE FOR OCULAR ADVERSE EVENTS (BASE CASE ANALYSIS)	28
SUPPLEMENTARY FIGURE 5. NETWORK OF EVIDENCE FOR NON-OCULAR ADVERSE EVENTS (BASE CASE ANALYSIS).....	29
SUPPLEMENTARY FIGURE 6. FOREST PLOT FOR ODDS RATIO FOR COMPARISON AFL 8 MG VS COMPARATORS REGARDING PROPORTION OF PATIENTS WITH NON-OCULAR ADVERSE EVENTS, BASE CASE ANALYSIS	30
SUPPLEMENTARY FIGURE 7. ANALYSIS OF HETEROGENEITY PER COMPARISON – RESULTS FOR BCVA MEAN CHANGE FROM BASELINE (BASE CASE ANALYSIS)	31
SUPPLEMENTARY FIGURE 8. ANALYSIS OF HETEROGENEITY PER COMPARISON – CRT/CST CHANGE FROM BASELINE (BASE CASE ANALYSIS)	32
SUPPLEMENTARY FIGURE 9. ANALYSIS OF HETEROGENEITY PER COMPARISON – OCULAR ADVERSE EVENTS (BASE CASE ANALYSIS)	33
SUPPLEMENTARY FIGURE 10. ANALYSIS OF HETEROGENEITY PER COMPARISON – NON-OCULAR ADVERSE EVENTS.....	33
SUPPLEMENTARY FIGURE 11. NETWORK OF EVIDENCE IN THE SCENARIO ANALYSIS INCLUDING BEVACIZUMAB AND BROLUCIZUMAB.....	34
SUPPLEMENTARY FIGURE 12. FOREST PLOT FOR COMPARISON AFL 8 MG VS COMPARATORS REGARDING BCVA CHANGE FROM BASELINE, SCENARIO ANALYSIS INCLUDING BEVACIZUMAB AND BROLUCIZUMAB.....	35
SUPPLEMENTARY FIGURE 13. FOREST PLOT FOR COMPARISON AFL 8 MG VS COMPARATORS REGARDING PROPORTION OF PATIENTS WHO GAINED OR LOST $\geq$ 15 ETDRS LETTERS, SCENARIO ANALYSIS INCLUDING BEVACIZUMAB AND BROLUCIZUMAB	37
SUPPLEMENTARY FIGURE 14. FOREST PLOT FOR ODDS RATIO FOR COMPARISON AFL 8 MG VS COMPARATORS REGARDING PROPORTION OF PATIENTS WITH OCULAR ADVERSE EVENTS, SCENARIO ANALYSIS INCLUDING BEVACIZUMAB AND BROLUCIZUMAB	41

Supplementary Table 1. Inclusion and exclusion criteria [Population, Intervention, Comparators, Outcomes, and Study Design (PICOS)] of SLR

PICOS	Inclusion	Exclusion
<u>P</u> opulation	Treatment-naïve patients with nAMD [#]	Other disease conditions
<u>I</u> ntervention* ^	• Aflibercept (2 mg, 8 mg) • Bevacizumab • Ranibizumab • Ranibizumab PDS • Brolucizumab • Faricimab	Other interventions
<u>C</u> omparators	No restrictions	
<u>O</u> utcomes	• Mean change in BCVA from baseline • Mean change in CRT from baseline • Mean change in CST from baseline • Mean change in lesion size • % of patients gaining or losing 15 letters^{^^} • % of patients gaining or losing 10 letters^{^^^} • % of patients with a dry retina or no fluid (IRF/SRF) • % of patients treated in Q12 intervals • % of patients treated in Q16 intervals • Treatment discontinuation rates • Treatment burden measure as mean injection frequency <u>Safety:</u> • Total SAE (overall) • Total ocular AE (overall) • Total non-ocular AE (overall) • Total ocular SAE (overall) • Ocular SAE: • Intraocular inflammation • Endophthalmitis • IOP • Retinal tear • Cataract	Other outcomes
<u>S</u> tudy design	RCTs**	Studies without randomization
Additional restrictions	Only studies reporting data on 40 or more patients/eyes were included ^{##} Only manuscripts reporting results at timepoint of approximate 1-year were included	

Additional restrictions after full text review	• Pilot studies, phase I and phase I/II studies were excluded • Only English language • Only manuscripts (abstracts and clinical trials records were excluded) • Pooled analysis (except the articles that presented the results of pooled analysis for trials without available separate data) were excluded • Manuscripts reporting data only for not relevant subgroups^{&} were excluded
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Abbreviations: BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; DRSS, Diabetic Retinopathy Severity Scale; IOP, intraocular pressure; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; RCT, randomised controlled trial; SLR, Systematic literature review; SRF, subretinal fluid; VEGF, vascular endothelial growth factor

[#]Only references presenting data for overall population and/or relevant subgroups (age, baseline BCVA, baseline CNV area/CNV leakage area, CNV type, baseline CRT, retinal fluid presence, Asian population) were included

^{###}Exclusion of small studies aims to reduce publication bias and uncertainty associated with small sample sizes

^{*}Only anti-VEGF monotherapies

^{**} Pooled results from pivotal studies to be included and extracted, only if data per each study not available. Pooled results from pivotal studies for subgroups according to baseline CRT will be extracted. Pooled data for different drugs or drug doses or treatment regimens were not included/extracted

[&] Relevant subgroups: age, baseline BCVA, baseline CRT, CNV type, baseline CNV area/CNV leakage area, retinal fluid presence, Asian patients,

[^] any regimen (including pro re nata and treat-and-extend) was included

^{^^} which corresponds to 3 lines

^{^^^} which corresponds to 2 lines

Supplementary Table 2. Search strategy – MEDLINE and EMBASE (via OVID interface) (The search was run on 24th of May 2022)

#	PICOS	Searches	Results
1	Population	macular degeneration/	21330
2		Age related macular degeneration/	29692
3		macular degeneration\$.mp.	66818
4		((neovascular or neo-vascular or wet) adj2 (age-related macular degeneration* or macular dystroph* or maculopath* or age related maculopath*)).mp.	10479
5		(nAMD or AMD or wAMD).mp.	41227
6		1 or 2 or 3 or 4 or 5	78568
7		exp Macular edema/ or diabetic macular edema/	26973
8		(diabetic macula\$ \$edema or diabetic retina macula\$ \$edema).mp.	13275
9		(DME or DMO).mp.	12230
10		7 or 8 or 9	35095
11		6 or 10	110856
12	Intervention	(anti-VEGF or anti VEGF).mp.	21546
13		(anti-vascular endothelial growth factor or anti vascular endothelial growth factor).mp.	10086
14		Aflibercept/	7748
15		(Aflibercept or VEGF Trap - regeneron or VEGF Trap-Eye or VEGF-Trap or eylea or AVE-0005 or AVE0005 or AVE-005 or AVE005 or Bay 86-5321 or BAY-865321 or Bay86-5321).mp.	11346
16		Ranibizumab/	15754
17		(Ranibizumab or (RhuFab adj1 V2) or Lucentis or RG-3645 or byooviz or susvimo).mp.	17701
18		Bevacizumab/	79981
19		(Bevacizumab or Avastin or Ainex or Altuzan or Mvasi or Bryxta or Zirabev or Bevax or rhuMAb-VEGF or ABP-215 or R-435 or Abevmy or Alymsys or Aybintio or Bambevi or Equidacent or Onbevzi or Oyavas or Zirabev).mp.	90113
20		(Bevacizumab adj3 (awwb or beta or bvzr)).mp.	65
21		(abp215 or ainex or altuzan or ankeda or ask b1202 or askb1202 or avastin or aybintio or bat 1706 or bat1706 or "bcd 021" or bcd021 or bevz 92 or bevz92 or bi 695502 or bi695502 or bryxta or byvasda or cbt 124 or cbt124 or chs 5217 or chs5217 or cizumab or ct p16 or ctp16 or equidacent or fkb 238 or fkb238 or gb 222 or gb222 or hd 204 or hd204 or "hlx 04" or hlx04 or ibi 305 or ibi305 or "jy 028" or jy028 or krabeva or kyomarc or "ly 01008" or ly01008 or "mb 02" or mb02 or mil 60 or mil60 or mvasi or myl 14020 or myl 1402o or myl14020 or myl1402o or nsc 704865 or nsc704865 or onbevzi or ons 1045 or ons 5010 or ons1045 or ons5010 or "pf 06439535" or pf 6439535 or pf06439535 or pf6439535 or pusintin or ql 1101 or ql1101 or r435 or rg 435 or rg435 or ro 4876646 or ro4876646 or "rph	12832

		001" or rph001 or sb 8 or sb8 or sct 510 or sct510 or stc 103 or stc103 or "tab 008" or tab008 or tot 102 or tot102 or "trs 003" or trs003 or tx 16 or tx16 or versavo or zirabev or zrc 113 or zrc113).mp.	
22		Faricimab.mp.	177
23		(RG 7716 or RG7716 or RO6867461 or RO-6867461 or Vabysmo).mp.	48
24		Dexamethasone/	225144
25		(dexamethasone or Ozurdex).mp.	264393
26		((intravitreal or intravitreal or IVT) adj2 (corticosteroid* or steroid*)).mp.	1090
27		brovacizumab/	356
28		(RTH258 or RTH-258 or ESBA1008 or ESBA-1008 or Brovacizumab or brovacizumab-dbl).mp.	570
29		or/12-28	376843
30	Study design	Randomized controlled trials as Topic/	318608
31		Randomized controlled trial/	1278269
32		Random allocation/	196831
33		Double blind method/	342456
34		Single blind method/	76091
35		clinical trial/	1569784
36		clinical trial, phase i.pt.	23841
37		clinical trial, phase ii.pt.	38017
38		clinical trial, phase iii.pt.	20552
39		clinical trial, phase iv.pt.	2330
40		controlled clinical trial.pt.	94878
41		randomized controlled trial.pt.	568807
42		multicenter study.pt.	321491
43		clinical trial.pt.	535118
44		exp Clinical Trials as topic/	765125
45		(clinical adj trial\$.tw.	1059986
46		((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.	451879
47		PLACEBOS/	360688
48		placebo\$.tw.	578690
49		randomly allocated.tw.	74901
50		randomization/	200647
51		single blind procedure/	46163
52		double blind procedure/	195047
53		crossover procedure/	70423
54		placebo/	380496
55		randomi?ed controlled trial\$.tw.	506465
56		rct.tw.	74280
57		random allocation.tw.	4212
58		Allocated randomly.tw.	5210

59		(allocated adj2 random\$.tw.	82781
60		Single blind\$.tw.	50202
61		Double blind\$.tw.	393525
62		((treble or triple) adj blind\$.tw.	2812
63		Prospective study/	1394569
64		or/30-63	5351346
65		case report.tw.	849440
66		case study/ or letter/ or historical article/ or editorial/ or note/ or Abstract report/	7033961
67		review/ or ("literature" adj2 "review").ti,ab.	5931105
68		exp "meta analysis"/ or (("systematic" adj2 "review") or "meta-analysis" or "meta-analysis").ti,ab.	836127
69		or/65-68	13671814
70		64 not 69	4233368
71	P+I+S	11 and 29 and 70	6306
72	Time limit	limit 71 to yr="1860 - 2015"	2720
73		remove duplicates from 72	2092
74		limit 71 to yr="2016 -Current"	3580
75		remove duplicates from 74	2678
76	Final result	73 or 75	4770

Supplementary Table 3. Search strategy – Cochrane CENTRAL (The search was run on 26th of May 2022)

#	PICOS	Searches	Results
1	Population	MeSH descriptor: [Macular Degeneration] explode all trees	2760
2		(macular degeneration*):ti,ab,kw	3566
3		((neovascular or neo-vascular or wet) NEAR/2 (age-related macular degeneration* or macular dystroph* or maculopath* or age related maculopath*)):ti,ab,kw	1330
4		(nAMD or AMD or wAMD):ti,ab,kw	2610
5		#1 or #2 or #3 or #4	5319
6		MeSH descriptor: [Macular Edema] explode all trees	1253
7		(diabetic macula\$ \$edema or diabetic retina macula\$ \$edema):ti,ab,kw	449
8		(DME or DMO):ti,ab,kw	1930
9		#6 or #7 or #8	2950
10		#5 or #9	6962
11	Intervention	(anti-VEGF or anti VEGF):ti,ab,kw	1994
12		(anti-vascular endothelial growth factor or anti vascular endothelial growth factor):ti,ab,kw	1177
13		(Aflibercept or VEGF Trap regeneron or VEGF Trap Eye or VEGF Trap or eylea or AVE 0005 or AVE0005 or AVE 005 or AVE005 or Bay 86 5321 or BAY-865321 or Bay86 5321):ti,ab,kw	1097
14		MeSH descriptor: [Ranibizumab] explode all trees	947
15		(Ranibizumab or (Rhu Fab NEAR/1 V2) or Lucentis or RG-3645 or byooviz or susvimo):ti,ab,kw	2164
16		MeSH descriptor: [Bevacizumab] explode all trees	2192
17		(Bevacizumab or Avastin or Ainex or Altuzan or Mvasi or Bryxta or Zirabev or Bevax or rhuMab-VEGF or ABP-215 or R-435 or Abevmy or Alymsys or Aybintio or Bambevi or Equidacent or Onbevzi or Oyavas or Zirabev):ti,ab,kw	6898
18		(Bevacizumab NEAR/3 (awwb or beta or bvzr)):ti,ab,kw	4
19		(abp215 or ainex or altuzan or ankeda or ask b1202 or askb1202 or avastin or aybintio or bat 1706 or bat1706 or "bcd 021" or bcd021 or bevz 92 or bevz92 or bi 695502 or bi695502 or bryxta or byvasda or cbt 124 or cbt124 or chs 5217 or chs5217 or cizumab or ct p16 or ctp16 or equidacent or fkb 238 or fkb238 or gb 222 or gb222 or hd 204 or hd204 or "hlx 04" or hlx04 or ibi 305 or ibi305 or "jy 028" or jy028 or krabeva or kyomarc or "ly 01008" or ly01008 or "mb 02" or mb02 or mil 60 or mil60 or mvasi or myl 14020 or myl 1402o or myl14020 or myl1402o or nsc 704865 or nsc704865 or onbevzi or ons 1045 or ons 5010 or ons1045 or ons5010 or "pf 06439535" or pf 6439535 or pf06439535 or pf6439535 or pusintin or ql 1101 or ql1101 or r435 or rg 435 or rg435 or ro 4876646 or ro4876646 or "rph 001" or rph001 or sb 8 or sb8 or sct 510 or sct510 or stc 103 or stc103 or "tab 008" or tab008 or tot 102 or tot102 or "trs 003" or trs003 or tx 16 or tx16 or versavo or zirabev or zrc 113 or zrc113):ti,ab,kw	2591

20		Faricimab:ti,ab,kw	34
21		(RG 7716 or RG7716 or RO6867461 or RO-6867461 or Vabysmo):ti,ab,kw	20
22		MeSH descriptor: [Dexamethasone] explode all trees	5022
23		(dexamethasone or Ozurdex):ti,ab,kw	13440
24		((intravitreal or intravitreous or IVT) NEAR/2 (corticosteroid* or steroid*)):ti,ab,kw	80
25		(RTH258 or RTH-258 or ESBA1008 or ESBA-1008 or Brolucizumab or brolucizumab-dbl):ti,ab,kw	85
26		#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #25	25082
27	P + I	#10 and #26 in Trials	2718

Supplementary Table 4. Additional criteria for study inclusion in NMA

Criterium	Inclusion
Intervention / Comparator	Monotherapy with following anti-VEGF agents: • Aflibercept 8 mg administered at Q12 and Q16 intervals • Aflibercept (2 mg) in posology: • Fixed interval • PRN • T&E • Ranibizumab (0.5 mg) in posology: • Fixed interval • PRN • T&E • Faricimab (6 mg) in posology: • Fixed interval
Outcomes	• Mean change in BCVA from baseline • Mean change in CRT/CST from baseline • % of patients gaining/losing 15 letters • % of patients gaining/losing 10 letters • Treatment burden measure as mean injection frequency • Total ocular AE (overall) • Total non-ocular AE (overall)

Abbreviations: AE – adverse event; BCVA – best corrected visual acuity; CRT – central retinal thickness; CST – central subfield thickness; PRN – Pro re nata; QX – every X weeks; T&E – Treat and Extend; VEGF – Vascular Endothelial Growth Factor

Supplementary Table 5. Prior distributions for model parameters used for analysis in a Bayesian framework.

Model parameters	Prior distribution
Nuisance parameters	$\mu_{jb} \sim \text{norm}(0, 10\ 000)$
Treatment effect parameters	$d_{Ak} \sim \text{norm}(0, 10\ 000)$
Heterogeneity parameter (between-study SD)	$\sigma \sim \text{uniform}(0, 5)$

Supplementary Table 6. Input data for change from baseline in BCVA, base case analysis.

Study	Treatment arm	N	Mean	SE	Baseline BCVA	Analysis		
						B-C	Scenario 2	Scenario 3
PULSAR	AFL 8 mg Q12	335	6.06	0.77	59.6	ü	ü	ü
	AFL 8 mg Q16	338	5.89	0.72				
	AFL Q8	336	7.03	0.74				
ALTAIR	AFL T&E Q2	123	9	1.3	55	ü	ü	ü
	AFL T&E Q4	123	8.4	1.22				
ARIES	AFL T&E Q2	106	7.8	0.91	60.4	ü	ü	ü
	AFL Q8	104	10.2	0.91				
CANTREAT	RBZ Q4	293	6	0.7	59.2	ü	ü	ü
	RBZ T&E	287	8.4	0.7				
CATT	RBZ Q4	284	8.5	0.84	60.8	ü	ü	ü
	RBZ PRNnL	285	6.8	0.78				
DRAGON	RBZ PRN	166	9.6	1.01	53.6	ü	ü	ü
	RBZ Q4	165	12.3	0.89				
Haga 2018^a	AFL Q8	20	13.1	3.38	59.9	ü	ü	ü
	AFL T&E	21	15.9	2.93				
HARBOR	RBZ Q4	275	10.1	0.8	54.4	ü	ü	ü
	RBZ PRN	275	8.2	0.8				
In-EYE	RBZ Q8	103	7	1.53	56.9	ü	ü	ü
	RBZ T&E	99	6.7	1.51				
	RBZ PRN	104	7.3	1.53				
IVAN	RBZ PRN	143	5.1	0.87	61.8	ü	ü	ü
	RBZ Q4	140	7.8	1.2				
LUCERNE	FAR	331	6.6	0.64	58.8	ü	ü	ü
	Q8/Q12/Q16							
	AFL Q8	327	6.6	0.64				
RABIMO^b	RBZ PRN	20	6.5	2.65	60.5	ü	ü	ü
	RBZ Q8	20	8.5	2.32				
RIVAL	AFL T&E	121	5.2	1.17	65.1		ü	
	RBZ T&E	127	6.9	1.09				
STAIRWAY	RBZ Q4	16	10.22	2.84	58.4	ü	ü	ü
	FAR Q12/Q16	31	10.99	2.07				
	FAR Q12	24	9.53	2.36				

TENAYA	FAR	334	5.8	0.64	61.4	ü	ü	ü
	Q8/Q12/Q16							
	AFL Q8	337	5.1	0.64				
TREND	RBZ T&E	320	6.2	0.7	60.1	ü	ü	ü
	RBZ Q4	323	8.1	0.7				
TREX-AMD	RBZ T&E	28	10.5	2	60.5	ü	ü	ü
	RBZ Q4	20	9.2	1.4				
VIEW 1	AFL Q4	304	10.9	0.79	55	ü	ü	ü
	AFL Q8	301	7.9	0.86				
	RBZ Q4	304	8.1	0.88				
VIEW 2	AFL Q4	309	7.6	0.72	52.7	ü	ü	ü
	AFL Q8	306	8.9	0.82				
	RBZ Q4	291	9.4	0.79				
Mori 2017	AFL Q8	28	7.1	1.44	66.6	ü	ü	ü
	AFL PRN	30	3.4	1.04				
ARTIS	RBZ PRNnL	45	49	2.41	50.6	ü	ü	ü
	RBZ PRN	49	52	1.99				

a - Results in LogMAR scale, SE calculated based on proportionality assumption

b- Medians, SE Calculated from IQR

Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; CRT – central retinal thickness; CST – central subfield thickness; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; SE – standard error; T&E – Treat and Extend.

Supplementary Table 7. Input data for proportion of patients who gained/lost 15 ETDRS letters, base case analysis

Study	Arm	N	Gain	Loss	Baseline
			≥15	≥15	BCVA
ALTAIR	AFL T&E Q2	123	40	4	55.0
	AFL T&E Q4	123	38	5	
ARIES	AFL Q8	104	29	0	60.4
	AFL T&E Q2	106	21	0	
ARTIS	RBZ PRNnL	45	13	3	50.6
	RBZ PRN	49	22	3	
CANTREAT	RBZ Q4	258	52	12 ^a	59.2
	RBZ T&E	268	68	8 ^b	
CATT	RBZ Q4	284	97	16	60.8
	RBZ PRNnL	285	71	13	
DRAGON	RBZ PRN	166	52	6	53.6
	RBZ Q4	167	70	3	
HARBOR	RBZ PRN	275	83	15	54.4
	RBZ Q4	275	95	6	
In-EYE	RBZ T&E	99	24	8	56.9
	RBZ Q8	103	25	6	
	RBZ PRN	104	33	4	
IVAN	RBZ Q4	140	36	6	61.8
	RBZ PRN	143	29	6	
LUCERNE	AFL Q8	291	65	8	58.8
	FAR	302	61	13	
	Q8/Q12/Q16				
PULSAR	AFL 8 mg Q12	334	69	18	59.6
	AFL Q8	335	74	14	
	AFL 8 mg Q16	337	73	18	
RABIMO	RBZ PRN	20	8	1	60.5
	RBZ Q8	20	6	2	
RIVAL	AFL T&E	121	25	6	65.1
	RBZ T&E	127	28	4	
STAIRWAY	RBZ Q4	16	6	0	58.4
	FAR Q12	21	7	0	
	FAR	28	13	1	
	Q12/Q16				

TRENCH-AMD	RBZ Q4	20	3	0	60.5
	RBZ T&E	40	10	1	
TENAYA	FAR	292	58	13	61.4
	Q8/Q12/Q16				
	AFL Q8	300	47	18	
TREND	RBZ T&E	291	75	18	60.1
	RBZ Q4	295	77	11	
VIEW 1	AFL Q8	301	92	17	55.0
	AFL 2 Q4	304	114	15	
	RBZ Q4	304	94	19	
VIEW 2	RBZ Q4	291	99	15	52.7
	AFL Q8	306	96	14	
	AFL 2 Q4	309	91	17	

a - Calculated from proportion on population n=249

b- Calculated from proportion on population n=264

Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Table 8. Input data for CRT/CST change from baseline, base case analysis

Study	Arm	Outcome	N	Mean	SE	Mean (% change)	SE (% change)	Baseline BCVA
ALTAIR	AFL T&E Q2	CRT	123	-134.4	14.18	-34.80	3.67	55
	AFL T&E Q4		123	-126.1	10.71	-34.05	2.89	
ARIES	AFL Q8	CRT	104	-167.1	11.48	-37.27	2.56	60.4
	AFL T&E Q2		106	-164.9	11.39	-37.16	2.57	
ARTIS	RBZ PRNnL	CRT	45	-159.3	30.44	-34.04	6.50	50.6
	RBZ PRN		49	-120.5	18.16	-28.15	4.24	
CATT	RBZ Q4	CRT	284	-196	10.44	-78.09	4.16	60.8
	RBZ PRNnL		285	-168	11.02	-68.02	4.46	
DRAGON	RBZ Q4	CST	166	-155.7	13.46	-33.21	2.87	53.6
	RBZ PRN		167	-166.5	11.29	-34.08	2.31	
Haga 2018	AFL Q8	CRT	20	-157	20.12	-44.48	5.70	59.9
	AFL T&E		21	-161	29.02	-43.05	7.76	
HARBOR	RBZ Q4	CRT	275	-172	9.07	-49.38	2.60	54.4
	RBZ PRN		275	-161.2	9.18	-46.35	2.64	
In-EYE	RBZ PRN	CST	76	-119.6	12.6	-32.15	3.39	56.9
	RBZ Q8		91	-110.7	10.1	-30.75	2.81	
	RBZ T&E		71	-132.4	14.16	-34.98	3.74	
LUCERNE	AFL Q8	CST	327	-130.8	3.06	-36.43	0.85	58.8
	FAR Q8/Q12/Q16		331	-137.1	3.04	-38.83	0.86	
Mori 2017	AFL PRN	CRT	30	-85.4	41.76 ^a	-30.68	15.00	66.6
	AFL Q8		28	-114.9	56.00 ^a	-36.49	17.78	
PULSAR	AFL Q8	CST	336	-136.25	4.24	-37.12	1.15	59.6
	AFL 8 mg Q12		335	-147.37	4.01	-39.80	1.08	

	AFL 8 mg Q16		338	-146.76	3.76	-39.59	1.01	
RABIMO^b	RBZ PRN	CRT	20	-198	29.91	-46.26	6.99	60.5
	RBZ Q8		20	-123	21.54	-33.24	5.82	
RIVAL	AFL T&E	CST	120	-172	13.69	-35.61	2.83	65.1
	RBZ T&E		127	-147	11.36	-31.41	2.43	
STAIRWAY	FAR Q12/Q16	CST	28	-122.5	9.56	-32.05	2.50	58.4
	FAR Q12		21	-138.5	10.81	-33.14	2.59	
	RBZ Q4		16	-129.9	13.15	-29.32	2.97	
TENAYA	AFL Q8	CST	337	-129.4	2.98	-36.34	0.84	61.4
	FAR Q8/Q12/Q16		334	-136.8	2.96	-37.95	0.82	
TREND	RBZ Q4	CST	287	-173.3	9.1	-34.82	1.83	60.1
	RBZ T&E		291	-169.2	9.54	-33.57	1.89	
TREX-AMD	RBZ Q4	CRT	20	-246	43	-46.15	8.07	60.5
	RBZ T&E		40	-173	31	-35.38	6.34	
VIEW 1	AFL 2 Q4	CRT	304	-116.5	5.64	-37.15	1.80	55
	AFL Q8		301	-128.5	6.25	-39.61	1.93	
	RBZ Q4		304	-116.8	6.25	-37.04	1.98	
VIEW 2	AFL 2 Q4	CRT	309	-156.8	6.99	-46.86	2.09	52.7
	AFL Q8		306	-149.2	6.84	-43.55	2.00	
	RBZ Q4		291	-138.5	7.16	-42.50	2.20	

^a- SE calculated from timepoint data, correlation coefficient = 0.5 assumed; ^b – Percentage change reported, absolute change calculated from percentage change and baseline value

Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; CRT – central retinal thickness; CST – central subfield thickness; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; SE – standard error; T&E – Treat and Extend

Supplementary Table 9. Rankings for BCVA change from baseline – random effects model (base case analysis)

Treatment	Probability of being best [%]	SUCRA [%]	Probability for AFL 8 mg Q12 being better than comparators [%]	Probability for AFL 8 mg Q16 being better than comparators [%]
AFL 8 mg Q12	4	46	-	46
AFL 8 mg Q16	4	43	54	-
AFL PRN	1	18	80	79
AFL Q4	11	72	24	22
AFL Q8	1	60	31	28
AFL T&E Q2	2	38	58	56
AFL T&E Q4	6	35	63	61
FAR Q12	14	51	46	44
FAR Q12/Q16	29	65	34	32
FAR Q8/Q12/Q16	9	65	29	26
RBZ PRN	0	37	56	53
RBZ PRNnL	1	31	63	61
RBZ Q4	2	67	29	27
RBZ Q8	10	56	40	39
RBZ T&E	6	66	31	29

Abbreviations: AFL – aflibercept; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; SUCRA - Surface Under the Cumulative Ranking Curve; T&E – Treat and Extend.

Supplementary Table 10. Rankings for CRT/CST change from baseline – randoms effect model (base case analysis)

Treatment	Probability of being best [%]	SUCRA [%]	Probability for AFL 8 mg Q12 being better than comparators [%]	Probability for AFL 8 mg Q16 being better than comparators [%]
AFL 8 mg Q12	16	84	-	45
AFL 8 mg Q16	13	83	55	-
AFL PRN	33	53	61	60
AFL Q4	0	54	94	93
AFL Q8	0	60	96	95
AFL T&E Q2	8	64	73	71
AFL T&E Q4	12	56	72	72
FAR Q12	12	63	71	68
FAR Q12/Q16	1	36	92	91
FAR Q8/Q12/Q16	4	77	74	70
RBZ PRN	0	21	100	100
RBZ PRNnL	0	20	99	99
RBZ Q4	0	39	99	99
RBZ Q8	0	7	100	100
RBZ T&E	0	34	97	97

Abbreviations: AFL – aflibercept; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; SUCRA – Surface Under the Cumulative Ranking Curve; T&E – Treat and Extend

Supplementary Table 11. Input data for proportion of patients with ocular adverse events, base case analysis

Study	Arm	N	n	Proportion [%]	Baseline BCVA
PULSAR	AFL 8 mg Q12	335	159	47	59.6
	AFL 8 mg Q16	338	157	46	
	AFL Q8	336	160	48	
CATT	RBZ Q4	301	248	82	60.8
	RBZ PRNnL	298	229	77	
HARBOR	RBZ Q4	274	176	64	54.4
	RBZ PRN	275	171	62	
In-EYE	RBZ Q8	101	48	48	56.9
	RBZ T&E	98	34	35	
	RBZ PRN	104	50	48	
LUCERNE	FAR Q8/Q12/Q16	331	133	40	58.8
	AFL Q8	326	118	36	
RABIMO	RBZ PRN	20	4	20	60.5
	RBZ Q8	20	11	55	
STAIRWAY	RBZ Q4	16	8	50	58.4
	FAR Q12/Q16	31	11	35	
	FAR Q12	24	9	38	
TENAYA	FAR Q8/Q12/Q16	333	121	36	61.4
	AFL Q8	336	128	38	
TREND	RBZ T&E	323	116	36	60.1
	RBZ Q4	326	120	37	
TREX-AMD	RBZ T&E	40	10	25	60.5
	RBZ Q4	20	2	10	
VIEW 1	AFL Q8	303	238	79	55.0
	AFL 2 Q4	304	228	75	
	RBZ Q4	304	246	81	
VIEW 2	AFL Q8	307	198	64	52.7
	AFL 2 Q4	309	191	62	
	RBZ Q4	291	187	64	

Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; FAR – faricimab; HD – high dose (8 mg); N - number of patients; n - number of patients with events; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Table 12. Input data for proportion of patients with non-ocular adverse events, base case analysis

Study	Arm	N	n	Proportion [%]	Baseline BCVA
PULSAR	AFL 8 mg Q12	335	175	52	59.6
	AFL 8 mg Q16	338	182	54	
	AFL Q8	336	178	53	
DRAGON	RBZ PRN	166	82	49	53.6
	RBZ Q4	166	98	59	
LUCERNE	FAR Q8/Q12/Q16	331	172	52	58.8
	AFL Q8	326	189	58	
RABIMO	RBZ PRN	20	10	50	60.5
	RBZ Q8	20	13	65	
STAIRWAY	RBZ Q4	16	9	56	58.4
	FAR Q12/Q16	31	20	65	
	FAR Q12	24	14	58	
TENAYA	FAR Q8/Q12/Q16	333	174	52	61.4
	AFL Q8	336	174	52	
TREND	RBZ T&E	323	150	46	60.1
	RBZ Q4	326	161	49	
VIEW 1	AFL Q8	303	223	74	55.0
	AFL Q4	304	220	72	
	RBZ Q4	304	234	77	
VIEW 2	AFL Q8	307	213	69	52.7
	AFL Q4	309	231	75	
	RBZ Q4	291	181	62	

Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; FAR – faricimab; HD – high dose (8 mg); N - number of patients; n - number of patients with events; PRN – Pro re nata; QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Table 13. Rankings for proportion of patients with ocular adverse events – random effects model, base case analysis

Treatment	Probability of being best [%]	SUCRA [%]	Probability for AFL 8 mg Q12 being better than comparators [%]	Probability for AFL 8 mg Q16 being better than comparators [%]
AFL 8 mg Q12	4	47	-	57
AFL 8 mg Q16	5	52	43	-
AFL Q4	4	65	32	37
AFL Q8	0	47	50	57
FAR Q12	28	69	30	31
FAR Q12/Q16	35	74	25	27
FAR Q8/Q12/Q16	2	42	56	61
RBZ PRN	1	34	63	68
RBZ PRNnL	18	72	26	29
RBZ Q4	0	39	58	63
RBZ Q8	0	1	86	88
RBZ T&E	2	47	52	56

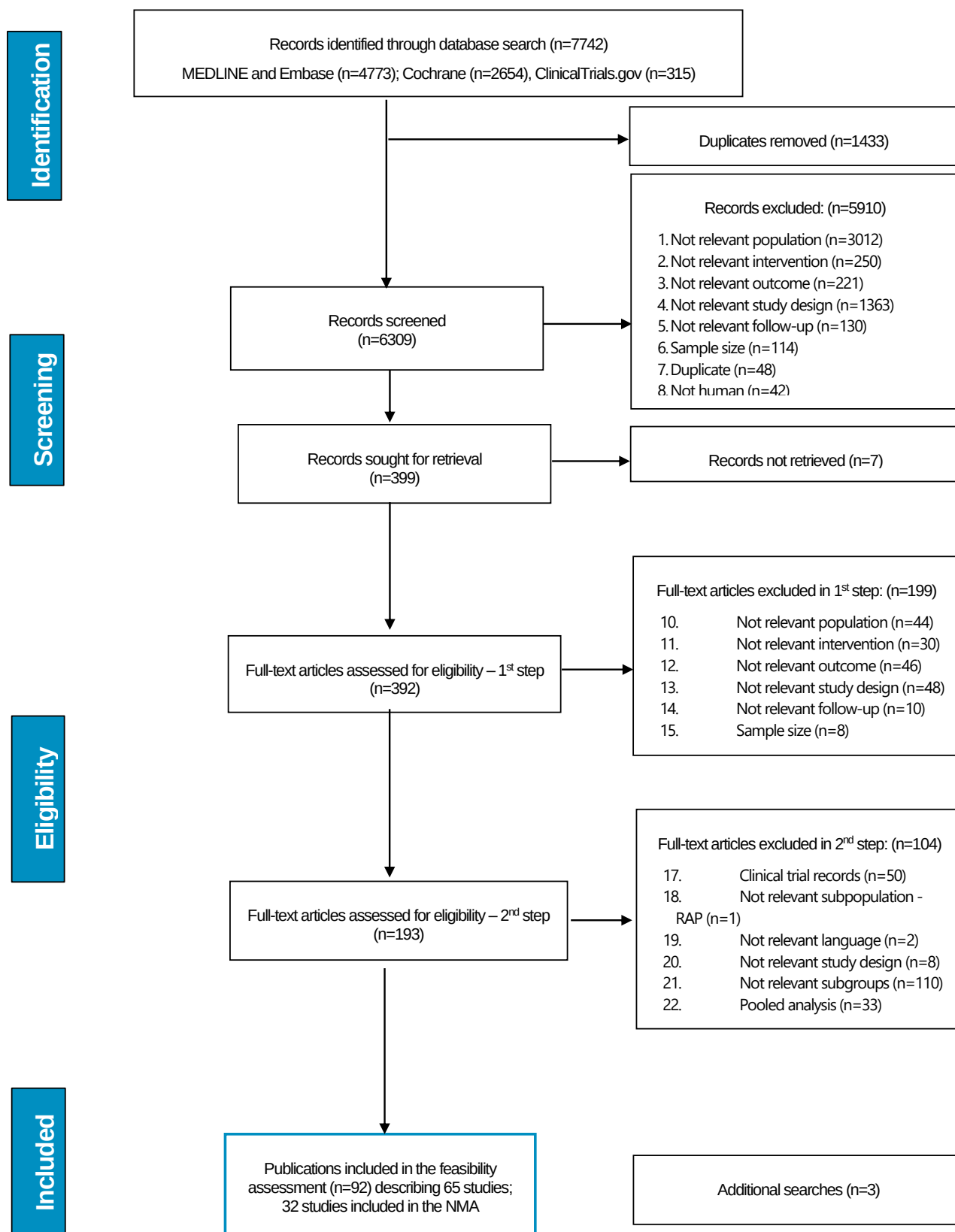
Abbreviations: AFL – aflibercept; FAR – faricimab; HD – high dose (8 mg); PRN – Pro re nata; PRNnL – Pro re nata no loading phase; QX – every X weeks; RBZ – ranibizumab; SUCRA - Surface Under the Cumulative Ranking Curve; T&E – Treat and Extend

Supplementary Table 14. Rankings for proportion of patients with non-ocular adverse events – random effects model (base case analysis)

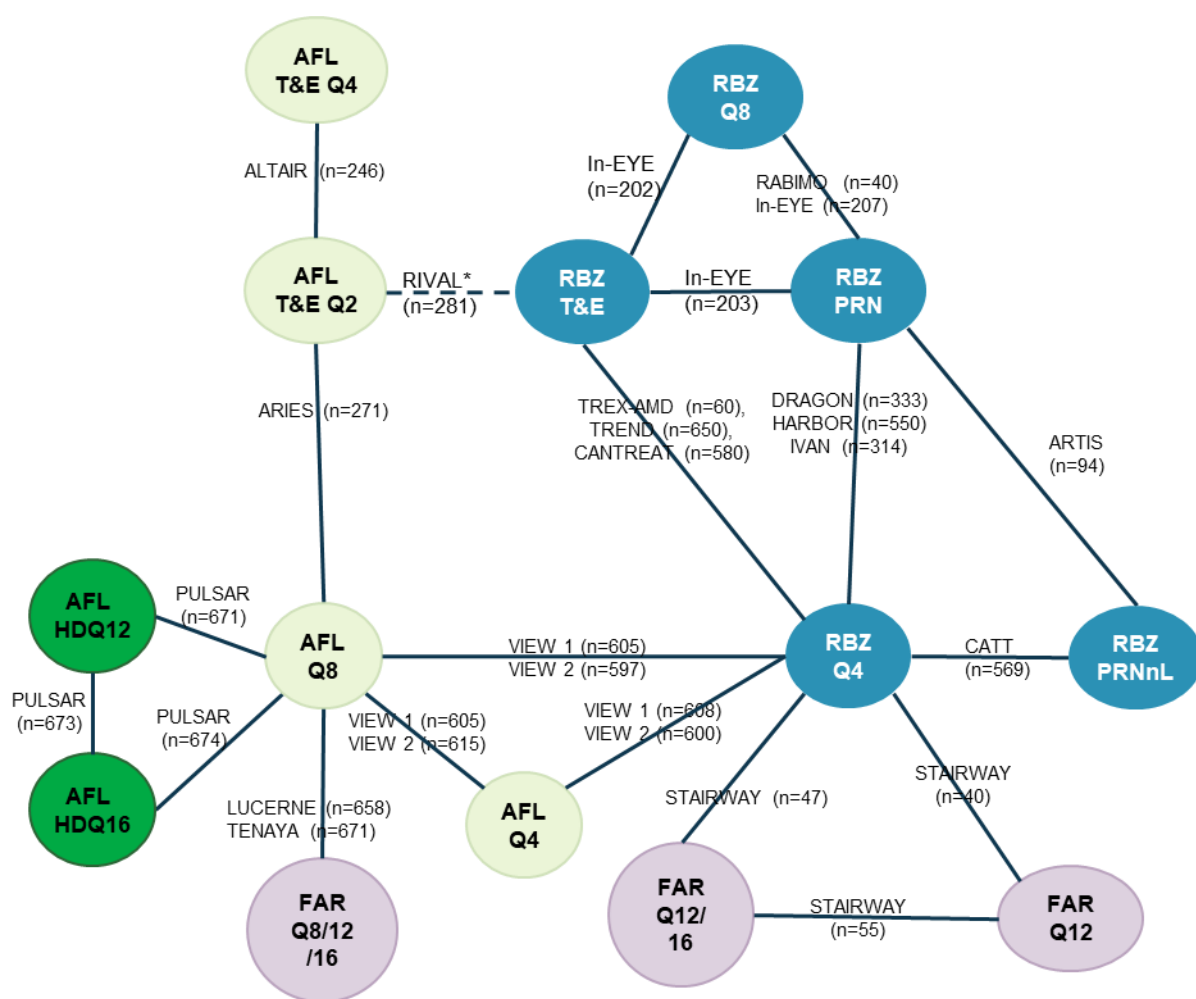
Treatment	Probability of being best [%]	SUCRA [%]	Probability for AFL 8 mg Q12 being better than comparators [%]	Probability for AFL 8 mg Q16 being better than comparators [%]
AFL 8 mg Q12	8	50	-	44
AFL 8 mg Q16	6	45	56	-
AFL Q4	1	39	60	55
AFL Q8	1	47	52	46
FAR Q12	15	49	51	49
FAR Q12/Q16	7	36	62	60
FAR Q8/Q12/Q16	8	56	43	39
RBZ PRN	28	75	28	25
RBZ Q4	1	53	46	41
RBZ Q8	12	41	58	56
RBZ T&E	13	60	40	37

Abbreviations: AFL – aflibercept; FAR – faricimab; HD – high dose (8 mg); PRN – Pro re nata; QX – every X weeks; RBZ – ranibizumab; SUCRA - Surface Under the Cumulative Ranking Curve; T&E – Treat and Extend

Supplementary Figure 1. PRISMA diagram of search results in scenario including bevacizumab and brolucizumab



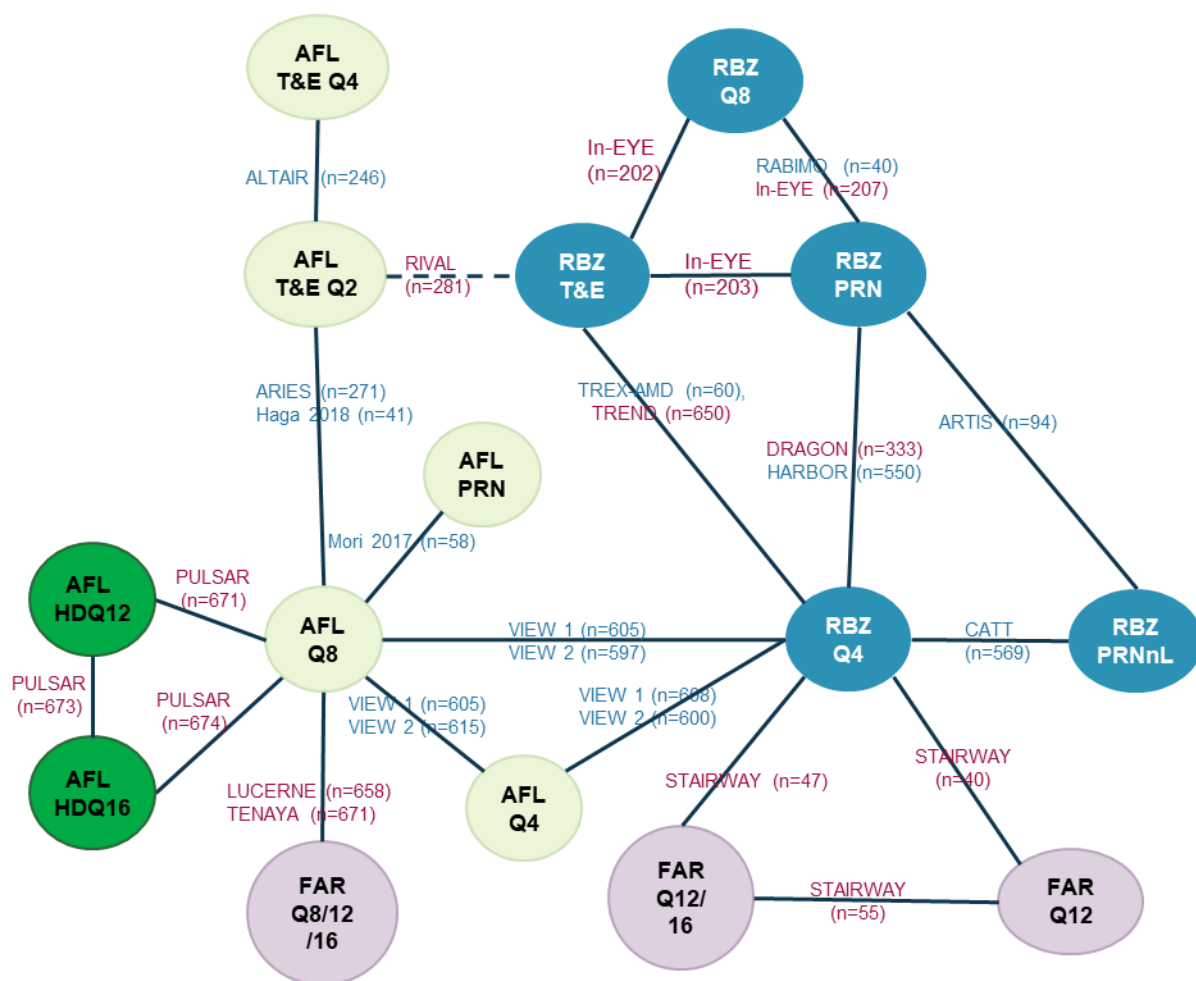
Supplementary Figure 2. Network of evidence for proportion of patients who gained/lost $\geq$ /15 ETDRS letters (base case analysis)



* - Study RIVAL was included in the sensitivity analysis

Abbreviations: AFL – aflibercept; FAR – faricimab; HD – high dose (8 mg); PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Figure 3. Network of evidence for CRT/CST change from baseline (base case analysis)

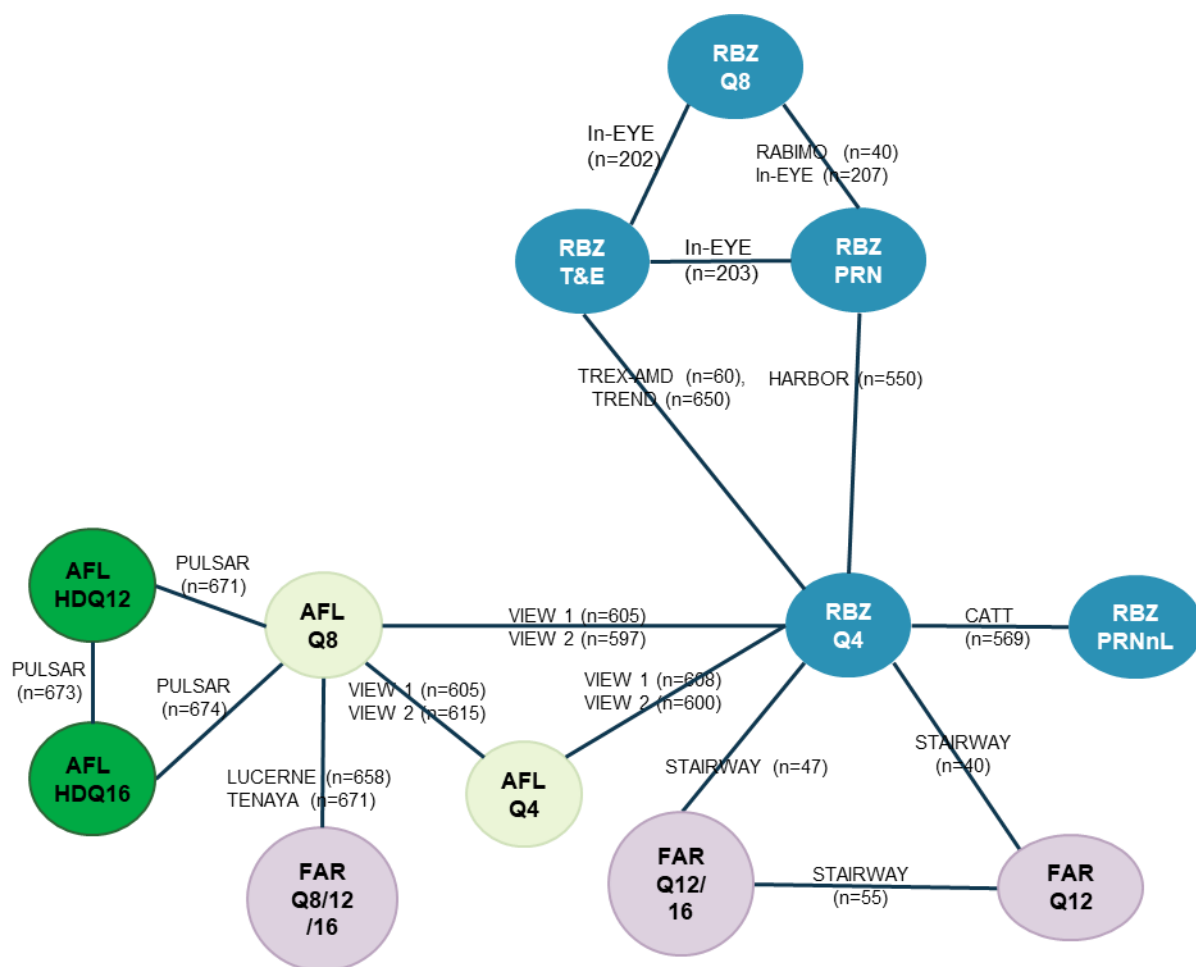


Blue – CRT, Red – CST

* - Study RIVAL was included in the sensitivity analysis

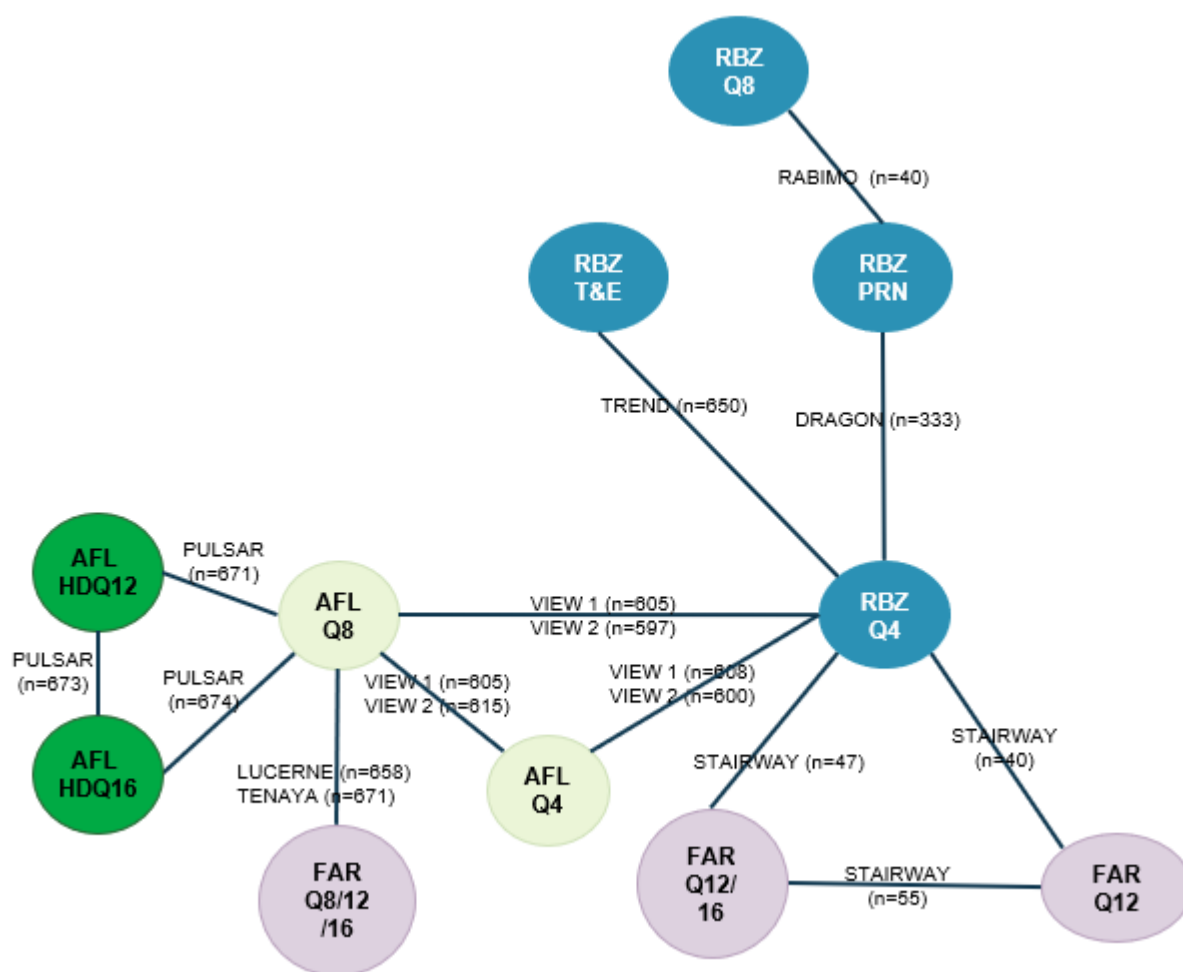
Abbreviations: AFL – aflibercept; FAR – faricimab; PRN – Pro re nata; PRnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Figure 4. Network of evidence for ocular adverse events (base case analysis)



Abbreviations: AFL – aflibercept; FAR – faricimab; PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

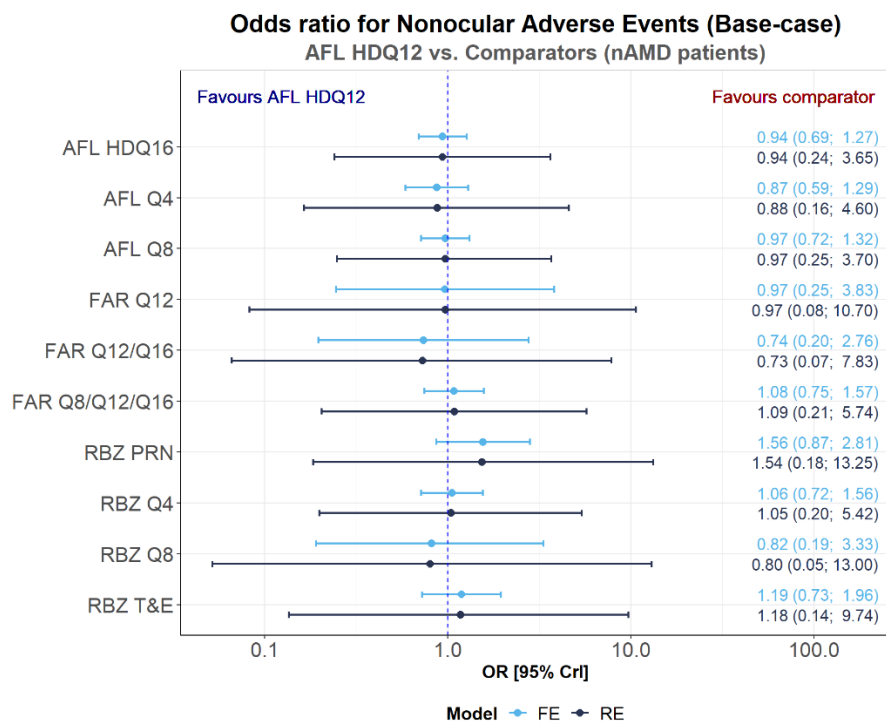
Supplementary Figure 5. Network of evidence for non-ocular adverse events (base case analysis)



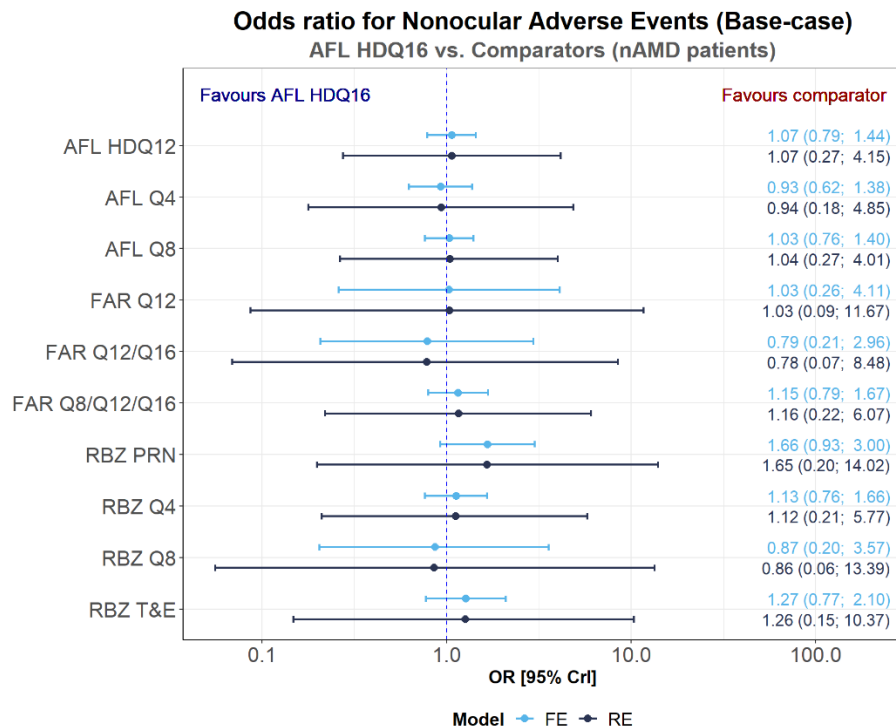
Abbreviations: AFL – aflibercept; FAR – faricimab; HD – high dose (8 mg); PRN – Pro re nata; QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

Supplementary Figure 6. Forest plot for odds ratio for comparison AFL 8 mg vs comparators regarding proportion of patients with non-ocular adverse events, base case analysis

a) AFL 8 mg Q12 vs comparators



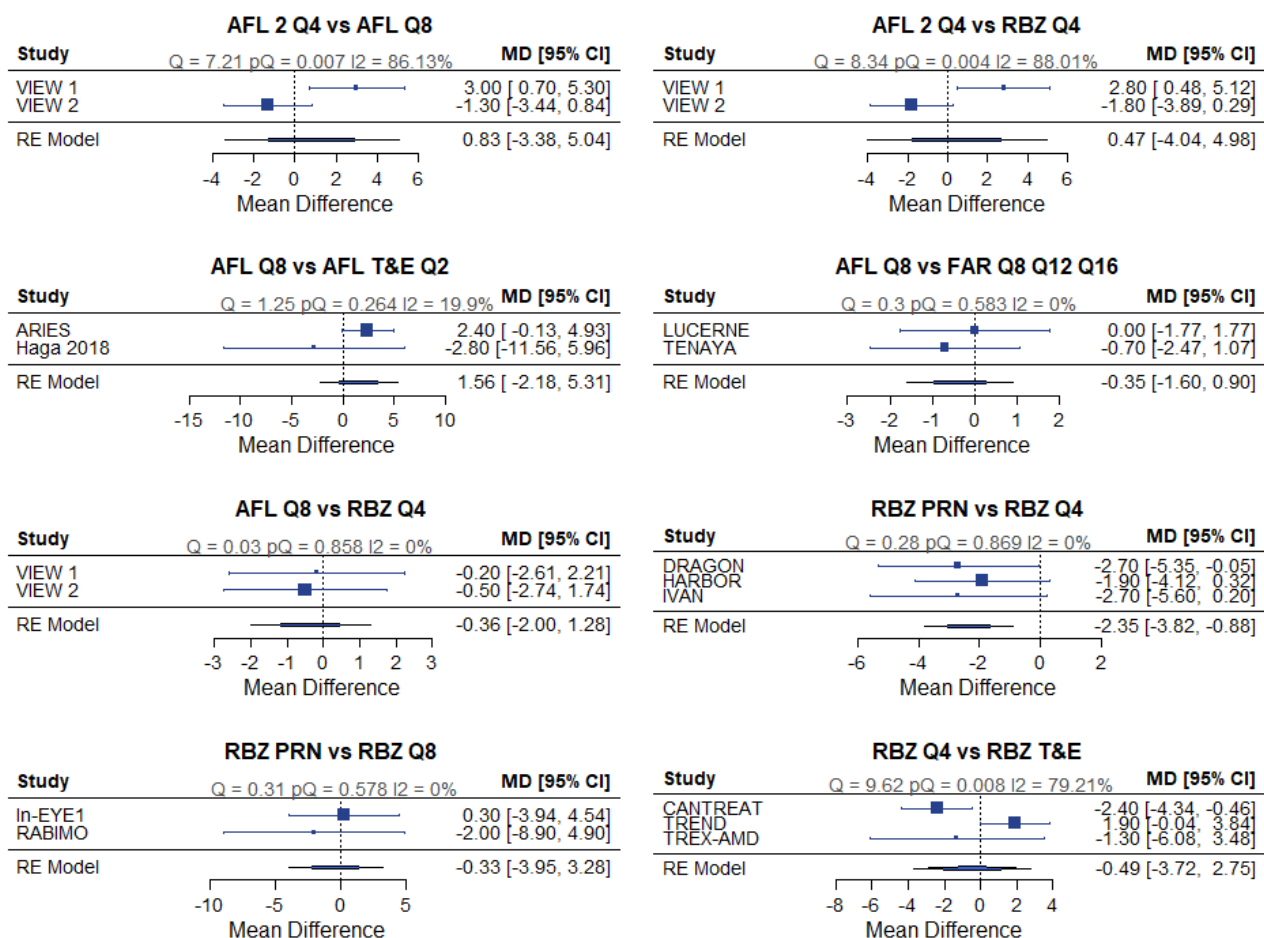
b) AFL 8 mg Q16 vs comparators



Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; CrI – credible interval; FAR – faricimab; FE – fixed effects; RE – random effects; HD – high dose (8 mg); OR – odds ratio; PRN – Pro re nata; QX – every X weeks; RBZ – ranibizumab; T&E – Treat and Extend

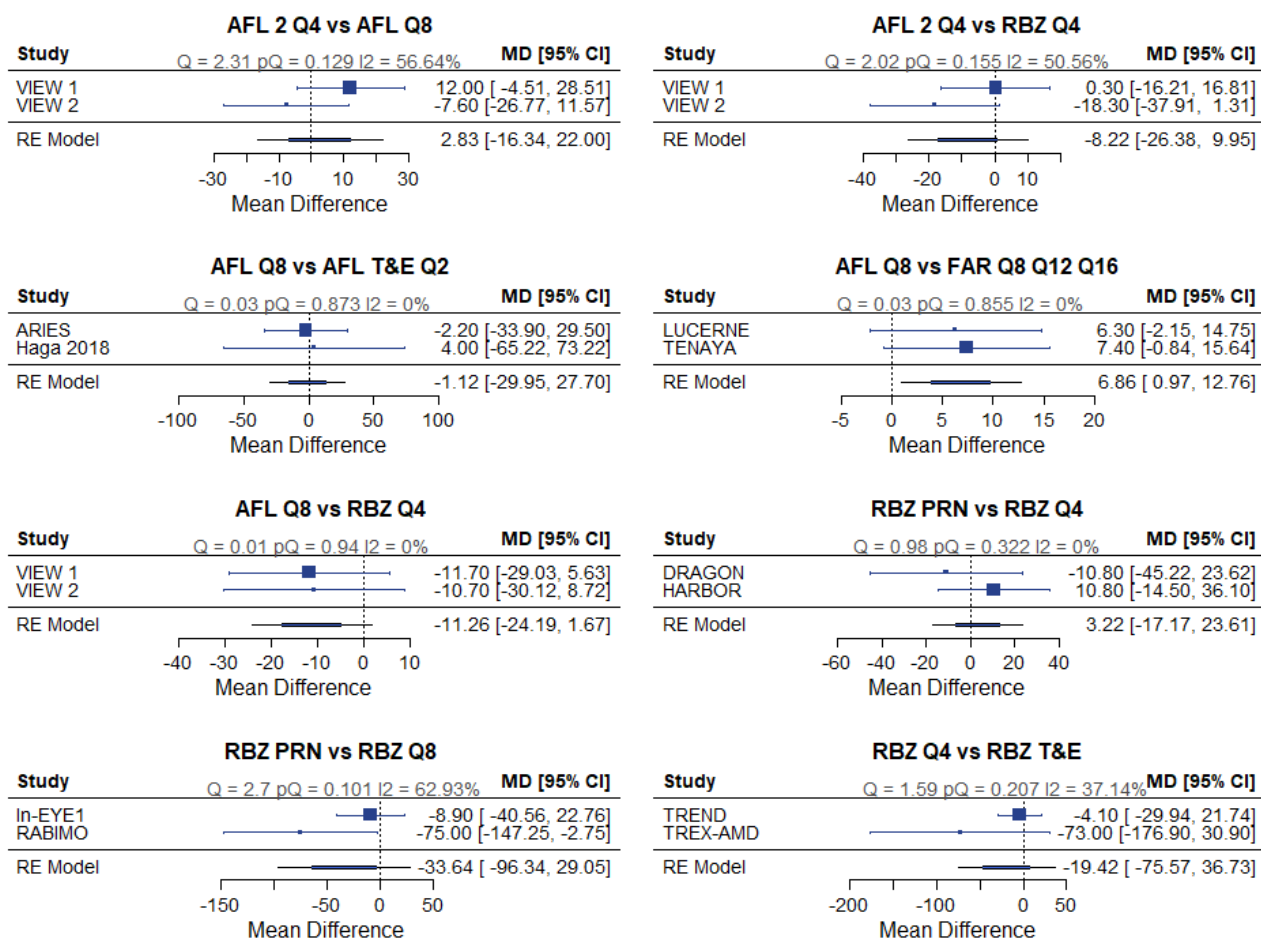
Supplementary Figure 7. Analysis of heterogeneity per comparison – Results for BCVA mean change from baseline (base case analysis)

BCVA Mean change from baseline



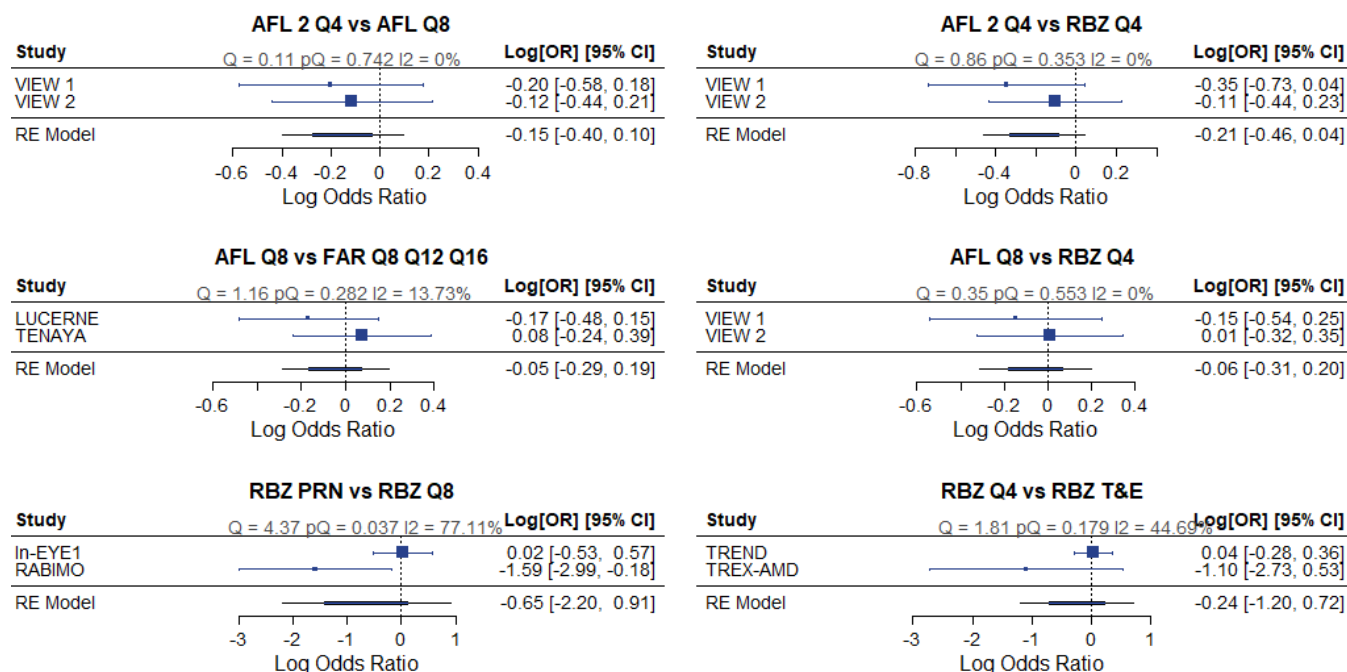
Supplementary Figure 8. Analysis of heterogeneity per comparison – CRT/CST change from baseline (base case analysis)

CRT/CST change from baseline



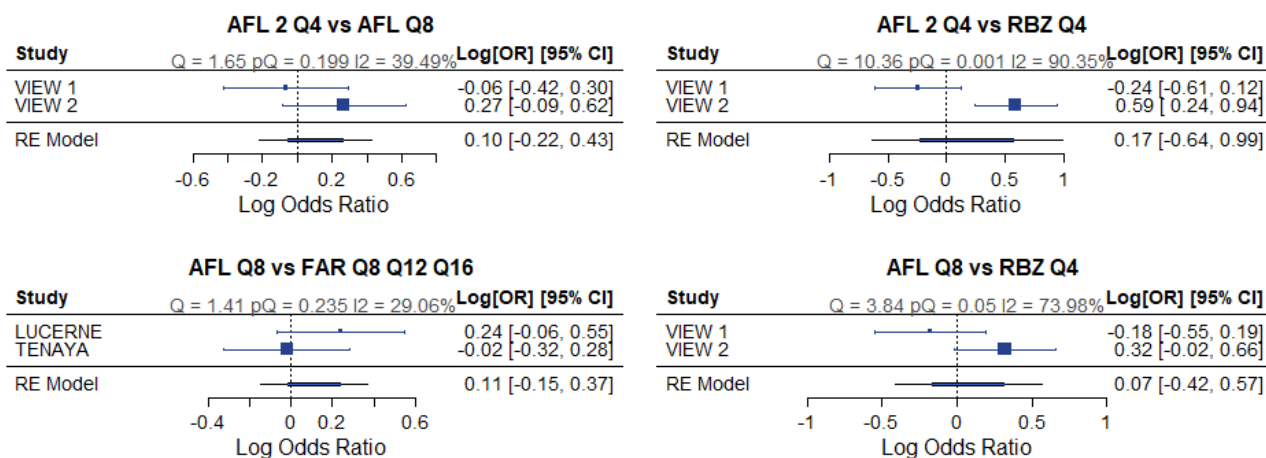
Supplementary Figure 9. Analysis of heterogeneity per comparison – Ocular adverse events (base case analysis)

Ocular Adverse Events



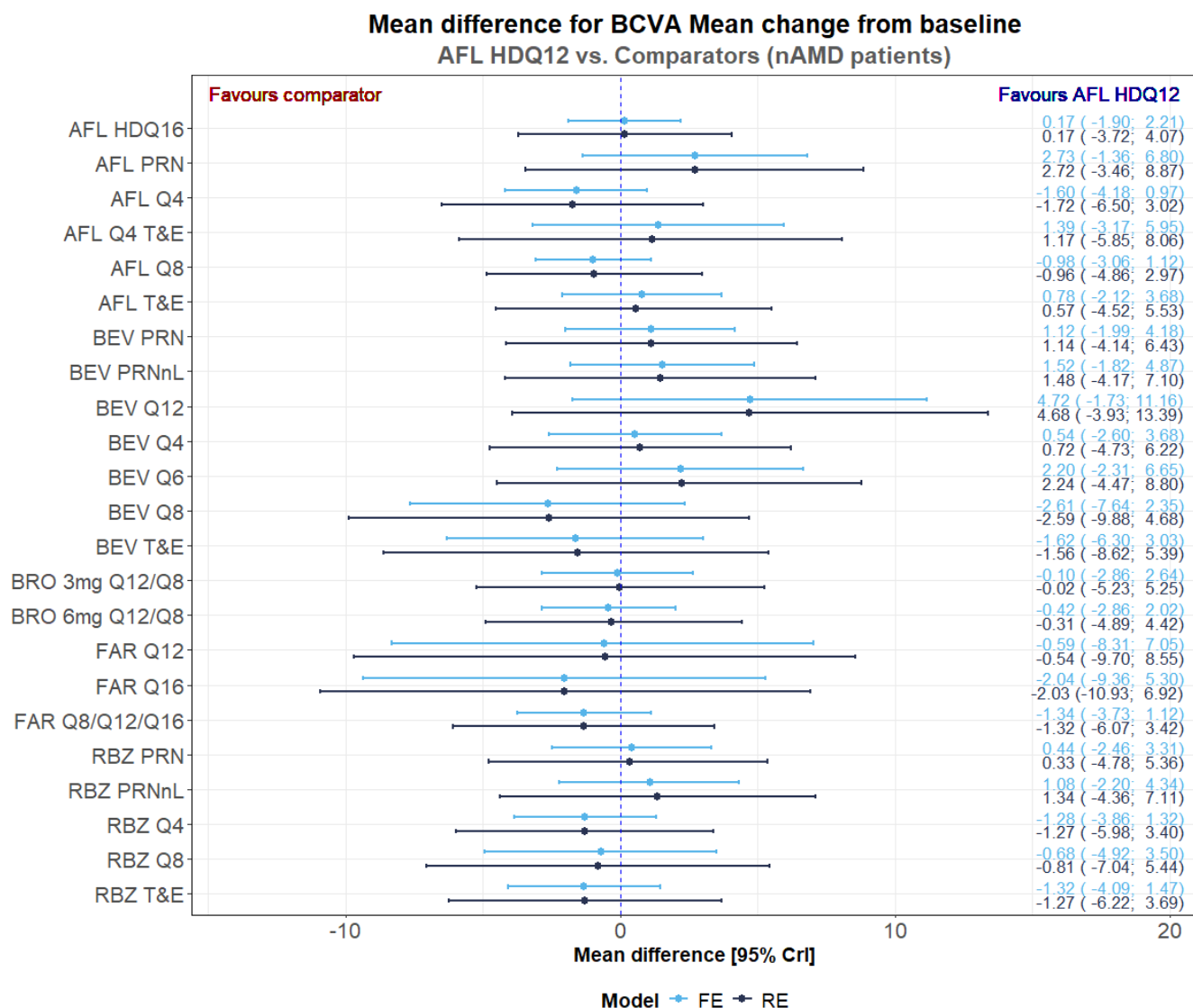
Supplementary Figure 10. Analysis of heterogeneity per comparison – Non-ocular adverse events

Non-ocular Adverse Events

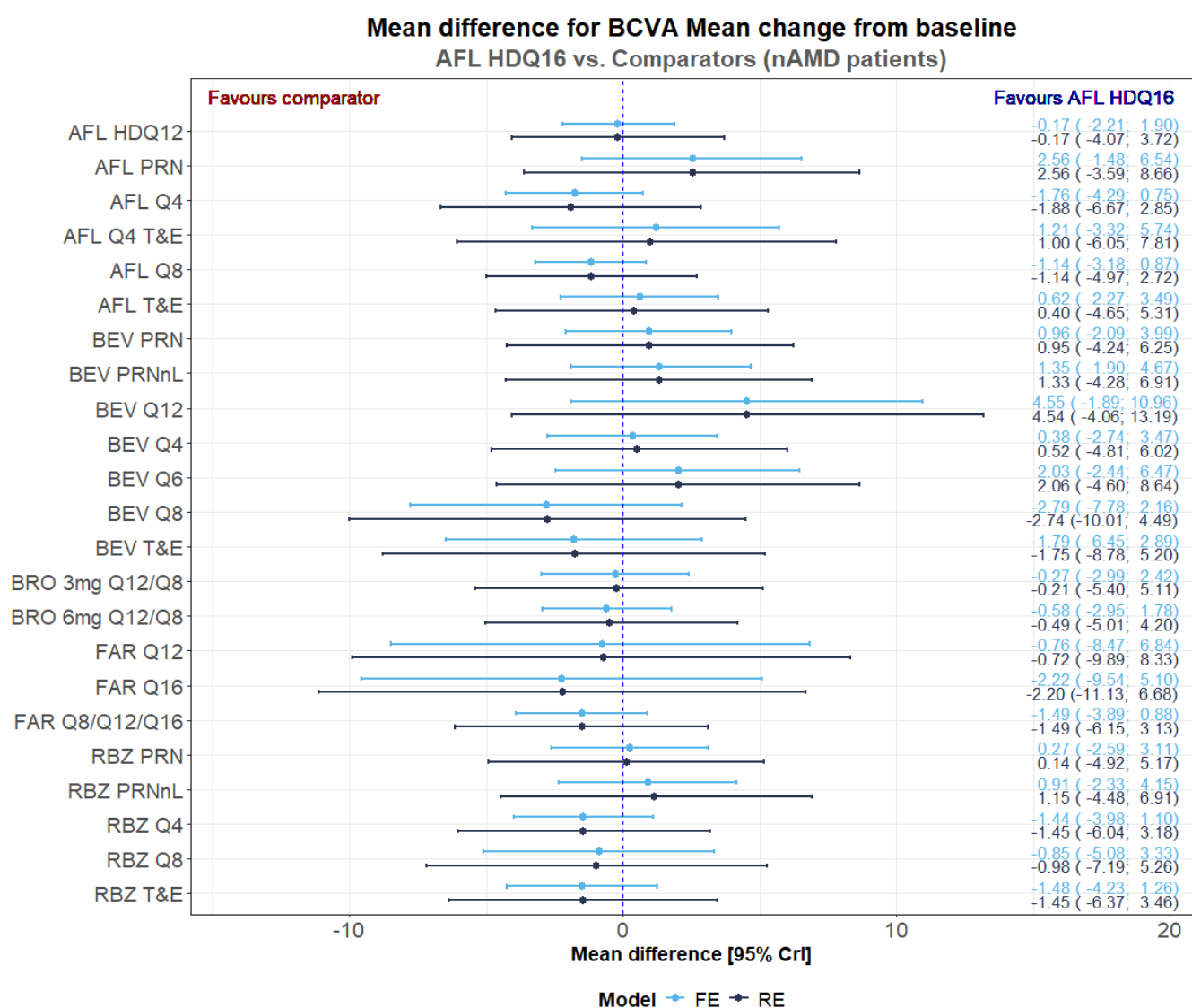


Supplementary Figure 12. Forest plot for comparison AFL 8 mg vs comparators regarding BCVA change from baseline, scenario analysis including bevacizumab and brolucizumab

a) AFL 8 mg Q12 vs comparators



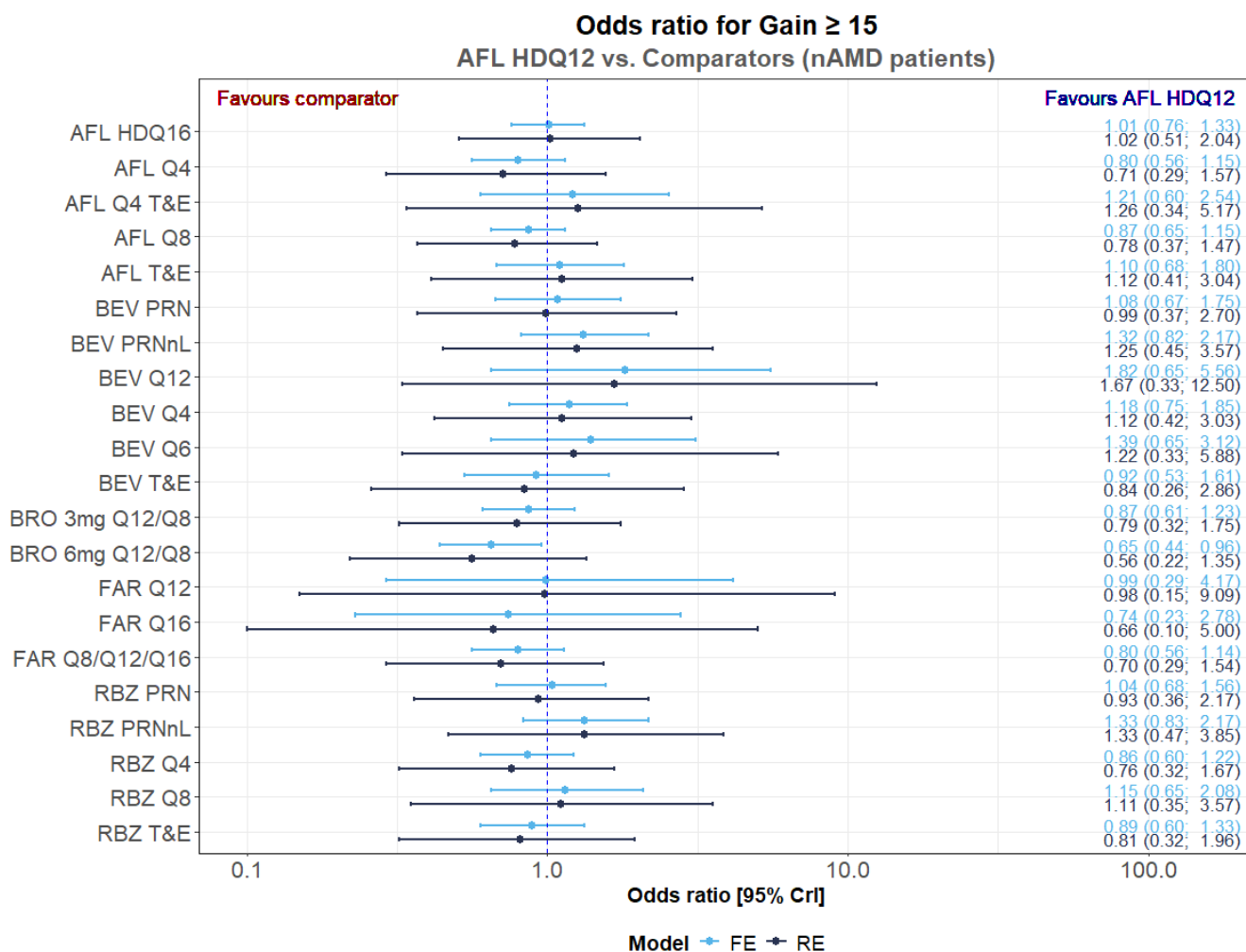
b) AFL 8 mg Q16 vs comparators



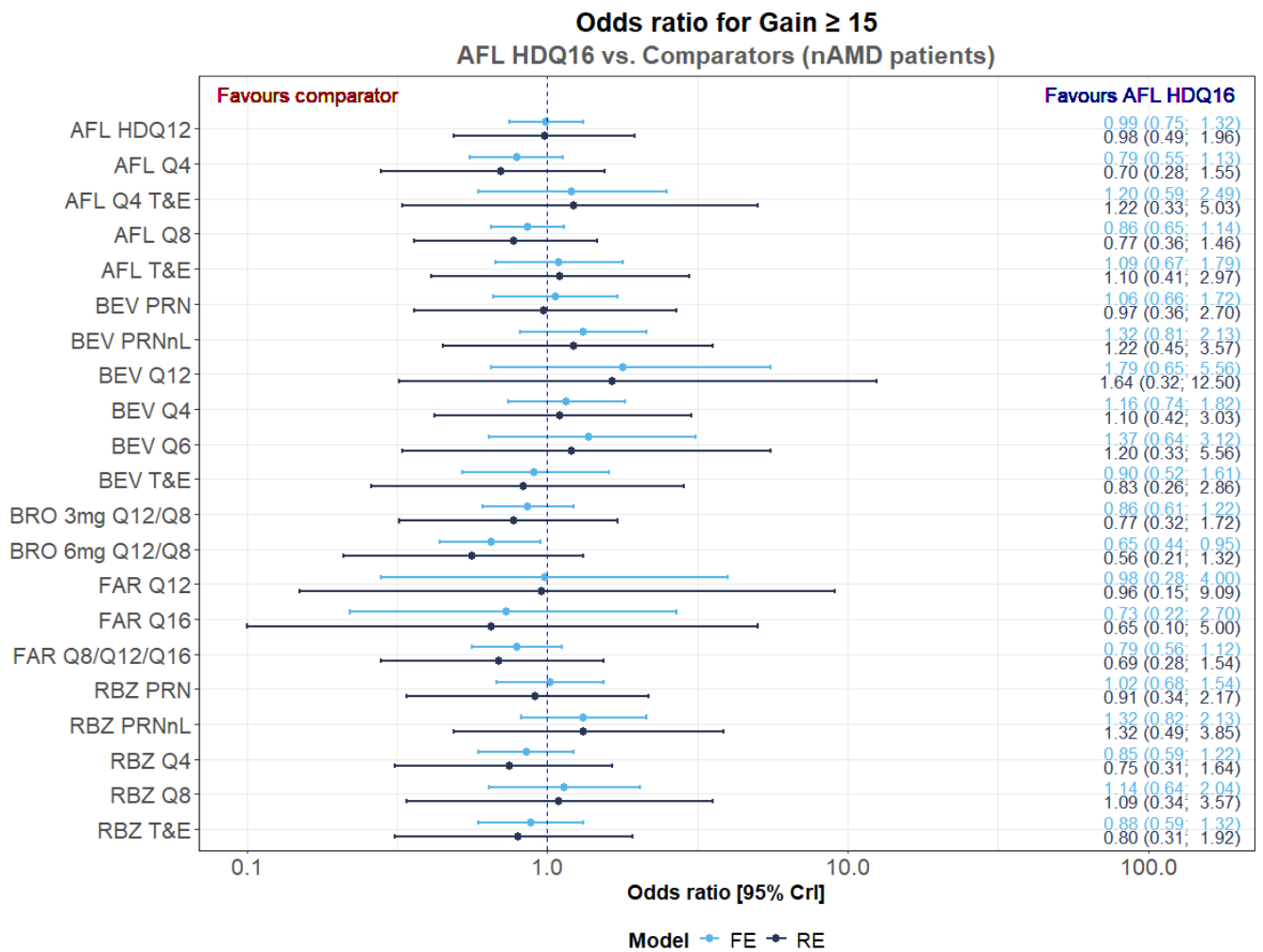
Abbreviations: AFL – aflibercept; BCVA – best corrected visual acuity; BEV – bevacizumab; BRO – brolocizumab; CrI – credible interval; FAR – faricimab; FE – fixed effects; HD – high dose (8 mg); PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; RE – random effects; T&E – Treat and Extend

Supplementary Figure 13. Forest plot for comparison AFL 8 mg vs comparators regarding proportion of patients who gained or lost ≥ 15 ETDRS letters, scenario analysis including bevacizumab and brolucizumab

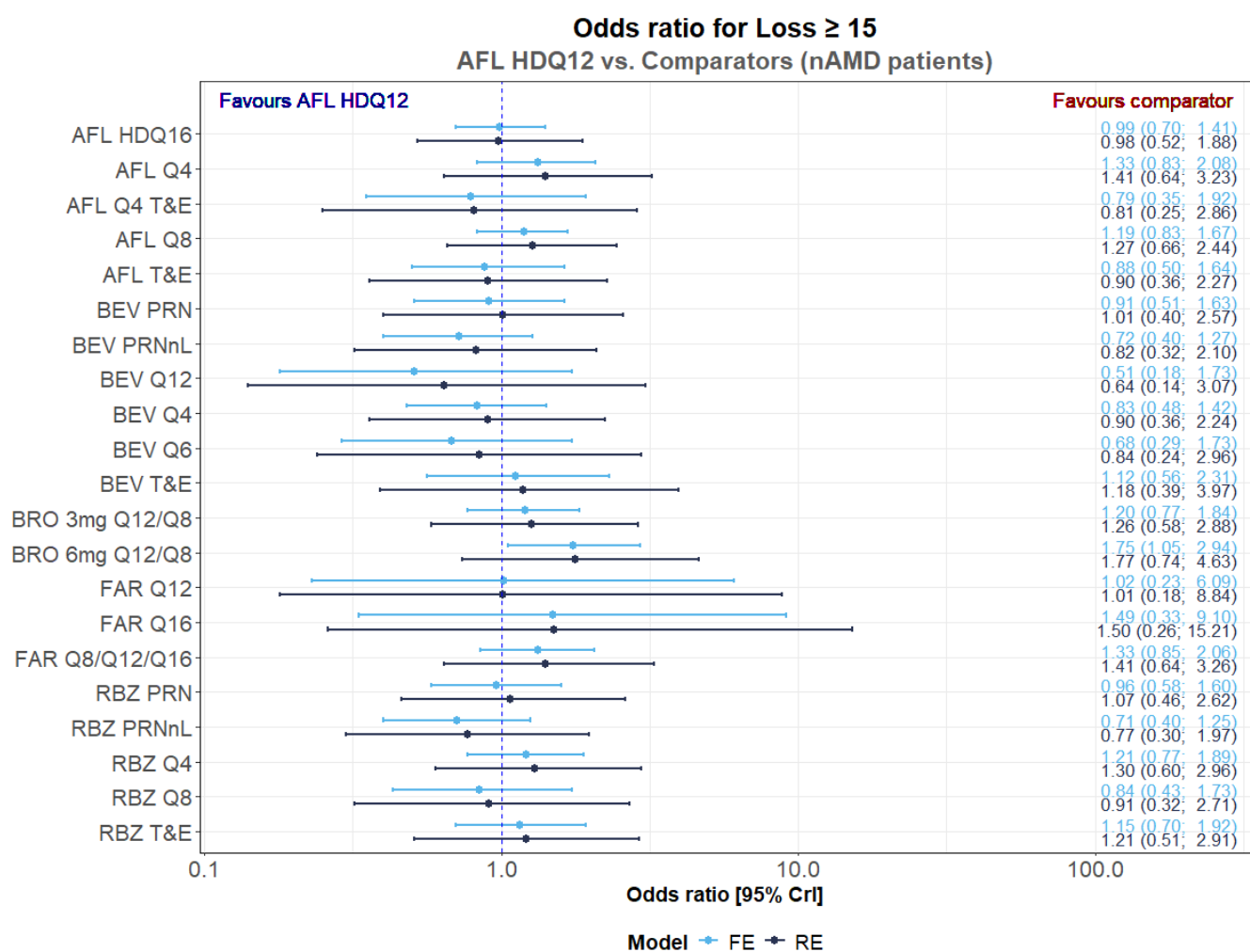
a) Proportion of patients who gained ≥ 15 ETDRS letters, AFL 8 mg Q12 vs comparators



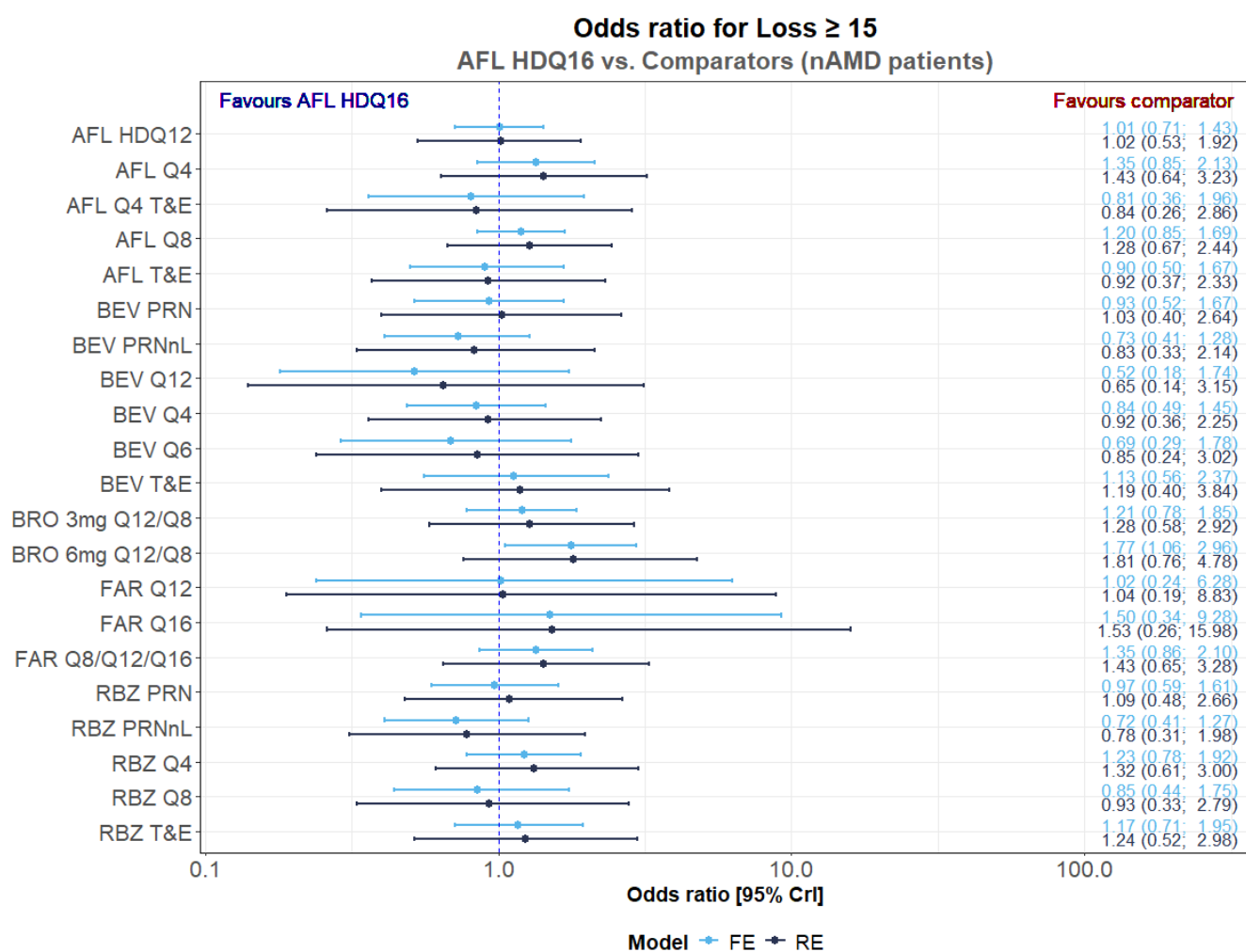
b) Proportion of patients who gained ≥ 15 ETDRS letters, AFL 8 mg Q16 vs comparators



c) Proportion of patients who lost ≥ 15 ETDRS letters, AFL 8 mg Q12 vs comparators



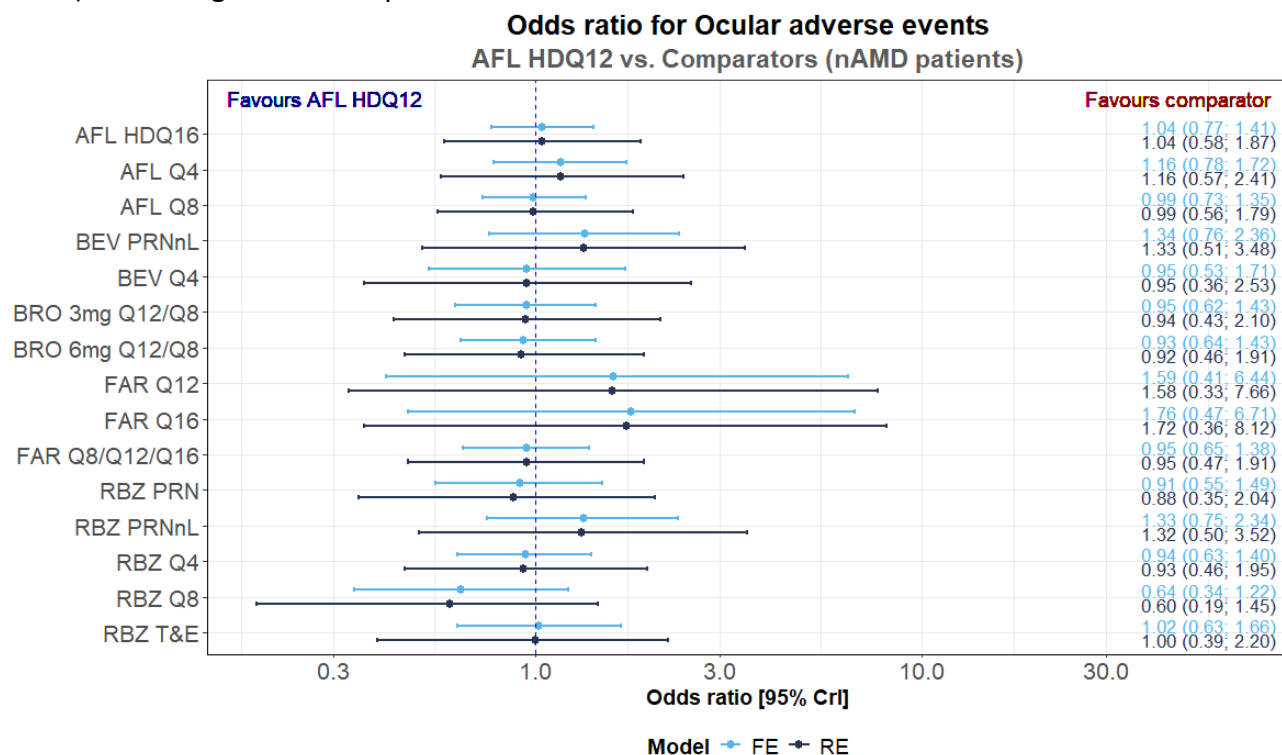
d) Proportion of patients who lost ≥ 15 ETDRS letters, AFL 8 mg Q16 vs comparators



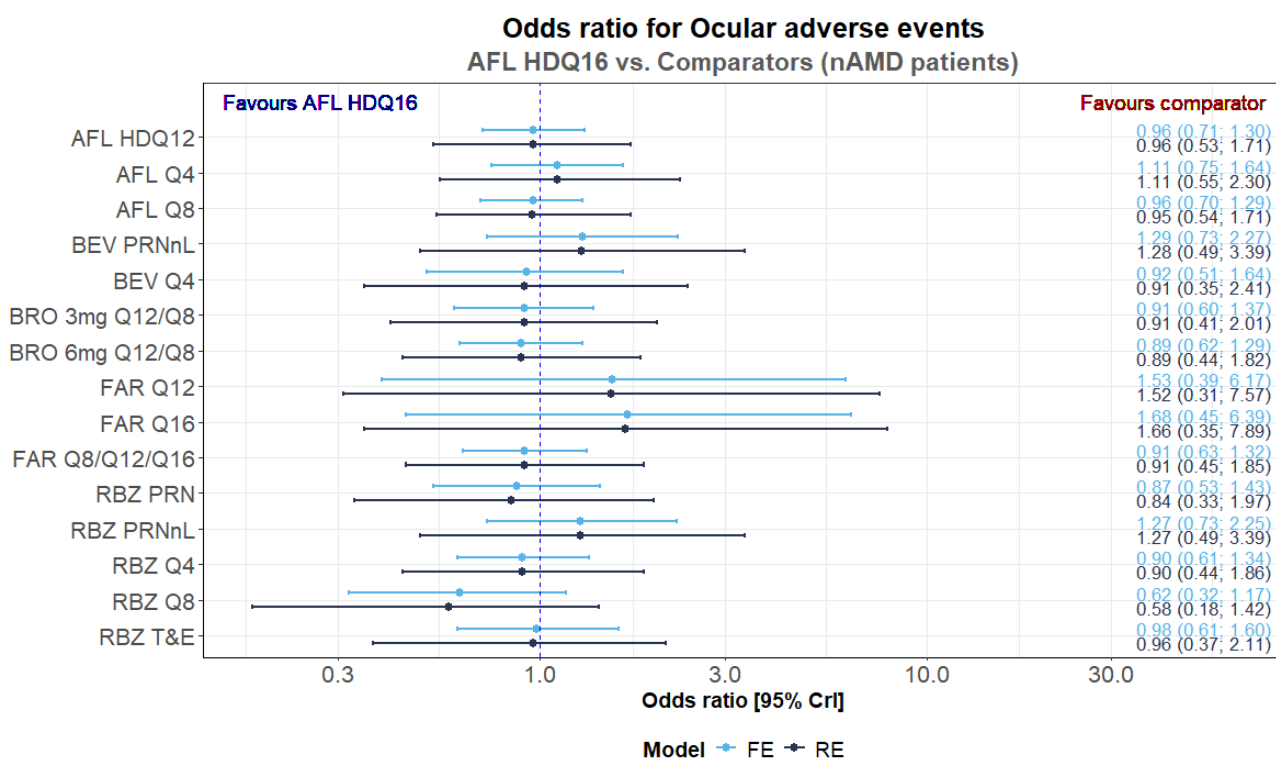
Abbreviations: AFL – aflibercept; BEV – bevacizumab; BRO – brolocizumab; CrI – credible interval; FAR – faricimab; FE – fixed effects; HD – high dose (8 mg); PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; RE – random effects; T&E – Treat and Extend

Supplementary Figure 14. Forest plot for odds ratio for comparison AFL 8 mg vs comparators regarding proportion of patients with ocular adverse events, scenario analysis including bevacizumab and brolucizumab

a) AFL 8 mg Q12 vs comparators



b) AFL 8 mg Q16 vs comparators



Abbreviations: AFL – aflibercept; BEV – bevacizumab; BRO – brolucizumab; CrI – credible interval; FAR – faricimab; FE – fixed effects; HD – high dose (8 mg); PRN – Pro re nata; PRNnL – Pro re nata (no loading phase); QX – every X weeks; RBZ – ranibizumab; RE – random effects; T&E – Treat and Extend