Supplementary Table S1 Treatments received before and after randomization until Day 14. Values are n (%**).**

A Tocilizumab.

	Tocilizumab (N=49)			UC (N=43)		
Time from randomization	Before	After	Any	Before	After	Any
Anticoagulants	17 (35)	24 (49)	34 (69)	14 (40)	20 (47)	29(67)
Antibiotics	36 (73)	32 (65)	46 (94)	27 (63)	31 (72)	38 (88)
- Azithromycin	5 (10)	1 (2)	5 (10)	6 (14)	3 (7)	8 (19)
Hydroxychloroquine	10 (20)	0 (0)	10 (20)	6 (14)	0 (0)	6 (14)
Antiviral drugs	5 (10)	3 (6)	8 (16)	3 (7)	2 (5)	4 (9)
- Lopinavir/Ritonavir	2 (4)	3 (6)	5 (10)	1 (2)	1 (2)	2 (5)
- Osteltamivir	3 (6)	0 (0)	3 (6)	2 (5)	1 (2)	2 (5)
Immuno-modulators	0 (0)	0 (0)	0 (0)	0 (0)	1 (2) *	1 (2) *
Corticosteroids	8 (16)	17 (35)	20 (41)	4 (9)	14 (33)	17 (40)
- Dexamethasone	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)

* Tocilizumab provided at day 4 and at day 6

B Sarilumab.

	Sarilumab (N=48)			UC (N=33)		
Time from randomization	Before	After	Any	Before	After	Any
Anticoagulants	26 (55)	29 (62)	43 (91)	17 (52)	19 (58)	30 (91)
Antibiotics	24 (51)	28 (60)	34 (72)	18(55)	23 (70)	30 (91)
- Azithromycin	7 (15)	1 (2)	8 (17)	3 ()	1 (3)	4 (12)
Hydroxychloroquine	3 (6)	3 (6)	6 (13)	2 (6)	1 (3)	3 (9)
Antiviral drugs	2 (4)	1 (2)	3 (7)	1 (3)	0 (0)	1 (3)
- Lopinavir/Ritonavir	2 (4)	1 (2)	3 (7)	1 (3)	0 (0)	1 (3)
Immuno-modulators	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids	0 (0)	10 (21)	10 (21)	2 (6)	6 (18)	7 (21)
- Dexamethasone	0 (0)	1 (2)	1 (2)	0 (0)	1 (3)	1 (3)

Supplementary Table S2. Day 4 outcome

A TOCILZUMAB

	Tocilizumab	Usual care	Risk Difference	Adjusted Odds Ratio
N	49	43		
N (%) not improved	35 (71%)	30 (70%)		
Posterior Median	70.9%	69.2	+1.7%	1.04
90% CrI			-13.6 to +17.1	0.47 to 2.29
95% CrI	57.5 to 82.1	54.8 to 81.4	-16.4 to +20.0	0.40 to 2.65
Posterior probabilities*				
P(any benefit)			0.429	0.465
P(at least moderate benefit)			0.220	0.333

P(any benefit)=P(RD<0) or P(OR<1), P(at least moderate benefit)=P(RD<5.5%) or P(OR<0.85)

B SARILUMAB

	Sarilumab	Usual care	Risk Difference	Adjusted Odds Ratio
N	48	33		
N (%) not improved	34 (71%)	26 (79%)		
Posterior Median	70.3%	77.7	-7.3%	0.57
90% CrI			-22.5 to +8.7	0.21 to 1.42
95% CrI	56.7 to 81.7	62.1 to 89.3	-25.3 to +11.9	0.17 to 1.69
Posterior probabilities*				
P(any benefit)			0.777	0.846
P(at least moderate benefit)			0.575	0.764

P(any benefit)=P(RD<0) or P(OR<1), P(at least moderate benefit)=P(RD<5.5%) or P(OR<0.85)

Supplementary Table S3. Summary of the posterior distribution of the hazard ratio (HR) adjusted for age and center. A HR>1 indicates efficacy of tocilizumab or sarilumab.

A TOCILIZUMAB

Parameter	Value
Median HR	1.19
90% CrI	0.71 to 2.04
95% CrI	0.64 to 2.27
P(HR > 1)	0.714
P(HR > 1/0.95)	0.656
P(HR > 1/0.85)	0.519
P(HR > 1/0.8)	0.443

B SARILUMAB

Parameter	Value
Median HR	1.05
90% CrI	0.55 to 2.07
95% CrI	0.49 to 2.37
P(HR > 1)	0.549
P(HR > 1/0.95)	0.498
P(HR > 1/0.85)	0.389
P(HR > 1/0.8)	0.334

Supplementary Table S4. Summary of the posterior distribution of the unadjusted hazard ratio (HR). A HR>1 indicates efficacy of tocilizumab or sarilumab

A TOCILIZUMAB

Parameter	Value
Median HR	1.20
90% CrI	0.72 to 2.04
95% CrI	0.65 to 2.27
P(HR > 1)	0.719
P(HR > 1/0.95)	0.662
P(HR > 1/0.85)	0.527
P(HR > 1/0.8)	0.451

B SARILUMAB

Parameter	Value
Median HR	1.17
90% CrI	0.63 to 2.26
95% CrI	0.56 to 2.59
P(HR > 1)	0.662
P(HR > 1/0.95)	0.610
P(HR > 1/0.85)	0.496
P(HR > 1/0.8)	0.433

Supplementary Table S5: Subgroup analyses for the primary outcome (TOCI-2 protocol)
Analyses according to antivirals at baseline were pre-specified in the protocol, but only 8 patients (5 tocilizumab, 3 usual care) were on antivirals at randomization.
Additional analyses according to corticosteroids and dexamethasone were added post-hoc to the SAP hoc in the light of publications or press releases. No patient was on dexamethasone at randomization, and only 12 (8 tocilizumab, 4 usual care) were receiving corticosteroids. Accordingly, no subgroup analysis was performed.
Post-hoc subgroup analyses according to the WHO-CPS score and the time from ICU admission to randomization (≤ 1 day vs. > 1 day) have been performed, as requested by the trial Scientific Committee.

	Tocilizumab (n=49)	Usual care (n=43)		Interaction
Subgroup	N events/N (%)	N events/N (%)	Adjusted HR (95% CI)	P-value
Antivirals at baseline				—
Yes	1/5 (20%)	2/3 (67%)	—	
No	22/44 (50%)	16/40 (40%)	—	
Corticosteroids at baseline				—
Yes	2/8 (25%)	1/4 (25%)	—	
No	21/41 (51%)	17/39 (44%)	—	
Dexamethasone at baseline				—
Yes	0/0 (—)	0/0 (—)	—	
No	23/49 (47%)	18/43 (42%)	—	
Delay from ICU admission*				0.15
≤ 1 day	13/25 (52%)	6/16 (38%)	1.75 (0.63 to 4.83)	
> 1 day	4/17 (24%)	8/22 (36%)	0.58 (0.17 to 1.93)	
WHO-CPS score at randomization				0.65
6	11/13 (85%)	8/12 (67%)	1.60 (0.61 to 4.20)	
≥ 7	12/36 (33%)	10/31 (32%)	1.12 (0.48 to 2.62)	
CRP**				0.002
≤ 150 mg/L	14/19 (74%)	2/13 (15%)	6.60 (2.50 to 17.4)	
> 150 mg/L	9/26 (35%)	11/20 (55%)	0.36 (0.15 to 0.83)	

* Excluded 7 and 4 patients not in the ICU at randomization in the tocilizumab and usual care arm, respectively, and 1 patient with unknown date of ICU admission. ** 4 and 10 missing data in the tocilizumab and usual care arm, respectively.

Supplementary Table S6 : Subgroup analyses for the primary outcome (SARI-2 protocol)
Analyses according to antivirals at baseline were pre-specified in the protocol, but only 3 patients (2 sarilumab, 1 usual care) were on antivirals at randomization.
Additional analyses according to corticosteroids and dexamethasone were added post-hoc to the SAP in the light of publications. No patient was on dexamethasone at randomization, and only 2 (0 sarilumab, 2 usual care) were receiving corticosteroids.
Accordingly, no subgroup analysis stratified on these variables was performed.
Post-hoc subgroup analyses according to the WHO-CPS score and the time from ICU admission to randomization (≤ 1 day vs. > 1 day) have been performed, as requested by the trial Scientific Committee.

	Sarilumab (n=48)	Usual care (n=33)		Interaction
Subgroup	N events/N (%)	N events/N (%)	Adjusted HR (95% CI)	*P*-value
Antivirals at baseline				—
Yes	0/2 (0%)	0/1 (0%)	—	
No	18/46 (39%)	11/32 (34%)	—	
Corticosteroids at baseline				—
Yes	0/0 (—)	1/2 (50%)	—	
No	18/48 (38%)	10/31 (32%)	—	
Dexamethasone at baseline				—
Yes	0/0 (—)	0/0 (—)	—	
No	18/48 (38%)	11/33 (33%)	—	
Delay from ICU admission*				0.086
≤ 1 day	1/11 (9%)	3/10 (30%)	0.22 (0.022 to 2.26)	
> 1 day	11/27 (41%)	4/18 (22%)	1.78 (0.54 to 5.80)	
WHO-CPS score at randomization				0.074
6	8/16 (50%)	7/9 (78%)	0.45 (0.16 to 1.30)	
≥ 7	10/32 (31%)	10/24 (17%)	1.84 (0.57 to 4.98)	
CRP**				0.78
≤ 150 mg/L	8/14 (57%)	5/10 (50%)	1.17 (0.41 to 3.32)	
> 150 mg/L	10/34 (29%)	6/21 (29%)	1.00 (0.31 to 3.24)	

* Excluded 10 and 5 patients not in the ICU at randomization in the sarilumab and usual care arm, respectively.
** Two missing data

Supplementary Table S7. WHO scores during follow-up. OR was obtained from Bayesian proportional odds models adjusted for baseline WHO-CPS score, age and center. For longitudinal data, time was used as a main effect in the model. No imputation was performed, but a window of plus/minus 2 days was used for day 14 scores.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N	Median (IQR)	N	Median (IQR)	Adjusted OR (95% CrI)
Day 1	49	7 (6 to 8)	43	8 (6 to 8)	—
Day 4	49	7 (7 to 8)	43	8 (7 to 8)	0.85 (0.39 to 1.82)
Day 7	48	7 (5 to 8)	43	8 (7 to 8)	0.69 (0.32 to 1.47)
Day 14	48	7 (5 to 8)	43	7 (5 to 9)	0.68 (0.32 to 1.43)
Longitudinal analysis	49	-	43	-	0.76 (0.27 to 2.13)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N	Median (IQR)	N	Median (IQR)	Adjusted OR (95% CrI)
Day 1	48	8 (6 to 8)	33	7 (6 to 8)	—
Day 4	48	7 (7 to 8)	33	8 (7 to 8)	0.88 (0.38 to 2.02)
Day 7	48	8 (7 to 8)	33	8 (7 to 8)	1.07 (0.47 to 2.40)
Day 14	47	7 (5 to 10)	33	7 (5 to 10)	1.13 (0.50 to 2.57)
Longitudinal analysis	48	—	33	—	0.720.21 to 2.41)

Supplementary Table S8. Day 28 ventilator-free days

For patients not ventilated at baseline, the time before ventilation (if it occurred) was considered as ventilator-free. Those never intubated during the first 28 days had 28 ventilator-free days. In all cases, the time horizon (28 days) was counted from randomization. A separate analysis was performed excluding patients not ventilated at randomization (WHO-CPS scores 6). Results are mean (SD). Confidence intervals were obtained by bootstrapping.

A TOCILIZUMAB

	Tocilizumab		Usual care		Mean difference
	N	CIF (95% CI)	N	CIF (95% CI)	(95% CI)
All patients	49	12.8 (10.7)	43	10.3 (11.1)	-2.5 (-6.9 to +1.7)
WHO-CPS ≥ 7	36	9.8 (9.5)	31	7.2 (9.4)	-2.5 (-6.6 to +2.7)

B SARILUMAB

	Sarilumab		Usual care		Mean difference
	N	Mean (SD)	N	Mean (SD)	(95% CI)
All patients	48	10.3 (11.1)	33	8.7 (11.0)	-1.5 (-6.1 to +3.9)
WHO-CPS ≥ 7	32	7.5 (9.5)	24	4.6 (7.6)	-2.9 (-7.4 to +1.7)

Supplementary Table S9. Cumulative incidence of oxygen supply independency until 28 days. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	13	26% (15 to 40)	7	16% (7 to 29)	—
Day 28	29	59% (44 to 72)	21	49% (33 to 63)	1.44 (0.82 to 2.52)
Day 90	34	69% (53 to 80)	28	64% (47 to 77)	1.28 (0.80 to 2.03)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	12	25% (14 to 38)	6	18% (7 to 33)	—
Day 28	21	44% (29 to 57)	12	36% (20 to 53)	1.20 (0.59 to 2.44)
Day 90	33	71% (52 to 83)	18	56% (35 to 72)	1.29 (0.74 to 2.25)

Supplementary Table S10. Cumulative incidence of discharge. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	13	26% (15 to 40)	7	16% (7 to 29)	—
Day 28	29	59% (44 to 72)	21	49% (33 to 63)	1.44 (0.82 to 2.52)
Day 90	34	69% (53 to 80)	28	64% (47 to 77)	1.28 (0.80 to 2.03)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	12	25% (14 to 38)	6	18% (7 to 33)	—
Day 28	21	44% (29 to 57)	12	36% (20 to 53)	1.20 (0.59 to 2.44)
Day 90	33	71% (52 to 83)	18	56% (35 to 72)	1.29 (0.74 to 2.25)

Supplementary Table S11. Cumulative incidence of ICU discharge for patients in the ICU at inclusion. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=40)		Usual care (n=37)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	16	40% (25 to 55)	16	43% (27 to 58)	—
Day 28	29	72% (55 to 84)	22	60% (42 to 74)	1.28 (0.73 to 2.24)
Day 90	33	84% (66 to 93)	30	83% (63 to 93)	1.15 (0.73 to 1.81)

B SARILUMAB

	Sarilumab (n=38)		Usual care (n=28)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	16	42% (26 to 57)	14	50% (30 to 67)	—
Day 28	23	60% (43 to 74)	20	71% (50 to 85)	0.78 (0.42 to 1.44)
Day 90	30	79% (61 to 89)	23	82% (57 to 93)	0.84 (0.49 to 1.47)

Supplementary Table S12. **Overall survival at 14, 28 and 90 days.**

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N deaths	OS (95% CI)	N deaths	OS (95% CI)	Adjusted HR (95% CI)
Day 14	5	90% (82 to 99)	9	79% (68 to 92)	0.37 (0.12 to 1.15)
Day 28	8	84% (74 to 95)	10	77% (65 to 90)	0.56 (0.22 to 1.46)
Day 90	12	76% (64 to 89)	13	70% (57 to 85)	0.67 (0.30 to 1.49)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N deaths	OS (95% CI)	N deaths	OS (95% CI)	Adjusted HR (95% CI)
Day 14	12	75% (64 to 88)	9	73% (59 to 90)	0.95 (0.40 to 2.25)
Day 28	14	71% (59 to 85)	11	67% (52 to 85)	0.89 (0.40 to 1.96)
Day 90	14	71% (59 to 85)	13	61% (46 to 80)	0.74 (0.35 to 1.58)

Supplementary Table S13. Serious adverse events and causes of deaths.

A TOCILIZUMAB

	Tocilizumab (N=49)	**UC (N=43)**	***P***
Adverse events			
- Patients with at least one AE*	33 (67%)	30 (70%)	0.83*
- Patients with multiple AE	24 (49%)	24 (56%)	
- Number of events**	176	177	0.20**
Serious adverse events			
- Patients with at least one SAE	31 (63%)	27 (63%)	1.00*
- Patients with multiple SAE	19 (39%)	23 (9%)	
- Number of events	93	55	0.020**
Angina	1	0	
Arthritis	1	0	
Hemorrhagic stroke	1	2	
Ischemic stroke	1	2	
Hypovolemic shock	1	0	
Diabetes	1	0	
Anemia	7	7	
Hepatic cholestasis	3	2	
Hepatic cytolysis	9	3	
Pneumothorax	1	1	
Pulmonary embolism	4	1	
Thrombophlebitis	1	0	
Thrombopenia	1	1	
ARDS	13	15	
Bacterial sepsis	25	12	
Fungal sepsis	2	1	
Severe acute pancreatis	1	0	
Thrombopenia	1	0	
Neutropenia	1	0	
Renal failure	4	4	
Adrenal insufficiency	1	0	
Hyperleukocytosis	1	0	
Arterial hypertension	1	0	
Metabolic acidosis	1	0	
Guillain Barré syndrome	1	0	
Hemoptysis	1	0	
Gastrointestinal bleeding	1	0	
Bleeding	1	0	
Limb ischemia	1	0	
Neuropathy	1	0	
Acute pulmonary oedema	2	0	
Tracheotomy	1	1	
Psoas hematoma	1	0	
Bradycardia	0	1	
Heart failure	0	1	

	Tocilizumab (N=49)	UC (N=43)	*P*
Facial paralysis	0	1	
Death	12 (24%)	13 (30%)	
- Causes			
ARDS	7	7	
Bacterial sepsis	2	2	
Fungal sepsis	0	1	
Multiple organ failure	0	1	
Hemorrhagic stroke	1	2	
Pulmonary embolism	2	0	

* Fisher's exact test
** Poisson model

B SARILUMAB

	Sarilumab (N=48)	UC (N=33)	*P*
Adverse events			
- Patients with at least one AE*	32 (68%)	22 (68%)	1.00*
- Patients with multiple AE	18 (38%)	17 (52%)	
- Number of events**	79	67	0.2062**
Serious adverse events			
- Patients with at least one SAE	31 (64.6%)	19 (57.6%)	0.6426*
- Patients with multiple SAE	14 (29.2%)	7 (21.2%)	
- Number of events	69	34	0.1119**
Acidosis	1	0	
Allergy to sarilumab	1	0	
Severe constipation	1	0	
Accidental extubation	1	0	
Cerebral hemorrhage	1	0	
Hyperkalemia	1	0	
Lymphopenia	2	1	
Neuromuscular abnormalities acquired in ICU	2	1	
Cardiac rythm disorder	2	0	
Diabetes	2	0	
Anemia	4	2	
Hepatic cytolysis	5	3	
Pulmonary embolism	2	2	
ARDS	15	9	
Bacterial sepsis	18	4	
Fungal sepsis	1	0	
Neutropenia	2	0	
Renal failure	4	4	
Gastrointestinal bleeding	1	2	
Lower limbs ischemia	1	0	
Heart failure	2	0	
Complication of tracheostomy	0	1	
Bone fracture	0	1	
Hypoalbuminemia	0	1	
Hypotension	0	2	
Transient ischemic attack	0	1	
Death	14 (29%)	13 (39%)	
- Causes			
ARDS	11	7	
Bacterial sepsis	0	1	
Multiple organ failure	0	5	
Cerebral hemorrhage	1	0	

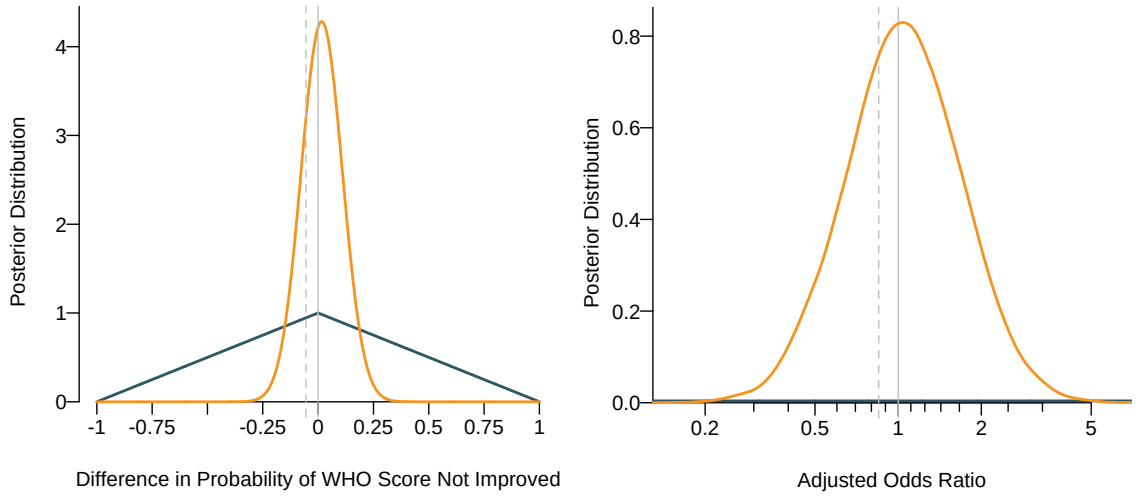
	Sarilumab (N=48)	UC (N=33)	*P*
Pulmonary embolism	1	0	
Heart failure	1	0	

* Fisher's exact test

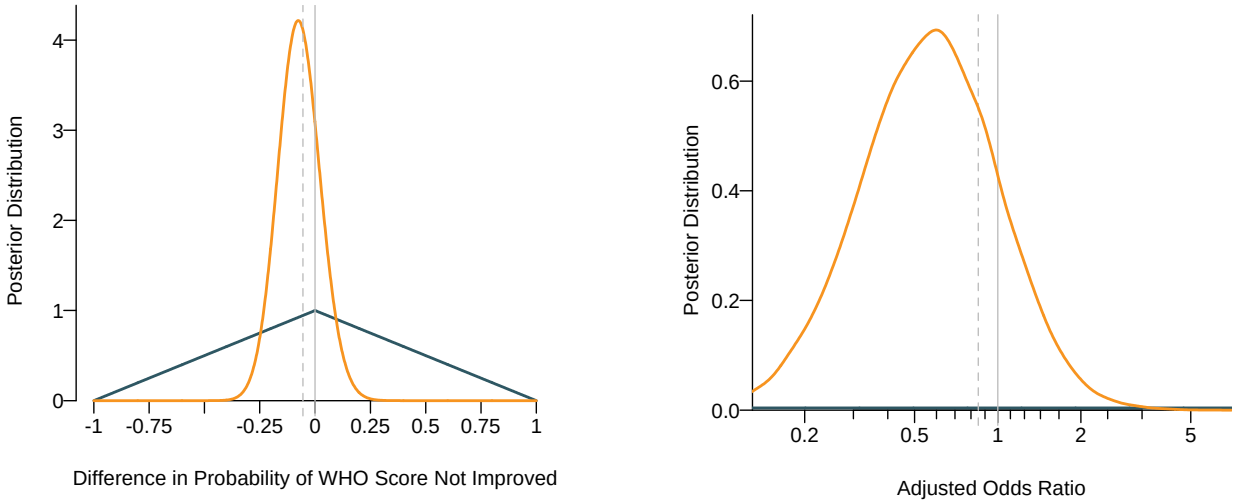
** Poisson model

Supplementary Figure S1 A (TOCI-2) and B (SARI-2).
Posterior density of the risk difference and adjusted odds ratio for the day 4 outcome (golden line). The dark blue line represents the minimally informative priors. The solid gray lines indicates an RD of 0 or an OR of 1, representing no treatment effect, and the dashed gray lines indicate a moderate benefit (RD = 5.5%, OR=0.85).

A TOCILIZUMAB

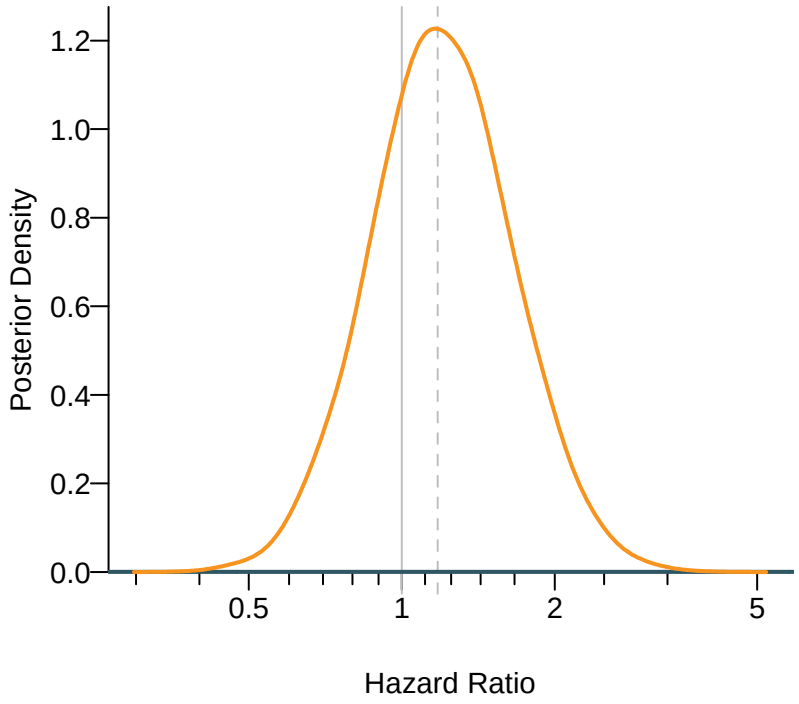


B SARILUMAB

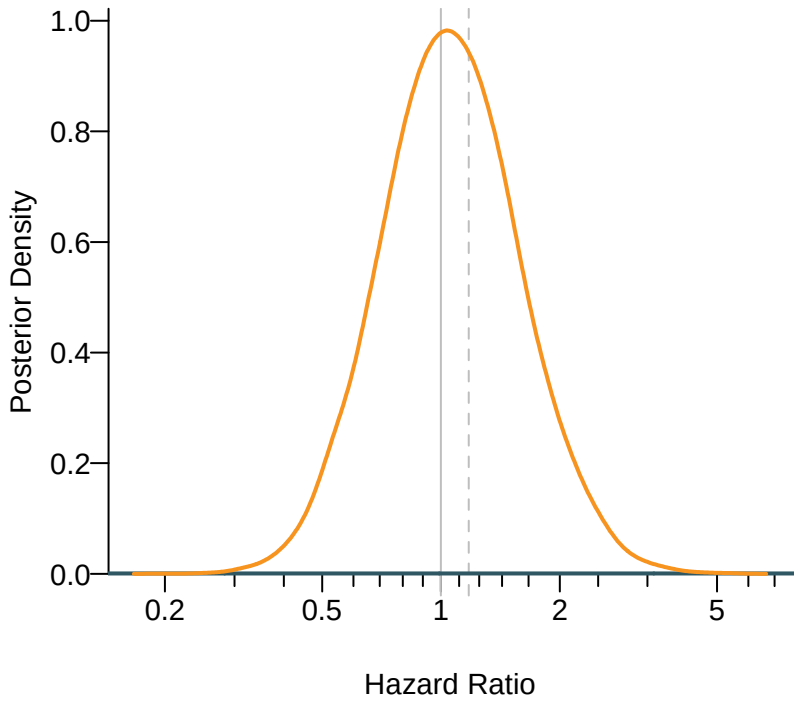


Supplementary Figure S2 A (TOCI-2) and B (SARI-2). Posterior density of the adjusted hazard ratio for the primary outcome (golden line). The dark blue line represents the minimally informative prior. The solid gray line indicates a HR of 1 representing no treatment effect. The dashed gray line indicates a HR of 1.18 (1/0.85) indicating a moderate benefit.

A TOCILIZUMAB

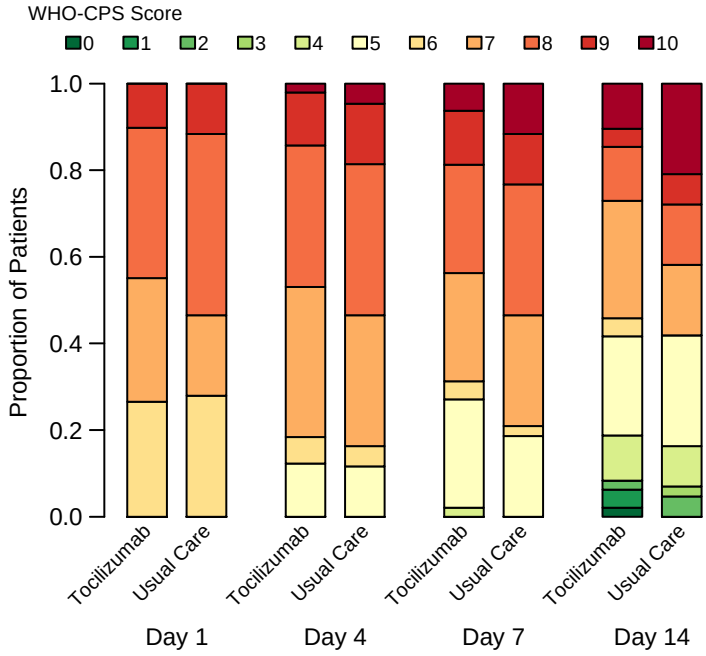


B SARILUMAB

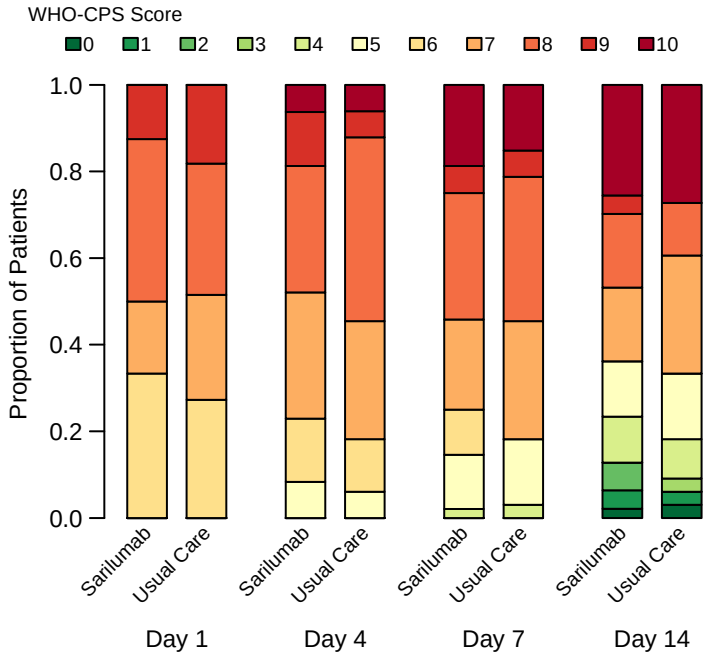


Supplementary Figure S3. WHO score during follow-up. (TOCI-2) and B (SARI-2).

A TOCILIZUMAB

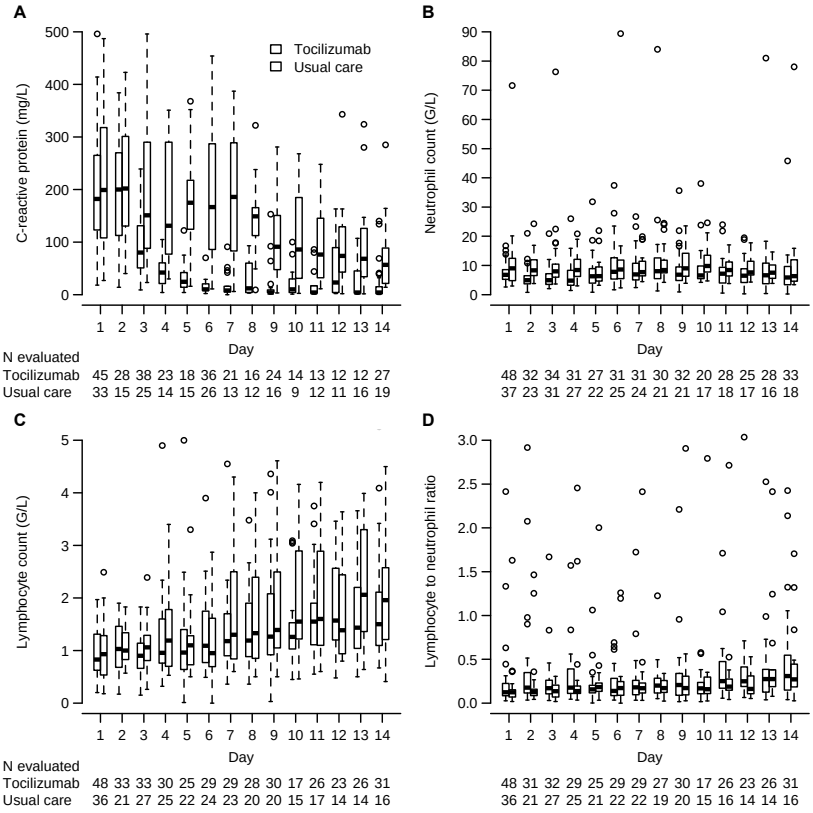


B SARILUMAB

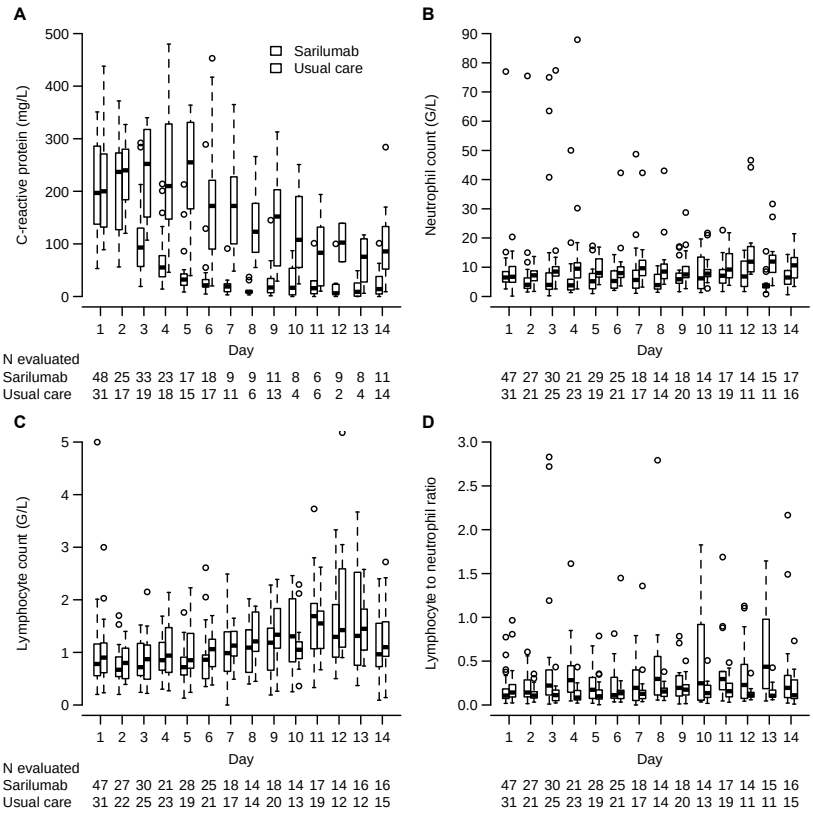


Supplementary Figure S4. Evolution of biological parameters TOCI-2 and SARI-2 protocols

A TOCILIZUMAB



B SARILUMAB

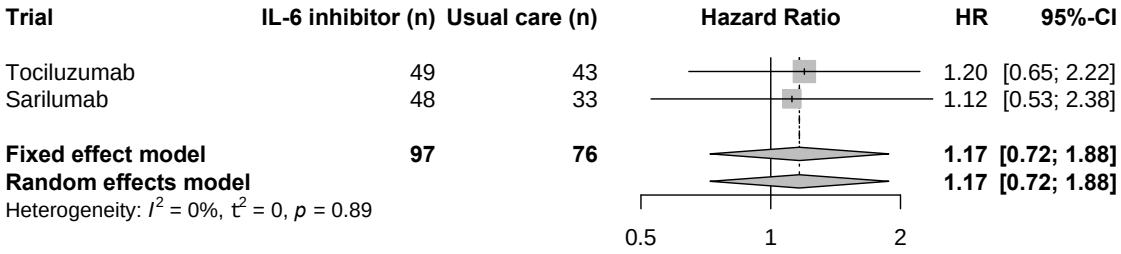


Supplementary Figure S5

(A) Forest plot of the two-stage pooled analysis of the day 14 co-primary outcome. A HR > 1 indicates the efficacy of tocilizumab/sarilumab compared to usual care. No heterogeneity was found ($\tau^2 = 0$).

(B) Forest plot of the two-stage pooled analysis of the day 90 survival outcome. A HR < 1 indicates the efficacy of tocilizumab/sarilumab compared to usual care. No heterogeneity was found ($\tau^2 = 0$).

A



B