Supplementary materials for Efficacy, Safety and Immunogenicity of Etanercept
Biosimilars versus Reference Biologics in Patients with Rheumatoid Arthritis: A Metaanalysis

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### **Section 1. PRISMA checklist**

#### Table S1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Lines 1-3
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Lines 17-40
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 43-63
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 63-66
METHODS	-		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Lines 80-95
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Lines 73-78
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2 in supplementary materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 97-100
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 100-103
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 100-103
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Lines 100-103
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 105-110
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Lines 120-121
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Lines 83-89

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Lines 121
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Lines 124-129
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Lines 124-128
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Lines 123-124
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Lines 134
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Lines 105-110
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Lines 112-118
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1, lines140-144
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2, lines 153-157
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3, 4, 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 3, 4, 5; lines 160-192
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 3, 4, 5; lines 160-192
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Lines 215-217
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section 3 in supplementary materials
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Section 4 in supplementary materials
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 5 in supplementary materials

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION	•		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Lines 204-214
	23b	Discuss any limitations of the evidence included in the review.	Lines 240-256
	23c	Discuss any limitations of the review processes used.	Lines 240-256
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 250-251
OTHER INFORMAT	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Lines 70-71
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Lines 276-278
Competing interests	26	Declare any competing interests of review authors.	Lines 280-281
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Lines 265-267

# Section 2. Search strategy

Table S2. Peer-reviewed literature search strategy.

PubMed search terms	((("Arthritis, Rheumatoid"[Mesh]) OR (Rheumatoid arthritis[Title/Abstract]))							
	AND (("Etanercept"[Mesh]) OR (etanercept[Title/Abstract]))) AND							
	(("Biosimilar Pharmaceuticals"[Mesh] OR "etanercept biosimilar SB4"							
	[Supplementary Concept]) OR (biosimilar[Title/Abstract])) AND							
	("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized							
	Controlled Trial" [Publication Type] OR							
	"randomized controlled trials")							
Embase search terms	'Rheumatoid arthritis'/mp OR 'rheumatoid arthritis '/ AND ([etanercept]/mp							
	OR [etanercept]/ AND [biosimilar]/mp OR [biosimilar agent]/) AND							
	[randomized controlled trial]/mp OR [randomized controlled trial]/)							
Central search terms	'Rheumatoid arthritis'/mp OR 'rheumatoid, arthritis '/ AND ([etanercept]/mp							
	OR [etanercept]/ AND [biosimilar]/mp OR [biosimilar pharmaceuticals]/)							
	AND [randomized controlled trial]/mp OR [randomized controlled trial]/)							

# Section 3. The results of sensitivity analyses

3.1 ACR20, ACR5	0, ACR Experin			rate f	rom per-protocol set			Weight	Weight
Study			Events		Odds Ratio	OR	95%-CI	(common)	
ACR20_24weeks					10				
NCT01270997	96	115	96	118		1.16	[0.59; 2.28]	27.1%	29.9%
NCT01895309	193				-		[0.56; 1.36]		70.1%
Common effect model		362		352			[0.66; 1.38]		
Random effects model							[0.66; 1.38]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	0.50							
ACR20_1year									
NCT01270997	96	110	96	111		1.07	[0.49; 2.34]	26.1%	27.2%
NCT01895309	181	224	176	216		0.96	[0.59; 1.54]	73.9%	72.8%
Common effect model		334		327		0.99	[0.66; 1.48]	100.0%	
Random effects model						0.99	[0.66; 1.48]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	0.81							
ACR50_24weeks									
NCT01270997	75	115	62		- W	- 1.69	[1.00; 2.87]	28.1%	31.8%
NCT01895309	115	247	99	234		1.19	[0.83; 1.70]		68.2%
Common effect model		362		352			[0.99; 1.79]		
Random effects model					-	1.34	[0.97; 1.87]		100.0%
Heterogeneity: $I^2 = 16\%$ , $\tau$	$x^2 = 0.009$	8, p = 0	0.28						
ACR50_1year									
NCT01270997	75			112			[1.04; 3.10]		32.2%
NCT01895309	131		115		-		[0.85; 1.80]		67.8%
Common effect model		334		328			[1.02; 1.90]		
Random effects model						1.41	[1.00; 1.99]		100.0%
Heterogeneity: $I^2 = 16\%$ , $\tau$	$^2 = 0.011$	1, p = 0	0.27						
ACR70_24weeks									
NCT01270997	36		37				[0.57; 1.74]		36.4%
NCT01895309	63		53		-		[0.77; 1.78]		63.6%
Common effect model		362		352			[0.79; 1.54]		
Random effects model						1.10	[0.79; 1.54]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	0.65							
ACR70_1year		50 500000	2025-000-0			SC 109 West	TURNS 104 FEB 1791 ROSA 400	10,70 C - 10,007 Cat 144	in: 88 566353
NCT01270997	42						[0.69; 2.08]	35.3%	34.2%
NCT01895309	84		67		-		[0.90; 1.98]	64.7%	65.8%
Common effect model		334		328			[0.93; 1.77]		
Random effects model						1.29	[0.93; 1.77]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	).76							
					05 1				
					0.5 1 2				

3.2 ACR20, ACR5	0, ACR Experim			rate fr	om full-analysis set			Weight	Weight
Study	State of the state		Events	Tota!	Odds Ratio	OR	95%-CI	(common)	(random)
ACR20_24weeks					ſ				
NCT01270997	106	134	102	135		1.22	[0.69; 2.17]	27.5%	28.5%
NCT01895309	220	298	213	297			[0.78; 1.60]		71.5%
Common effect model		432		432			[0.84; 1.55]	100.0%	
Random effects model							[0.84; 1.55]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$		0.78							
ACR20_32weeks									
NCT01895309	226	298	224	298	-6-	1.04	[0.71; 1.51]	100.0%	100.0%
	10-703/50	68,895	: ————————————————————————————————————	VIII (200 B)	Γ		Less 22 22552		
ACR20_1year									
NCT01270997	110	134		135			[0.62; 2.11]	25.0%	24.2%
NCT01895309	210	298		297			[0.88; 1.76]	75.0%	75.8%
Common effect model		432		432			[0.91; 1.65]	100.0%	
Random effects model						1.22	[0.91; 1.65]	(	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	=0, p=0	).81							
ACR50_24weeks									
NCT01270997	79	134	63	135		- 1.64	[1.01; 2.66]	28.0%	31.5%
NCT01895309	128	298		297			[0.85; 1.63]	72.0%	68.5%
Common effect model		432		432			[1.00; 1.71]	100.0%	
Random effects model							[0.97; 1.81]		100.0%
Heterogeneity: $I^2 = 21\%$ , 1	$r^2 = 0.0117$	7, p = 0	0.26				.5. E		
ACR50_1year									
NCT01270997	82	134	67	134		- 158	[0.97; 2.56]	28.5%	30.8%
NCT01895309	143	298		297			[0.92; 1.75]	71.5%	69.2%
Common effect model	6.15	432		431			[1.04; 1.78]		
Random effects model							[1.04; 1.78]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$		).47				(Admin)	<u>.</u>		
ACR70_24weeks									
NCT01270997	38	134	38	135		1.01	[0.59; 1.72]	37.4%	35.3%
NCT01270997 NCT01895309	69	298		297	100		[0.82; 1.80]	62.6%	64.7%
Common effect model	US	432	Ja	432	1000		[0.83; 1.56]	100.0%	04.770
Random effects model		432		432			[0.83; 1.56]	100.076	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$		. 50				1.14	[0.83, 1.56]		100.076
neterogeneity. 7 - 0%, t	$-0$ , $\rho$ $-0$	).36							
ACR70_1year									
NCT01270997	45	134		135			[0.65; 1.80]	35.9%	33.5%
NCT01895309	91	298	73	297	*		[0.94; 1.94]	64.1%	66.5%
Common effect model		432		432			[0.93; 1.68]	100.0%	
Random effects model						1.25	[0.93; 1.68]	0.	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	).49							
					0.5 1 2				

3.3 Safety assessme			_						
Chudu	Experim		200	ntrol	Oddo Batio	OB	05% 0	Weight	
Study	Events	iotai	Events	iotai	Odds Ratio	OR	95%-0	(common)	(random)
Any_AEs					1				
NCT01270997	113	147	114	146	-	0.93	[0.54; 1.61]	27.3%	26.0%
NCT01895309	175	299	169	297	<del></del>	1.07	[0.77; 1.48]		74.0%
Common effect model		446		443	<b>*</b>	1.03	[0.78; 1.36]	100.0%	
Random effects model					<b>*</b>	1.03	[0.78; 1.36]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.68							
Serious_AEs					1		50 50 0 10		
NCT01270997	19	147	18	146		1.06	[0.53; 2.10]		51.1%
NCT01895309	18	299 <b>446</b>	15	297 <b>443</b>		1.20	[0.60; 2.44]		48.9%
Common effect model		446		443		1.13	[0.69; 1.84]		400.09/
Random effects model		70				1.13	[0.69; 1.84]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.79							
Withdrawal_due_to_A	Es								
NCT01270997	10	147	11	146	_	0.90	[0.37; 2.18]	35.1%	36.8%
NCT01895309	16	299	20	297	-	0.78	[0.40; 1.54]	64.9%	63.2%
Common effect model		446		443	-	0.82	[0.48; 1.41]	100.0%	
Random effects model					-	0.82	[0.48; 1.41]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.81					70)		
All_cause_deaths	664				_				
NCT01270997	0	147	2	146 -			[0.01; 4.12]		49.9%
NCT01895309	2		0	297	*		[0.24; 104.59]		50.1%
Common effect model		446		443			[0.20; 4.94]		
Random effects model		_				0.99	[0.04; 23.70]		100.0%
Heterogeneity: $I^2 = 54\%$ , $\tau$	= 2.8367	p = 0	).14	ſ					
				0.0	01 0.1 1 10 10	0			

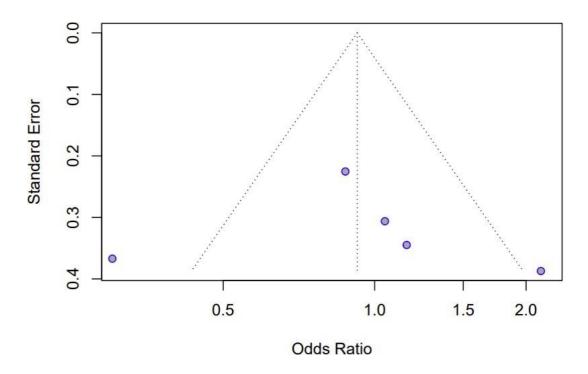
### 3.3 Immunogenicity assessments

Study	Experim Events		Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
NCT01270997 NCT01895309	8	147 299	3 39	146 297		2.74 0.07	[0.71; 10.55] [0.02; 0.22]	6.8% 93.2%	49.6% 50.4%
Common effect model Random effects model Heterogeneity: $I^2 = 94\%$ , $\tau$		<b>446</b> 1, <i>p</i> < 0	0.01	443	0.1 0.51 2 10		[0.13; 0.49] [0.01; 16.06]	100.0% 	100.0%

## Section 4. Assessment of publication bias

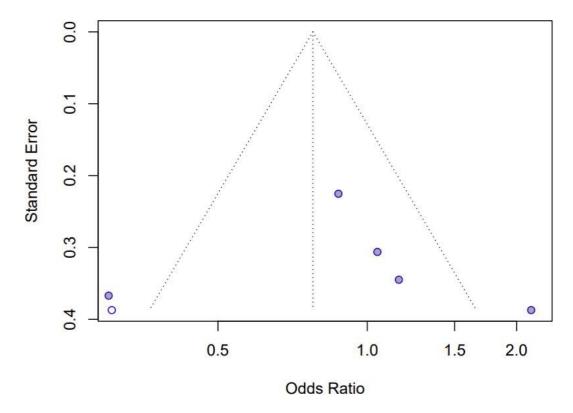
### 4.1 ACR20 response rate at 24 weeks

### 4.1.1 Original funnel plots



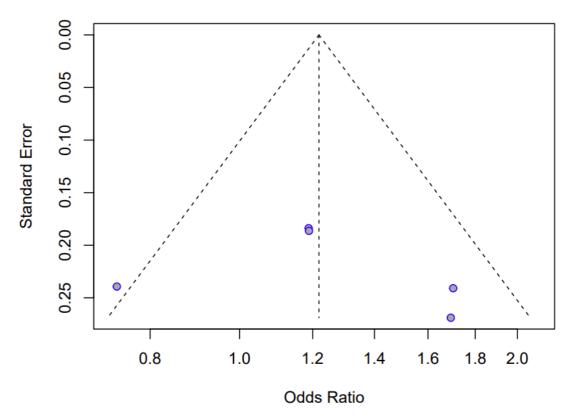
### 4.1.2 Trim-and-fill funnel plots

Note: Adjusted odds ratio with one filled study was 0.77 with 95% confidence interval 0.42 to 1.41.



### 4.2 ACR50 response rate at 24 weeks

### 4.2.1 Original funnel plots

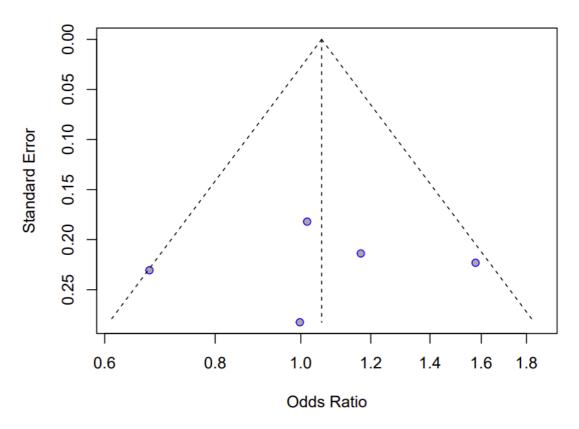


4.2.2 Trim-and-fill funnel plots

Note: No study was filled.

### 4.3 ACR70 response rate at 24 weeks

### 4.3.1 Original funnel plots

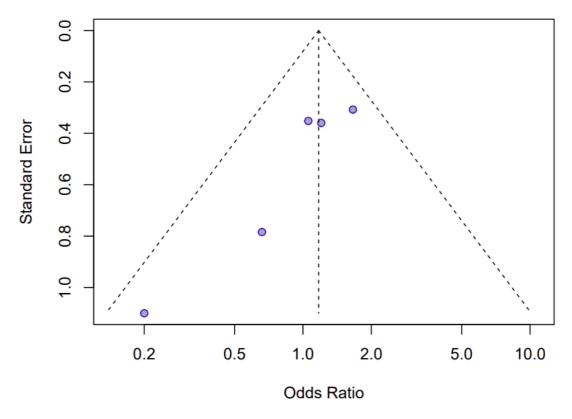


4.3.2 Trim-and-fill funnel plots

Note: No study was filled.

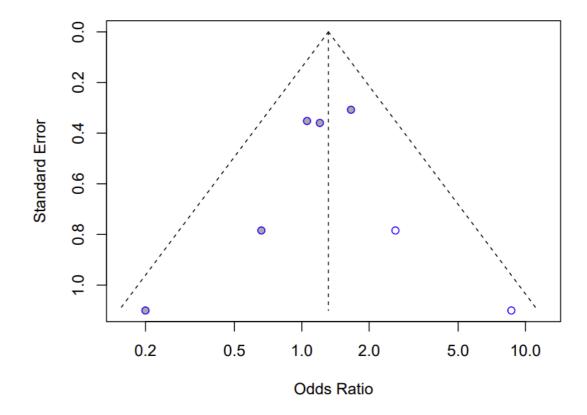
### 4.4 Incidence of serious adverse events

### 4.4.1 Original funnel plots



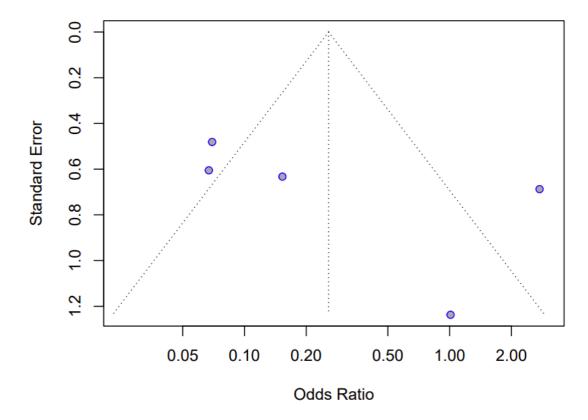
4.4.2 Trim-and-fill funnel plots

Note: Adjusted odds ratio with two filled study was 1.32 with 95% confidence interval 0.93 to 1.87.



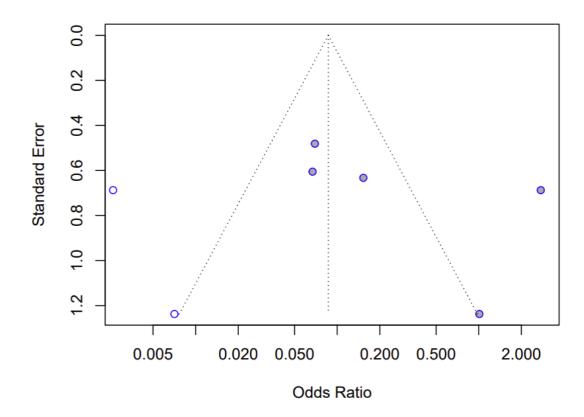
### 4.5 Assessment of immunogenicity

### 4.5.1 Original funnel plots



4.5.2 Trim-and-fill funnel plots

Note: Adjusted odds ratio with two filled study was 0.09 with 95% confidence interval 0.01 to 0.53.



### Section 5. Results of GRADE assessment

biosimiars compared to etanercept for RA Patient or population: patients with RA Settings: Intervention: biosimiars Comparison: etanercept

Comparison: etanercept					
Outcomes		ks* (95% CI) sponding risk miars	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence Comments (GRADE)
ACR20_24weeks_PPS	Study population		OR 0.92	1878	0000
	865 per 1000 855 p	er 1000 to 910)	(0.54 to 1.58)	(5 studies)	low <sup>1,2</sup>
	Moderate				
ACR20_1year_PPS	Study population		OR 1.08	957	⊕⊕⊕⊝
	(809 t	er 1000 o 896)	(0.76 to 1.55)	(3 studies)	moderate <sup>2</sup>
	Moderate			House	
ACR50_24weeks_PPS		er 1000	OR 1.22 (1.01 to 1.47)	1878 (5 studies)	⊕⊕⊕ high
	Moderate (582 t	to 670)	-		
ACR50 1year PPS			OR 1.43	958	0000
ACROU_IyeaI_FF3	Study population 574 per 1000 658 p	er 1000	(1.10 to 1.86)	(3 studies)	high
		to 715)			
ACR70_24weeks_PPS	Study population		OR 1.06	1878	0000
	343 per 1000 356 p	er 1000 to 400)	(0.87 to 1.28)	(5 studies)	moderate <sup>2</sup>
	Moderate				
ACR70_1year_PPS	Study population		OR 1.32	958	0000
	376 per 1000 443 p	er 1000 to 507)	(1.01 to 1.71)	(3 studies)	high
	Moderate				
ACR20_24weeks_FAS	Study population		OR 1.14	864	0000
	(693 t	er 1000 to 807)	(0.84 to 1.55)	(2 studies)	moderate <sup>2</sup>
	Moderate				
ACR20_32weeks_FAS	Study population		OR 1.02	746	⊕⊕⊕⊝
	(711 t	er 1000 to 832)	=(0.72 to 1.45)	(2 studies)	moderate <sup>2</sup>
	Moderate			DWW.	
ACR20_1year_FAS	Study population		OR 1.22 -(0.91 to 1.65)	864 (2 studies)	⊕⊕⊕⊝ moderate <sup>2</sup>
		er 1000 to 795)	(0.57 to 1.05)	(2 studies)	moderate
1 CDF0 04			OR 1.31	864	0000
ACR50_24weeks_FAS	Study population 414 per 1000 481 p (414 t	er 1000 to 547)	(1.00 to 1.71)	(2 studies)	moderate <sup>2</sup>
	Moderate				
ACR50_1year_FAS	Study population		OR 1.36	863	⊕⊕⊕⊕
	445 per 1000 522 p	er 1000 to 588)	(1.04 to 1.78)	(2 studies)	high
	Moderate				
ACR70_24weeks_FAS	Study population		OR 1.14	864	⊕⊕⊕⊝ ৢ
		<b>er 1000</b> to 311)	(0.83 to 1.56)	(2 studies)	moderate <sup>2</sup>
	Moderate				***********
ACR70_1year_FAS	Study population		OR 1.25	864 (2 studies)	⊕⊕⊕⊝ moderate <sup>2</sup>
	(255 t	er 1000 to 381)	(0.93 to 1.68)	(2 studies)	moderate
AF-	Moderate		OR 0.94	1639	⊕⊕⊕⊝
Any_AEs		er 1000 to 706)	(0.76 to 1.18)	(4 studies)	moderate <sup>2</sup>
	Moderate				
Serious_AEs	Study population		OR 1.17	1788	000
	0	er 1000 112)	(0.82 to 1.68)	(5 studies)	moderate <sup>2</sup>
	Moderate				
Nithdrawal_due_to_AEs	Study population		OR 0.75	1639	0000 j
	62 per 1000 47 pe (31 to	er <b>1000</b> (71)	(0.49 to 1.15)	(4 studies)	moderate <sup>2</sup>
	Moderate				***
All_cause_deaths	Study population		OR 1.18	1639	0000 13
	5 per 1000 6 per (2 to 1		(0.38 to 3.70)	(4 studies)	low <sup>3</sup>
	Moderate				- W-10-10-10
Immunogenicity		er 1000	OR 0.26 (0.06 to 1.09)	1788 (5 studies)	⊕⊕⊝⊝ low <sup>1,3,4</sup>
	(9 to 1			orresponding risk (and it	

\*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Ct: Confidence interval, OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

hetergeneity
 imprecision
 serious imprecision
 large effect