Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. DOI: 10.1056/NEJMoa2028700

SUPPLEMENTARY MATERIAL

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Appendix 2. Supplementary Methods.

Additional study design details

The study was designed and overseen by the sponsor, F. Hoffmann-La Roche Ltd., with input from selected investigators. Data were collected by the investigators and site staff and entered into an electronic data capture database designed and maintained by the sponsor. The manuscript was reviewed and revised by all authors, who approved the manuscript and agreed to submit it for publication.

Additional study procedure details

Informed consent

Informed consent was obtained for all enrolled patients. To accommodate the pandemic situation, if allowed by local regulations, as per the protocol, nonwritten consent could be obtained from the patient's legally authorized representative and documented by the investigator or designee.

Blinding of posttreatment IL-6 and CRP results

CRP levels after treatment, which typically decrease rapidly following tocilizumab administration, could have undone the blinding of investigators. Therefore, according to the protocol, investigators and sponsor were blinded to baseline and posttreatment IL-6 and CRP results during the study. Investigators were discouraged from measuring IL-6 or CRP at local laboratories.

Determination of ordinal scale categories

Clinical status was captured on the ordinal scale in the electronic case report form. However, death and discharge were also captured on additional electronic forms. Confirmation of death or discharge, which could be captured any time of day on these additional forms, was used

for the study day in preference to ordinal scale data if different or if missing because the ordinal scale was captured only once a day, in the morning. Death (ordinal scale category 7) or discharge (ordinal scale category 1) was used in the analysis of clinical status going forward (unless the patient was readmitted). Any remaining missing data for clinical status for the primary analysis (3.7% in the tocilizumab group and 2.1% in the placebo group) were imputed using the last postbaseline observation carried forward.

Investigators were instructed to assign patients who were "ready for discharge"—as evidenced by normal body temperature, normal respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen—to category 1 if they were still hospitalized for nonmedical reasons.

The prespecified point estimate of the treatment effect for the primary endpoint was an odds ratio; the assumption of proportional odds was not met for this analysis (score test P=0.0005 for treatment). Therefore, any odds ratios should not be used for statistical comparisons. They are included in this supplement for a complete representation of planned analyses.

Additional statistical analysis details

Sample size estimation

Assumed distribution of the ordinal scale in the placebo arm

Category	1 (discharge)	2	3	4	5	6	7 (death)
Proportion	0.58	0.05	0.09	0.09	0.02	0.02	0.15

Expected distribution of the ordinal scale in the tocilizumab arm (assuming proportional odds) with an odds ratio of 2

Category	1 (discharge)	2	3	4	5	6	7 (death)
Proportion	0.734	0.039	0.064	0.058	0.012	0.012	0.081

Under these assumptions, the total modified-intention-to-treat sample size of 450 patients with a 2:1 randomization of tocilizumab to placebo provides approximately 90% power to detect a difference in distribution of the ordinal scale at week 28 between the treatment arms using a 2-sided van Elteren test at the 5% significance level. The sample size also provides 90% power to detect a ratio of 2 (tocilizumab to placebo) for the odds of being in a category or a better category under the assumptions of the expected probability distribution of patients in the placebo arm using a proportional odds model with a 2-sided P value at the 5% significance level. Assuming proportional odds and the assumed distribution in the placebo arm, the smallest odds ratio that could be statistically significant would be approximately 1.5. Finally, the sample size provides approximately 90% power to detect a 10% absolute difference in mortality rate assuming a mortality rate of 15% in the placebo arm. Based on these assumptions, the minimal difference that could be statistically significant is approximately 7%.

Missing data handling for the primary endpoint

A multiple imputation approach for missing data (3 patients in the placebo arm and 11 patients in the tocilizumab arm) was performed using bootstrapping by sampling with replacement from nonmissing data within treatment group and strata, assuming the data were missing at random. The imputed data were combined with the nonmissing data to give complete data sets of the same size as the mITT population. This was repeated to obtain 10,000 complete data sets. The van Elteren P value and odds ratio were then derived as averages of the van Elteren P values and treatment estimates from the 10,000 data sets.

These treatment estimates and 95% CIs are provided in the [0,0] grid reference in Tables S4 and S5. To test the sensitivity of these results to the missing-at-random assumption for each of the 10,000 data sets, only the imputed data points were then adjusted independently by treatment group to worse or better outcomes according to a delta (addition of 1 to 6 or minus 1 to 6, as shown in Tables S4 and S5). After the delta was applied, adjusted scores below 1 or above 7 were capped at 1 or 7, respectively, so that the data were within the range of possible values for the ordinal scale. With this approach, the range of odds ratios and confidence intervals was consistent with our conclusion of no treatment effect.

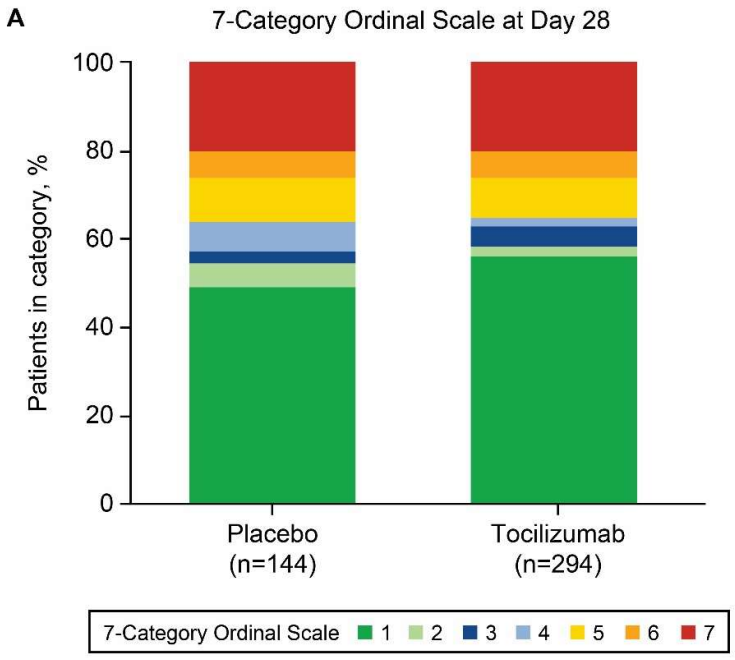
A prespecified analysis of the primary endpoint with last observation carried forward (LOCF) for missing data is included for completeness and shows similar results as the multiple imputation method.

Sensitivity analyses

To account for the competing risk for death, time to discharge/ready for discharge and time to improvement in clinical status were analyzed with the use of cause-specific Cox regression. Results are presented in Table S7.

Figure S1. Clinical Status Assessed Using 7-Category Ordinal Scale (A) at Day 28 and (B) Over Time (modified-intention-to-treat population).

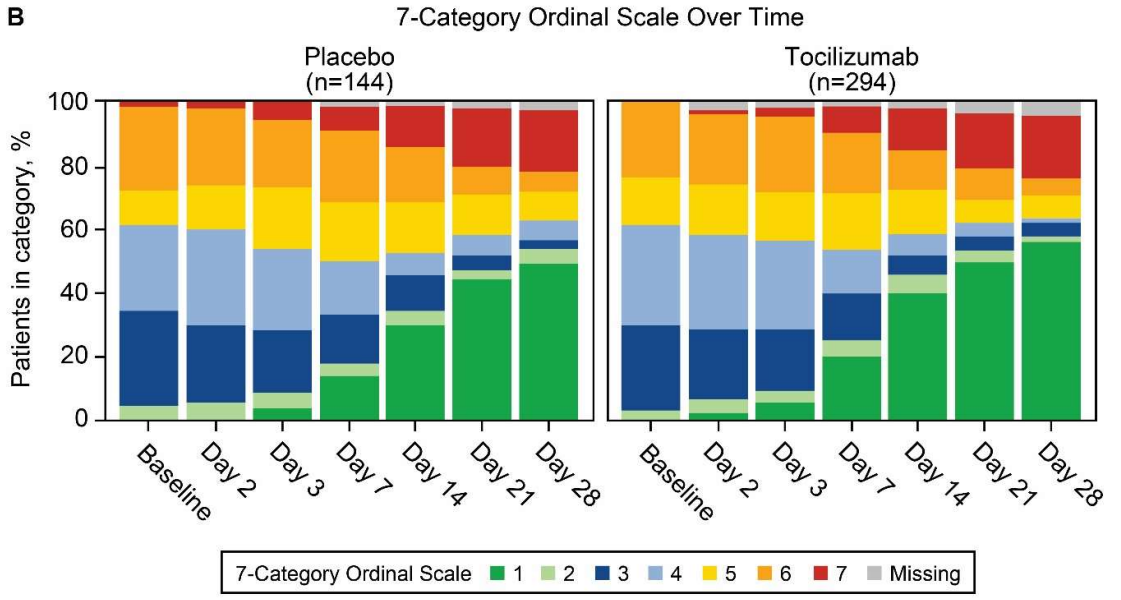
7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.



Number (%) of patients in category at day 28

	Placebo	Tocilizumab
7	28 (19.4)	58 (19.7)
6	9 (6.3)	18 (6.1)
5	14 (9.7)	26 (8.8)
4	10 (6.9)	6 (2.0)
3	4 (2.8)	14 (4.8)
2	8 (5.6)	6 (2.0)
1	71 (49.3)	166 (56.5)

B



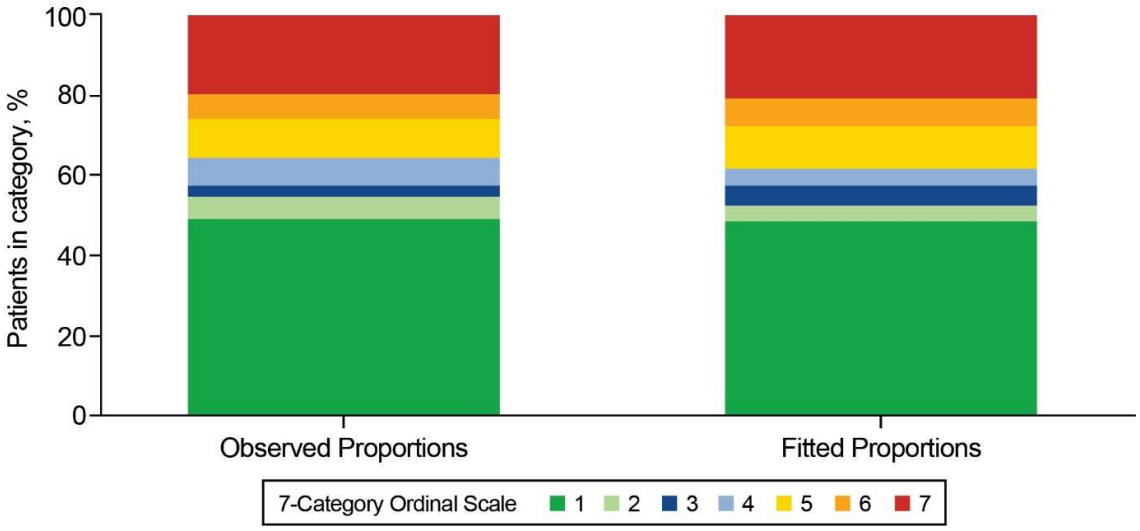
	Placebo, n (%)							Tocilizumab, n (%)						
Category	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
7	1 (0.7)	2 (1.4)	7 (4.9)	11 (7.6)	19 (13.2)	27 (18.8)	28 (19.4)	0	2 (0.7)	8 (2.7)	25 (8.5)	39 (13.3)	52 (17.7)	58 (19.7)
6	39 (27.1)	35 (24.3)	31 (21.5)	33 (22.9)	25 (17.4)	12 (8.3)	9 (6.3)	68 (23.1)	67 (22.8)	71 (24.1)	56 (19.0)	37 (12.6)	29 (9.9)	16 (5.4)
5	15 (10.4)	20 (13.9)	28 (19.4)	27 (18.8)	23 (16.0)	19 (13.2)	13 (9.0)	45 (15.3)	47 (16.0)	45 (15.3)	52 (17.7)	41 (13.9)	21 (7.1)	21 (7.1)
4	39 (27.1)	44 (30.6)	37 (25.7)	24 (16.7)	10 (6.9)	9 (6.3)	9 (6.3)	94 (32.0)	88 (29.9)	83 (28.2)	41 (13.9)	20 (6.8)	13 (4.4)	5 (1.7)
3	44 (30.6)	35 (24.3)	29 (20.1)	22 (15.3)	16 (11.1)	7 (4.9)	4 (2.8)	78 (26.5)	65 (22.1)	57 (19.4)	44 (15.0)	18 (6.1)	13 (4.4)	12 (4.1)
2	6 (4.2)	8 (5.6)	7 (4.9)	6 (4.2)	7 (4.9)	4 (2.8)	7 (4.9)	9 (3.1)	13 (4.4)	11 (3.7)	15 (5.1)	18 (6.1)	11 (3.7)	5 (1.7)
1	0	0	5 (3.5)	20 (13.9)	43 (29.9)	64 (44.4)	71 (49.3)	0	6 (2.0)	16 (5.4)	59 (20.1)	117 (39.8)	147 (50.0)	166 (56.5)
Missing	0	0	0	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.1)	0	6 (2.0)	3 (1.0)	2 (0.7)	4 (1.4)	8 (2.7)	11 (3.7)

Figure S2. Fitted and Observed Proportions of Clinical Status Assessed Using 7-Category Ordinal Scale (A) in the Placebo Arm and (B) in the Tocilizumab Arm (modified-intention-to-treat population).

7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Death or discharge (without readmittance to hospital within the time frame) were carried forward (from any source), including deaths that occurred after withdrawal. Any remaining missing data were imputed using the last postbaseline observation carried forward method. Observed proportions were measured in the modified intention-to-treat population at day 28, and fitted proportions were modelled at day 28 by ordinal logistic regression analysis. The proportional odds model included the stratification factors applied at randomization of region (North America, Europe) and mechanical ventilation status (yes, no).

A. Placebo (N=144)



B. Tocilizumab (N=294)

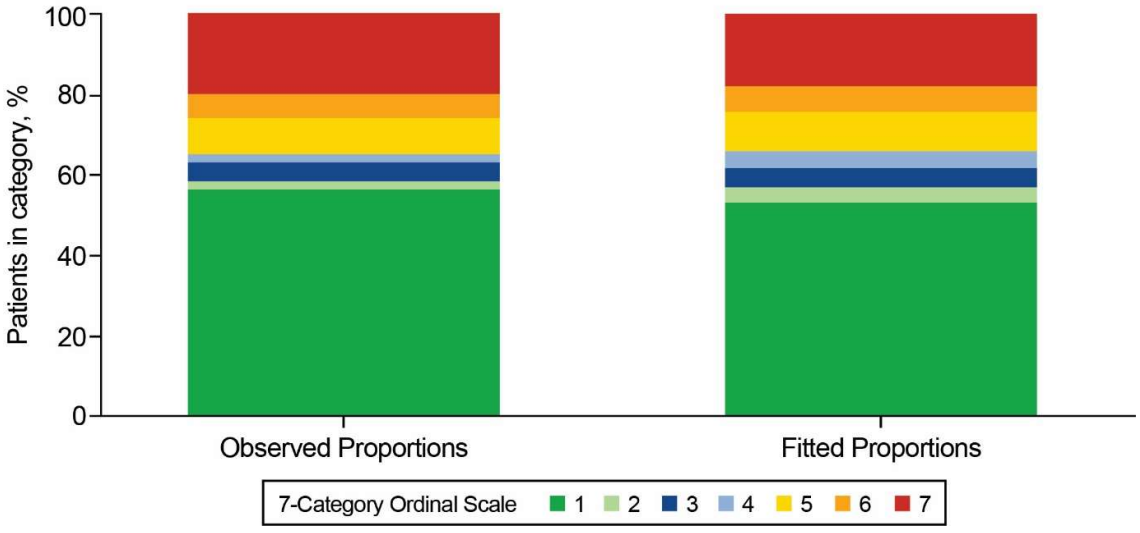
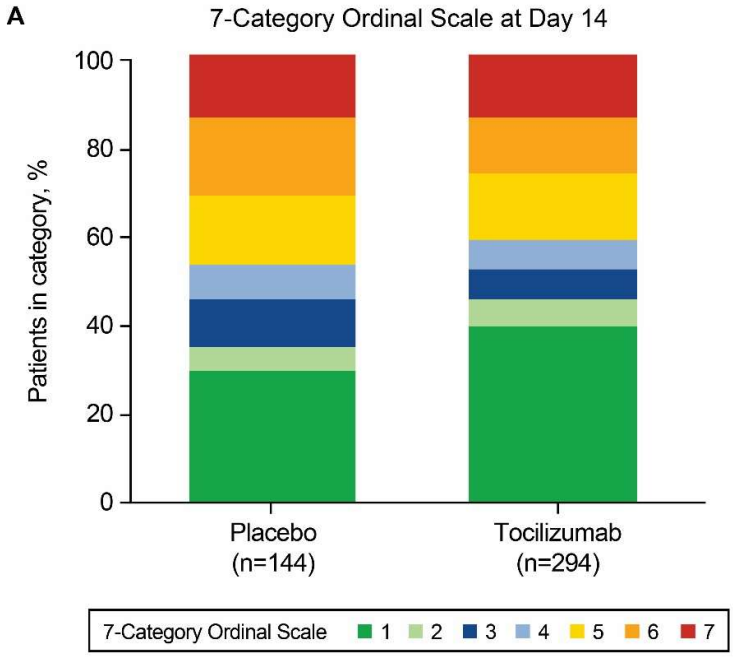


Figure S3. Clinical Status Assessed Using 7-Category Ordinal Scale (A) at Day 14 Overall and (B) According to Baseline Ordinal Scale Category (modified-intention-to-treat population).

7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Category 6 at baseline includes a patient who died on study day 1 (ordinal category 7) but was in category 6 on day 1 before receiving study treatment.

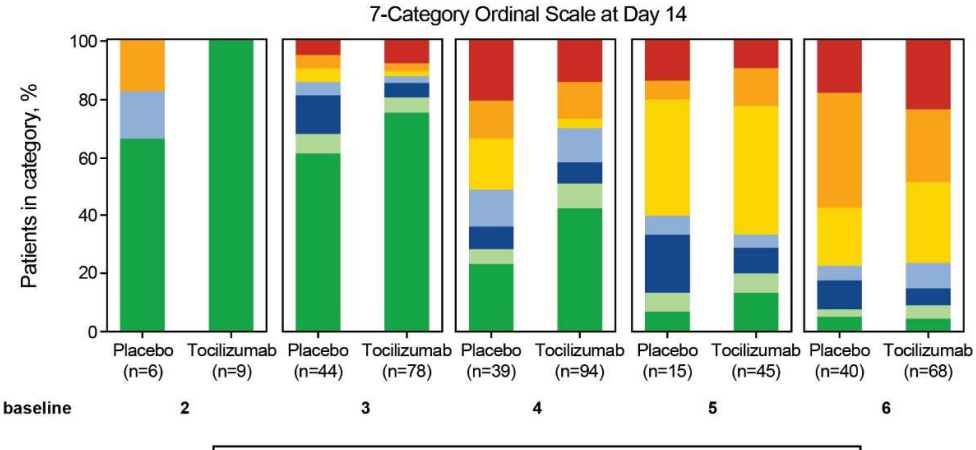
NE, not evaluable.



Number (%) of patients in category at day 14

	Placebo	Tocilizumab
7	19 (13.2)	39 (13.3)
6	25 (17.4)	37 (12.6)
5	23 (16.0)	43 (14.6)
4	11 (7.6)	21 (7.1)
3	16 (11.1)	19 (6.5)
2	7 (4.9)	18 (6.1)
1	43 (29.9)	117 (39.8)

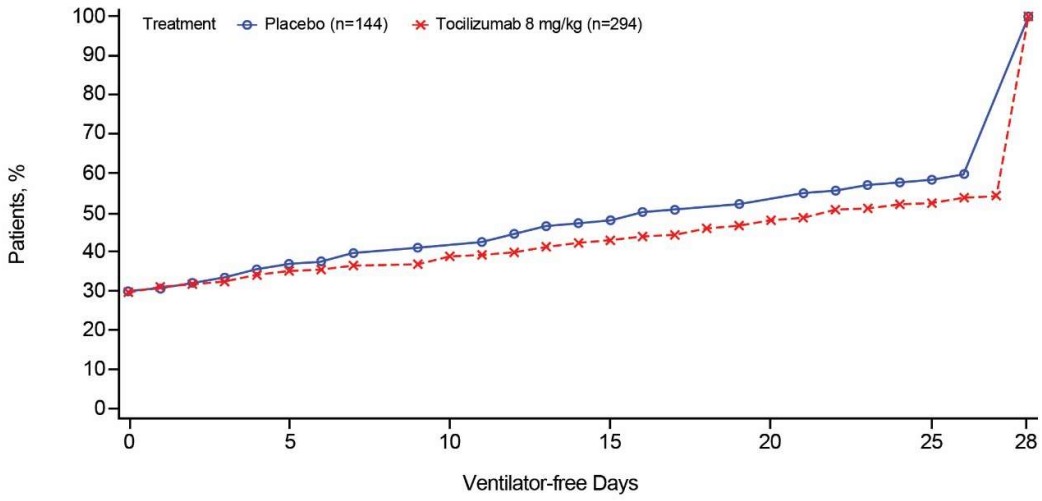
B



	Overall		Ordinal category at baseline									
			2		3		4		5		6	
Ordinal category at day 14, n (%)	**Placebo n=144**	**Tocilizumab n=294**	**Placebo n=6**	**Tocilizumab n=9**	**Placebo n=44**	**Tocilizumab n=78**	**Placebo n=39**	**Tocilizumab n=94**	**Placebo n=15**	**Tocilizumab n=45**	**Placebo n=40**	**Tocilizumab n=68**
7	19 (13.2)	39 (13.3)	0	0	2 (4.5)	6 (7.7)	8 (20.5)	13 (13.8)	2 (13.3)	4 (8.9)	7 (17.5)	16 (23.5)
6	25 (17.4)	37 (12.6)	1 (6.7)	0	2 (4.5)	2 (2.6)	5 (12.8)	12 (12.8)	1 (6.7)	6 (13.3)	16 (40.0)	17 (25.0)
5	23 (16.0)	43 (14.6)	0	0	2 (4.5)	1 (1.3)	7 (17.9)	3 (3.2)	6 (40.0)	20 (44.4)	8 (20.0)	19 (27.9)
4	11 (7.6)	21 (7.1)	1 (16.7)	0	2 (4.5)	2 (2.6)	5 (12.8)	11 (11.7)	1 (6.7)	2 (4.4)	2 (5.0)	6 (8.8)
3	16 (11.1)	19 (6.5)	0	0	6 (13.6)	4 (5.1)	3 (7.7)	7 (7.4)	3 (20.0)	4 (8.9)	4 (10.0)	4 (5.9)
2	7 (4.9)	18 (6.1)	0	0	3 (6.8)	4 (5.1)	2 (5.1)	8 (8.5)	1 (6.7)	3 (6.7)	1 (2.5)	3 (4.4)
1	43 (29.9)	117 (39.8)	4 (66.7)	9 (100)	27 (61.4)	59 (75.6)	9 (23.1)	40 (42.6)	1 (6.7)	6 (13.3)	2 (5.0)	3 (4.4)
OR (95% CI)	1.42 (0.99 to 2.05)		NE		1.80 (0.82 to 3.94)		2.10 (1.07 to 4.10)		0.89 (0.30 to 2.57)		1.06 (0.53 to 2.13)	
Median (95% CI)	4.0 (3.0 to 5.0)	3.0 (2.0 to 4.0)	1.0 (1.0 to 6.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 2.0)	1.0 (1.0 to 1.0)	5.0 (3.0 to 6.0)	2.0 (1.0 to 4.0)	5.0 (3.0 to 5.0)	5.0 (5.0 to 5.0)	6.0 (5.0 to 6.0)	5.0 (5.0 to 6.0)
Difference in medians (95% CI)	-1.0 (-2.0 to 0.5)		0.0 (-4.0 to 0.0)		0.0 (-1.0 to 0.0)		-3.0 (-4.0 to 0.0)		0.0 (0.0, 2.0)		-1.0 (-1.0 to 1.0)	

Figure S4. Cumulative Distribution of Ventilator-Free Days to Day 28 (modified-intention-to-treat population).

Patients who died up to day 28 were assigned zero ventilator-free days. Days from discharge to day 28 were counted as ventilator-free days. For patients withdrawn but not discharged, the remainder of days to day 28 were counted as ventilator-free days if they were not using mechanical ventilation at the time of withdrawal and the days were not ventilator-free days otherwise. If data were missing for patients who had not withdrawn, died, or been discharged, the last postbaseline observation was carried forward until the next observation. The table describes the distribution for the modified ITT population and also for the subset of patients alive at day 28 (with patients who died up to day 28 excluded from the summary).



Distribution of ventilator-free days	**Placebo N=144**	**Tocilizumab N=294**
Modified ITT population, n	144	294
Median (95% CI)*	16.5 (11.0 to 26.0)	22.0 (18.0 to 28.0)
25th percentile (95% CI)*	0.0 (0.0 to 3.0)	0.0 (0.0 to 1.0)
75th percentile (95% CI)*	28.0 (28.0 to 28.0)	28.0 (28.0 to 28.0)
Patients alive at day 28, n	116	236
Median (95% CI)	27 (21 to 28)	28 (28 to 28)
25th percentile (95% CI)	8 (3 to 13)	13 (6 to 18)
75th percentile (95% CI)	28 (28 to 28)	28 (28 to 28)
Patients assigned 0 ventilator-free days*	28	58

*Patients who died by day 28 were assigned 0 ventilator-free days.

Figure S5. Cumulative Incidence Function Plot of (A) Time to Improvement in Clinical Status on the 7-Category Ordinal Scale, (B) Time to Hospital Discharge/Ready for Discharge, and (C) Mortality to Day 28 (modified-intention-to-treat population).

Time to improvement in clinical status was defined as days from first dose of study drug to the time of at least a 2-category improvement in clinical status on the 7-category ordinal scale. Time to hospital discharge (or ready for discharge) was defined as days from the first dose of study drug to hospital discharge (or ready for discharge, defined as normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen). Patients who discontinued or who were lost to follow-up before improvement in clinical status or before ready for discharge criteria were met were censored at their last ordinal scale assessment. Cumulative incidence plots were produced using the nonparametric Aalen-Johansen estimator.

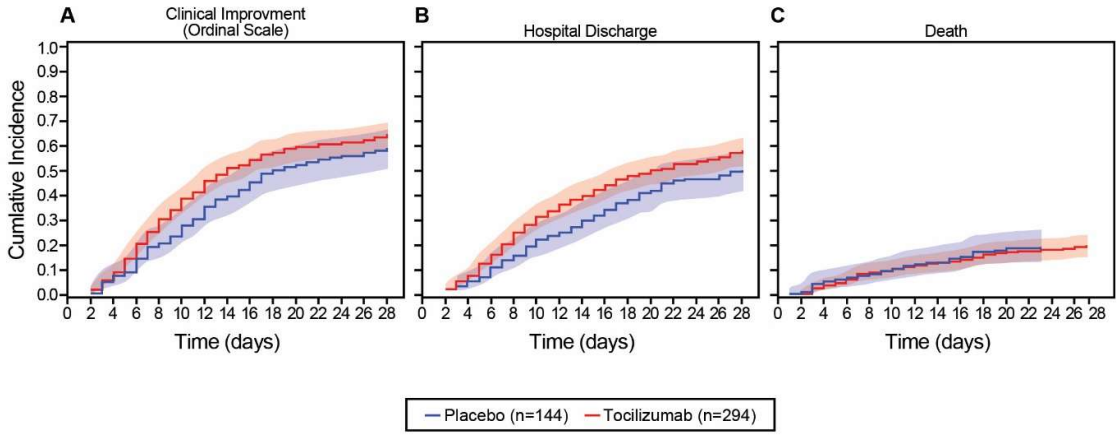
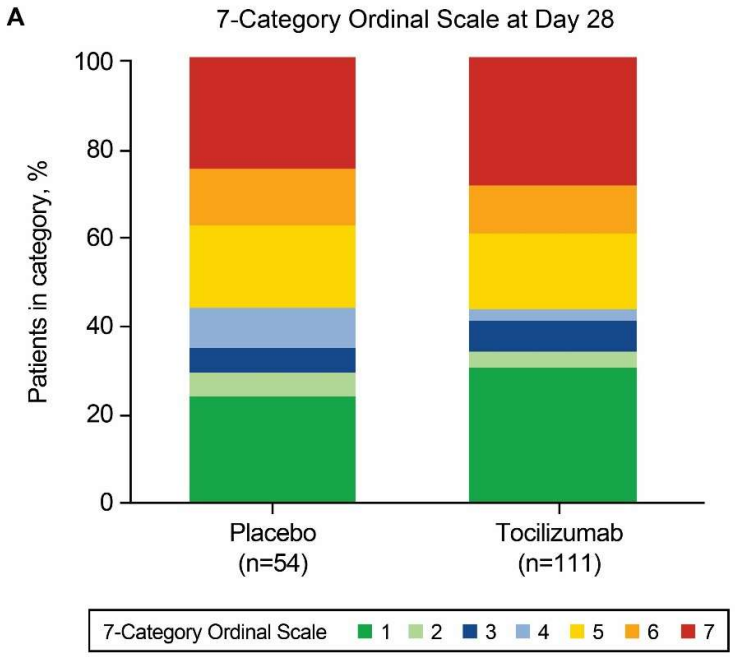


Figure S6. Clinical Status Assessed Using 7-Category Ordinal Scale at Day 28 and Over Time (A, B) in Patients Who Were Mechanically Ventilated at Randomization and (C, D) in Patients Who Were Not Mechanically Ventilated at Randomization (modified-intention-to-treat population).

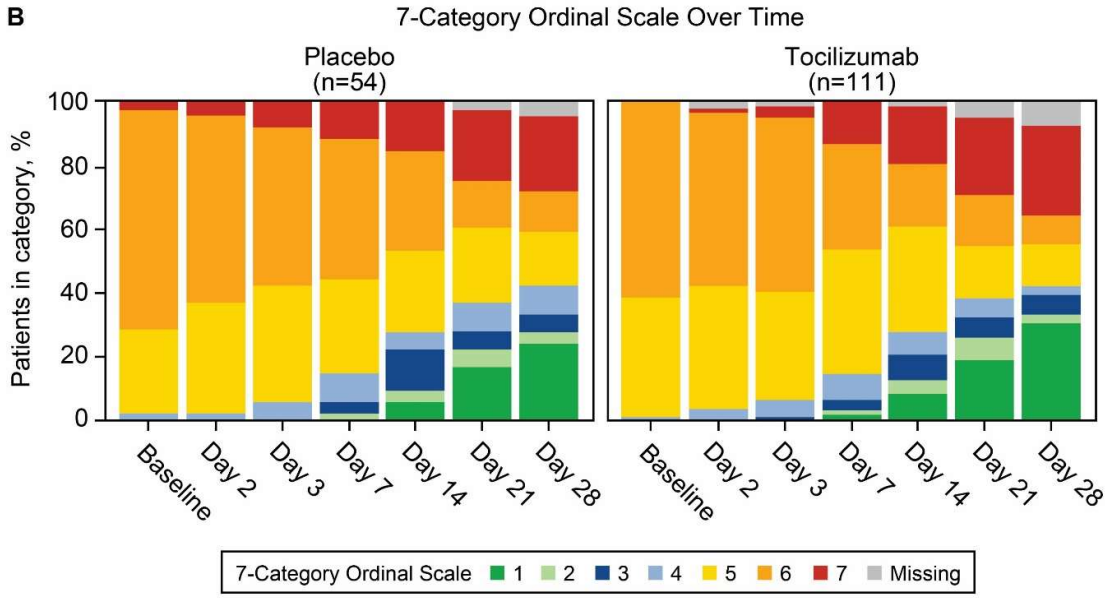
7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.



Number (%) of patients in category at day 28

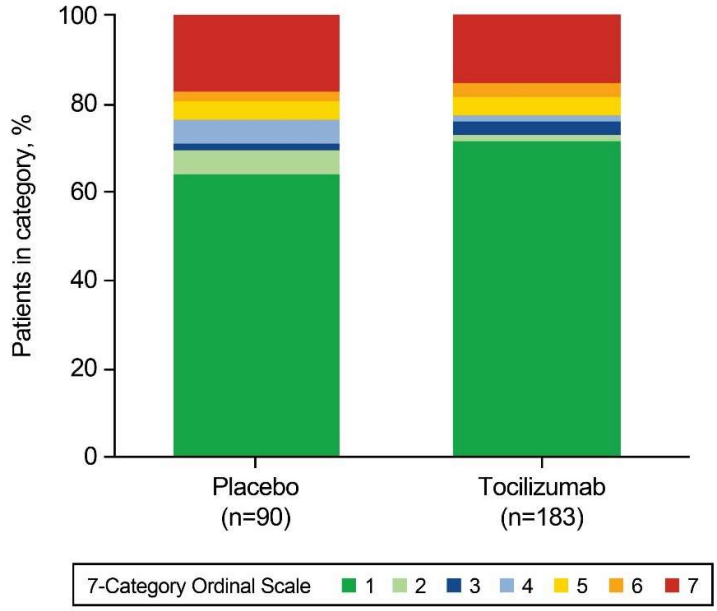
	Placebo	Tocilizumab
7	13 (24.1)	31 (27.9)
6	7 (13.0)	12 (10.8)
5	10 (18.5)	19 (17.1)
4	5 (9.3)	3 (2.7)
3	3 (5.6)	8 (7.2)
2	3 (5.6)	4 (3.6)
1	13 (24.1)	34 (30.6)

B



	Placebo, n (%)							Tocilizumab, n (%)						
Category	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
7	1 (1.9)	2 (3.7)	4 (7.4)	6 (11.1)	8 (14.8)	12 (22.2)	13 (24.1)	0	1 (0.9)	4 (3.6)	14 (12.6)	20 (18.0)	27 (24.3)	31 (27.9)
6	38 (70.4)	32 (59.3)	27 (50.0)	24 (44.4)	17 (31.5)	8 (14.8)	7 (13.0)	68 (61.3)	61 (55.0)	61 (55.0)	37 (33.3)	22 (19.8)	18 (16.2)	10 (9.0)
5	14 (25.9)	19 (35.2)	20 (37.0)	16 (29.6)	14 (25.9)	13 (24.1)	9 (16.7)	42 (37.8)	43 (38.7)	38 (34.2)	44 (39.6)	37 (33.3)	18 (16.2)	15 (13.5)
4	1 (1.9)	1 (1.9)	3 (5.6)	5 (9.3)	3 (5.6)	5 (9.3)	5 (9.3)	1 (0.9)	4 (3.6)	6 (5.4)	9 (8.1)	8 (7.2)	7 (6.3)	3 (2.7)
3	0	0	0	2 (3.7)	7 (13.0)	3 (5.6)	3 (5.6)	0	0	1 (0.9)	4 (3.6)	9 (8.1)	7 (6.3)	7 (6.3)
2	0	0	0	1 (1.9)	2 (3.7)	3 (5.6)	2 (3.7)	0	0	0	1 (0.9)	5 (4.5)	8 (7.2)	3 (2.7)
1	0	0	0	0	3 (5.6)	9 (16.7)	13 (24.1)	0	0	0	2 (1.8)	9 (8.1)	21 (18.9)	34 (30.6)
Missing	0	0	0	0	0	1 (1.9)	2 (3.7)	0	2 (1.8)	1 (0.9)	0	1 (0.9)	5 (4.5)	8 (7.2)

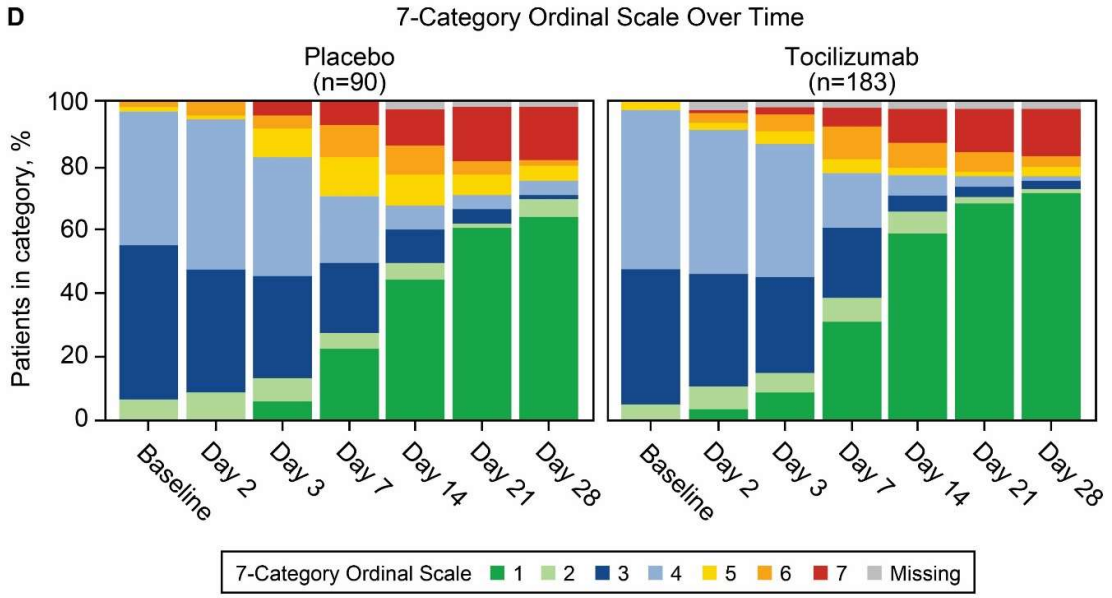
C



Number (%) of patients in category at day 28

	Placebo	Tocilizumab
7	15 (16.7)	27 (14.8)
6	2 (2.2)	6 (3.3)
5	4 (4.4)	7 (3.8)
4	5 (5.6)	3 (1.6)
3	1 (1.1)	6 (3.3)
2	5 (5.6)	2 (1.1)
1	58 (64.4)	132 (72.1)

D



	Placebo, n (%)							Tocilizumab, n (%)						
Category	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Baseline**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
7	0	0	3 (3.3)	5 (5.6)	11 (12.2)	15 (16.7)	15 (16.7)	0	1 (0.5)	4 (2.2)	11 (6.0)	19 (10.4)	25 (13.7)	27 (14.8)
6	1 (1.1)	3 (3.3)	4 (4.4)	9 (10.0)	8 (8.9)	4 (4.4)	2 (2.2)	0	6 (3.3)	10 (5.5)	19 (10.4)	15 (8.2)	11 (6.0)	6 (3.3)
5	1 (1.1)	1 (1.1)	8 (8.9)	11 (12.2)	9 (10.0)	6 (6.7)	4 (4.4)	3 (1.6)	4 (2.2)	7 (3.8)	8 (4.4)	4 (2.2)	3 (1.6)	6 (3.3)
4	38 (42.2)	43 (47.8)	34 (37.8)	19 (21.1)	7 (7.8)	4 (4.4)	4 (4.4)	93 (50.8)	84 (45.9)	77 (42.1)	32 (17.5)	12 (6.6)	6 (3.3)	2 (1.1)
3	44 (48.9)	35 (38.9)	29 (32.2)	20 (22.2)	9 (10.0)	4 (4.4)	1 (1.1)	78 (42.6)	65 (35.5)	56 (30.6)	40 (21.9)	9 (4.9)	6 (3.3)	5 (2.7)
2	6 (6.7)	8 (8.9)	7 (7.8)	5 (5.6)	5 (5.6)	1 (1.1)	5 (5.6)	9 (4.9)	13 (7.1)	11 (6.0)	14 (7.7)	13 (7.1)	3 (1.6)	2 (1.1)
1	0	0	5 (5.6)	20 (22.2)	40 (44.4)	55 (61.1)	58 (64.4)	0	6 (3.3)	16 (8.7)	57 (31.1)	108 (59.0)	126 (68.9)	132 (72.1)
Missing	0	0	0	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	0	4 (2.2)	2 (1.1)	2 (1.1)	3 (1.6)	3 (1.6)	3 (1.6)

Figure S7. Clinical Status Assessed on the 7-Category Ordinal Scale by Ordinal Logistic Regression Analysis at Day 28 According to Number of Doses Received, Region, and Days Since Symptom Onset (modified-intention-to-treat population).

Odds ratios within each subgroup were calculated using a proportional odds model including the stratification factors at randomization of region (North America, Europe [but not subgroup analysis by region]) and mechanical ventilation status (yes, no).

95% CIs were calculated using Wald method.

Death or hospital discharge were carried forward, including deaths that occurred after withdrawal. Any remaining missing data were imputed using last observation carried forward. Patients without a date of symptom onset were excluded from the analysis.

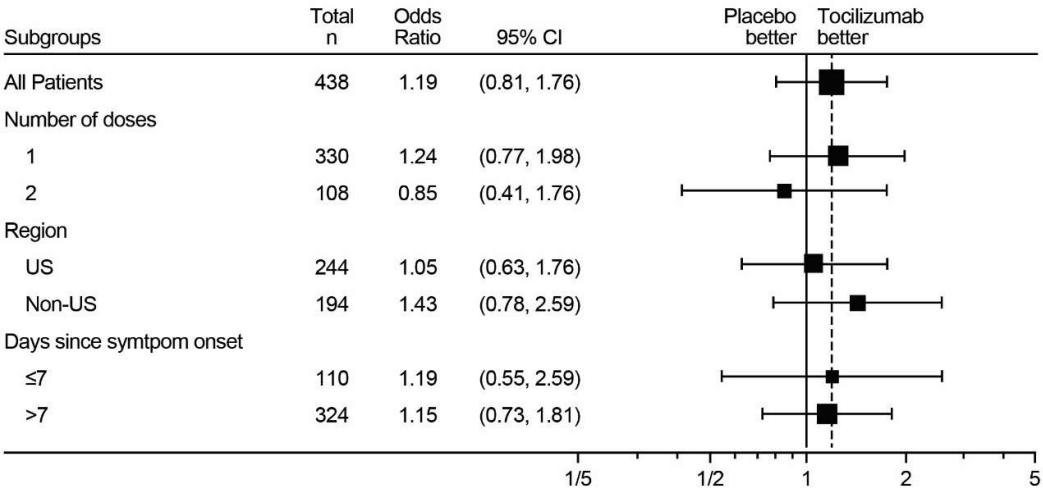


Table S1. Prespecified Analysis of Primary Endpoint With Last Observation Carried Forward for Missing Data.

	Tocilizumab N=294	Placebo N=144
Primary endpoint: clinical status based on 7-category ordinal scale at day 28, median (95% CI)*	1.0 (1.0 to 1.0)	2.0 (1.0 to 4.0)
Difference (95% CI)	–1.0 (–2.5 to 0.0)	
P value†	0.36	
Odds ratio (95% CI)‡	1.19 (0.81 to 1.76)	

*7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.
†P value based on van Elteren test stratified by region and mechanical ventilation at randomization.
‡Odds ratio based on ordinal logistic regression analysis adjusted for region and mechanical ventilation at randomization. The assumption of proportional odds was not met. Therefore, odds ratios cannot be used for statistical comparisons but are included for a complete representation of planned analyses as a summary measure of the treatment effect.

Table S2. Odds ratios for clinical status based on 7-category ordinal scale[*]

	Odds ratio (95% CI)[†]
Primary endpoint, clinical status at day 28[‡]	1.22 (0.82 to 1.80)
Key secondary endpoint, clinical status at day 14[§]	1.42 (0.99 to 2.05)
Subgroup analysis, clinical status at day 28[§]	
Mechanical ventilation at baseline	
Yes	1.04 (0.58 to 1.85)
No	1.34 (0.79 to 2.27)
Ordinal category at baseline	
2	Not evaluable
3	1.27 (0.48 to 3.37)
4	1.59 (0.78 to 3.24)
5	1.10 (0.38 to 3.15)
6	0.93 (0.46 to 1.87)

[*]7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring ECMO or mechanical ventilation and additional organ support; 7, death.

[†]Odds ratio based on ordinal logistic regression analysis adjusted for region and mechanical ventilation at randomization. The assumption of proportional odds was not met. Therefore, odds ratios cannot be used for statistical comparisons but are included for a complete representation of planned analyses as a summary measure of the treatment effect.

[‡]Multiple imputation for missing data.

[§]Last observation carried forward for missing data.

Table S3. Clinical Status According to 7-Category Ordinal Scale at Day 28 (modified intention-to-treat population): Odds Ratios With Relaxed Constraint for Proportional Odds.

Odds Ratio Estimates and Wald Confidence Intervals		
	Odds Ratio Estimate	**95% CI**
Partition 1	1.59	1.01 to 2.50
Partition 2	0.98	0.63 to 1.53
Partition 3	1.26	0.80 to 1.98
Partition 4	0.90	0.57 to 1.43
Partition 5	0.86	0.54 to 1.39
Partition 6	0.93	0.55 to 1.55

Odds ratios were based on ordinal logistic regression analysis adjusted for region and mechanical ventilation at randomization. Odds ratios for tocilizumab versus placebo for each dichotomization of the scale were produced using the "unequalslopes" option in Proc Logistic in SAS. Partition 1 is category 1 (discharged or ready for discharge) versus categories 2 to 7.

7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Table S4. Clinical Status According to 7-Category Ordinal Scale at Day 28 (modified intention-to-treat population): Odds Ratios After Multiple Imputation and Delta Adjustment.

Placebo Delta \ Tocilizumab Delta	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
-6	1.27	1.25	1.24	1.23	1.21	1.20	1.17	1.12	1.10	1.09	1.08	1.07	1.05
-5	1.28	1.26	1.25	1.24	1.22	1.20	1.18	1.13	1.11	1.10	1.09	1.08	1.06
-4	1.28	1.26	1.25	1.24	1.23	1.21	1.18	1.13	1.12	1.11	1.09	1.08	1.06
-3	1.29	1.27	1.26	1.25	1.23	1.22	1.19	1.14	1.12	1.11	1.10	1.09	1.07
-2	1.30	1.28	1.27	1.26	1.24	1.22	1.20	1.15	1.13	1.12	1.11	1.09	1.07
-1	1.31	1.29	1.28	1.26	1.25	1.23	1.20	1.15	1.14	1.13	1.11	1.10	1.08
0	1.32	1.30	1.29	1.28	1.27	1.25	1.22	1.17	1.15	1.14	1.13	1.11	1.09
+1	1.36	1.33	1.32	1.31	1.30	1.28	1.25	1.20	1.18	1.17	1.15	1.14	1.12
+2	1.37	1.35	1.34	1.32	1.31	1.29	1.26	1.21	1.19	1.18	1.16	1.15	1.13
+3	1.37	1.35	1.34	1.33	1.31	1.29	1.26	1.21	1.20	1.18	1.17	1.15	1.13
+4	1.38	1.36	1.35	1.33	1.32	1.30	1.27	1.22	1.20	1.19	1.17	1.16	1.14
+5	1.38	1.36	1.35	1.34	1.32	1.30	1.27	1.22	1.21	1.19	1.18	1.16	1.14
+6	1.40	1.37	1.36	1.35	1.34	1.32	1.29	1.23	1.22	1.21	1.19	1.18	1.15

Missing data for 3 patients in the placebo arm and 11 patients in the tocilizumab arm (after death and discharge were carried forward) were bootstrapped from non-missing data in each of the 4 strata within the treatment group to create a complete data set. This was repeated to obtain 10,000 complete data sets. Imputed data were then adjusted independently by treatment group according to a delta, as shown in the table (adjusted scores below 1 or above 7 were capped at 1 or 7, respectively). Each odds ratio in the table is the mean odds ratio from the 10,000 ordinal logistic regression models (adjusted for region and mechanical ventilation at randomization) fitted to the complete data sets after delta adjustment. An odds ratio above 1 favors tocilizumab over placebo. With the maximum favorable delta adjustment for the missing tocilizumab data (–6) and the maximum unfavorable delta adjustment for the missing placebo data (+6), the odds ratio (95% CI) is 1.40 (0.95 to 2.06). With the maximum unfavorable delta adjustment for the missing tocilizumab data (+6) and the maximum favorable delta adjustment for the missing placebo data (–6), the odds ratio (95% CI) is 1.05 (0.71 to 1.55). The results suggest that the missing data are unlikely to have influenced the finding of no clinically meaningful treatment effect for the primary endpoint.

Table S5. Clinical Status According to 7-Category Ordinal Scale at Day 28 (modified intention-to-treat population): 95% Confidence Intervals for the Odds Ratio After Multiple Imputation and Delta Adjustment.

Placebo Delta \ Tocilizumab Delta	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
-6	[0.86, 1.87]	[0.85, 1.84]	[0.84, 1.83]	[0.83, 1.81]	[0.82, 1.79]	[0.81, 1.76]	[0.79, 1.73]	[0.76, 1.65]	[0.75, 1.63]	[0.74, 1.61]	[0.73, 1.59]	[0.72, 1.57]	[0.71, 1.55]
-5	[0.87, 1.89]	[0.85, 1.86]	[0.85, 1.84]	[0.84, 1.82]	[0.83, 1.81]	[0.82, 1.78]	[0.80, 1.74]	[0.77, 1.67]	[0.75, 1.64]	[0.75, 1.63]	[0.74, 1.60]	[0.73, 1.59]	[0.72, 1.56]
-4	[0.87, 1.90]	[0.86, 1.86]	[0.85, 1.85]	[0.84, 1.83]	[0.83, 1.81]	[0.82, 1.79]	[0.80, 1.75]	[0.77, 1.67]	[0.76, 1.65]	[0.75, 1.63]	[0.74, 1.61]	[0.73, 1.59]	[0.72, 1.56]
-3	[0.88, 1.91]	[0.86, 1.88]	[0.86, 1.86]	[0.85, 1.84]	[0.84, 1.82]	[0.82, 1.80]	[0.80, 1.76]	[0.77, 1.68]	[0.76, 1.66]	[0.76, 1.64]	[0.75, 1.62]	[0.74, 1.60]	[0.72, 1.57]
-2	[0.88, 1.92]	[0.87, 1.89]	[0.86, 1.87]	[0.85, 1.85]	[0.84, 1.83]	[0.83, 1.81]	[0.81, 1.77]	[0.78, 1.69]	[0.77, 1.67]	[0.76, 1.65]	[0.75, 1.63]	[0.74, 1.61]	[0.73, 1.58]
-1	[0.89, 1.93]	[0.87, 1.90]	[0.87, 1.89]	[0.86, 1.87]	[0.85, 1.85]	[0.83, 1.82]	[0.81, 1.78]	[0.78, 1.70]	[0.77, 1.68]	[0.76, 1.66]	[0.75, 1.64]	[0.75, 1.62]	[0.73, 1.59]
0	[0.90, 1.95]	[0.88, 1.92]	[0.88, 1.91]	[0.87, 1.89]	[0.86, 1.87]	[0.84, 1.84]	[0.82, 1.80]	[0.79, 1.73]	[0.78, 1.70]	[0.77, 1.69]	[0.76, 1.66]	[0.75, 1.64]	[0.74, 1.61]
+1	[0.92, 2.00]	[0.91, 1.97]	[0.90, 1.95]	[0.89, 1.93]	[0.88, 1.91]	[0.87, 1.88]	[0.84, 1.84]	[0.81, 1.76]	[0.80, 1.74]	[0.79, 1.72]	[0.78, 1.70]	[0.77, 1.68]	[0.76, 1.65]
+2	[0.93, 2.01]	[0.91, 1.98]	[0.91, 1.97]	[0.90, 1.95]	[0.89, 1.93]	[0.87, 1.90]	[0.85, 1.86]	[0.82, 1.78]	[0.81, 1.75]	[0.80, 1.74]	[0.79, 1.71]	[0.78, 1.69]	[0.77, 1.66]
+3	[0.93, 2.02]	[0.92, 1.99]	[0.91, 1.98]	[0.90, 1.96]	[0.89, 1.94]	[0.88, 1.91]	[0.86, 1.87]	[0.82, 1.79]	[0.81, 1.76]	[0.80, 1.74]	[0.79, 1.72]	[0.78, 1.70]	[0.77, 1.67]
+4	[0.93, 2.03]	[0.92, 2.00]	[0.91, 1.98]	[0.90, 1.96]	[0.89, 1.94]	[0.88, 1.92]	[0.86, 1.87]	[0.83, 1.79]	[0.81, 1.77]	[0.81, 1.75]	[0.80, 1.73]	[0.79, 1.71]	[0.77, 1.67]
+5	[0.94, 2.04]	[0.92, 2.01]	[0.92, 1.99]	[0.91, 1.97]	[0.90, 1.95]	[0.88, 1.92]	[0.86, 1.88]	[0.83, 1.80]	[0.82, 1.78]	[0.81, 1.76]	[0.80, 1.73]	[0.79, 1.71]	[0.78, 1.68]
+6	[0.95, 2.06]	[0.93, 2.03]	[0.93, 2.01]	[0.92, 1.99]	[0.91, 1.97]	[0.89, 1.94]	[0.87, 1.90]	[0.84, 1.82]	[0.83, 1.79]	[0.82, 1.78]	[0.81, 1.75]	[0.80, 1.73]	[0.78, 1.70]

Each 95% CI in the table was calculated using the standard error estimates from the 10,000 ordinal logistic regression models (Table S2) (adjusted for region and mechanical ventilation at randomization) fitted to the complete data sets after delta adjustment. The method used for calculating the CI was Rubin's method as implemented in Proc Mianalyze in SAS. An odds ratio above 1 favors tocilizumab over placebo. With the maximum favorable delta adjustment for the missing tocilizumab data (–6) and the maximum unfavorable delta adjustment for the missing placebo data (+6), the odds ratio (95% CI) is 1.40 (0.95 to 2.06). With the maximum unfavorable delta adjustment for the missing tocilizumab data (+6) and the maximum favorable delta adjustment for the missing placebo data (–6), the odds ratio (95% CI) is 1.05 (0.71 to 1.55). The results suggest that the missing data are unlikely to have influenced the finding of no clinically meaningful treatment effect for the primary endpoint.

Table S6. Ventilator-Free Days to Day 28 Based on a Joint Model of Mortality and Ventilator-Free Days (modified intention-to-treat population).

	Tocilizumab N=294	**Placebo N=144**
Rate of ventilator-free days per 28 days (95% CI)	15.3 (14.1 to 16.5)	13.9 (12.5 to 15.5)
Treatment effect (95% CI)	1.1 (1.0 to 1.2)	

The rate of ventilator-free days was determined from a joint model of mortality (logistic regression) and ventilator-free days (negative binomial), with subject as a random effect using Proc Glimmix in SAS, with the log of duration of follow-up as an offset variable. The treatment effect shows the fold increase in ventilator-free days in the tocilizumab arm compared with the placebo arm.

Table S7. Cause-Specific Cox Regression of Death, Time to Improvement in Clinical Status on the 7-Category Ordinal Scale to Day 28, and Time to Discharge/Ready for Discharge (modified-intention-to-treat population).

	Cox Proportional Hazard Ratio [reference = placebo] (95% CI)*
Time to improvement in clinical status†	1.31 (1.00 to 1.71)
Death	1.16 (0.73 to 1.83)
Time to discharge/ready for discharge‡	1.42 (1.07 to 1.89)
Death	1.17 (0.74 to 1.84)

Death was a competing risk.

*Stratified proportional hazards model including the stratification factors region (North America, Europe) and mechanical ventilation status (yes, no) applied at randomization. Patients who discontinued or were lost to follow-up before improvement in clinical status or before discharge/ready for discharge criteria were met were censored at their last ordinal scale assessment.

†Defined as days from first dose of study drug to time of ≥2-category improvement in clinical status assessed on the 7-category ordinal scale (1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death).

‡Defined as days from first dose of study drug to hospital discharge/ready for discharge (normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen.

Table S8. Safety to the Clinical Cutoff Date (safety population).

	To Clinical Cutoff Date (June 24, 2020)	
	Tocilizumab N=295	**Placebo N=143**
Patients with ≥1 adverse event, n (%) Adverse events, n	237 (80.3) 906	118 (82.5) 423
Patients with ≥1 serious adverse event Serious adverse events, n	113 (38.3) 183	62 (43.4) 117
Patients with ≥1 fatal adverse event, n (%)	70 (23.7)	33 (23.1)
Patients with adverse events of special interest, n (%)		
Infections	126 (42.7)	62 (43.4)
Serious infections	70 (23.7)	41 (28.7)
Opportunistic infections*	1 (0.3)	4 (2.8)
Medically confirmed malignancies	1 (0.3)	0
Hypersensitivity†	19 (6.4)	4 (2.8)
Anaphylaxis per Sampson criteria	0	1 (0.7)
Hepatic events	6 (2.0)	3 (2.1)
Laboratory criteria of Hy's Law‡	6 (2.0)	7 (4.9)
Myocardial infarction	4 (1.4)	2 (1.4)
Stroke	3 (1.0)	4 (2.8)
Bleeding events	47 (15.9)	18 (12.6)
Serious bleeding events	13 (4.4)	5 (3.5)
Serious infections§ reported in >1% of patients in either treatment arm		
COVID-19¶	48 (16.3)	20 (14.0)
Septic shock	7 (2.4)	7 (4.9)
Pneumonia	7 (2.4)	4 (2.8)
Pneumonia bacterial	6 (2.0)	2 (1.4)
Sepsis	3 (1.0)	4 (2.8)
Bacteremia	2 (0.7)	3 (2.1)
Bacterial sepsis	3 (1.0)	0

Data are number (%) of patients unless stated otherwise.

**Candida* sepsis in the tocilizumab arm and respiratory moniliasis, *Candida* sepsis, *Pneumocystitis jirovecii pneumonia*, and fungal urinary tract infection in the placebo arm.

[†]Defined as all events that occurred during or within 24 hours of the infusion and were not assessed as "unrelated to study treatment" by the investigator, regardless of whether or not they were clinically consistent with hypersensitivity.

[‡]Alanine aminotransferase or aspartate aminotransferase levels >3× upper limit of normal with either bilirubin levels >2× upper limit of normal.

[§]Reported by Medical Dictionary for Regulatory Activities preferred term.

[¶]COVID-19 resulting in death was reported as a serious adverse event in the study.

Table S9. Serious Adverse Events Occurring in ≥1% of Patients in Either Treatment Group by System Organ Class and Preferred Term to the Clinical Cutoff Date (safety population).

	To Clinical Cutoff Date (June 24, 2020)	
	Tocilizumab N=295	**Placebo N=143**
Patients with ≥1 serious adverse event Serious adverse events, n	113 (38.3) 183	62 (43.4) 117
Infections and infestations		
COVID-19 pneumonia	35 (11.9)	19 (13.3)
COVID-19	13 (4.4)	1 (0.7)
Septic shock	7 (2.4)	7 (4.9)
Pneumonia	7 (2.4)	4 (2.8)
Pneumonia bacterial	6 (2.0)	2 (1.4)
Sepsis	3 (1.0)	4 (2.8)
Bacteremia	2 (0.7)	3 (2.1)
Bacterial sepsis	3 (1.0)	0
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	5 (1.7)	6 (4.2)
Pneumothorax	4 (1.4)	3 (2.1)
Pulmonary embolism	5 (1.7)	2 (1.4)
Acute respiratory distress syndrome	4 (1.4)	2 (1.4)
Acute respiratory failure	2 (0.7)	2 (1.4)
Hypoxia	0	2 (1.4)
Pharyngeal hemorrhage	0	2 (1.4)
Cardiac disorders		
Cardiac arrest	4 (1.4)	5 (3.5)
Atrial fibrillation	3 (1.0)	0
Pulseless electrical activity	1 (0.3)	2 (1.4)
Renal and urinary disorders		
Acute kidney injury	9 (3.1)	4 (2.8)
Renal failure	2 (0.7)	2 (1.4)
Blood and lymphatic disorders		

Neutropenia	4 (1.4)	0
General disorders and administration site conditions		
Multiple organ dysfunction syndrome	5 (1.7)	1 (0.7)

Data are shown as number (%) of patients unless stated otherwise.

Multiple ocurrences of the same adverse event in an individual were counted once. System organ class and preferred terms were determined according to the Medical Dictionary for Regulatory Activities, version 23.0.

Table S10. Clinical Status According to 7-Category Ordinal Scale at Day 28 According to Steroid Treatment at Baseline or Any Time During the Study (modified-intention-to-treat population).

	With Steroids		Without Steroids	
	Tocilizumab n=106	**Placebo n=79**	**Tocilizumab n=188**	**Placebo n=65**
Ordinal scale category at day 28, n (%)				
1	42 (39.6)	36 (45.6)	124 (66.0)	35 (53.8)
2	2 (1.9)	3 (3.8)	4 (2.1)	5 (7.7)
3	7 (6.6)	3 (3.8)	7 (3.7)	1 (1.5)
4	3 (2.8)	4 (5.1)	3 (1.6)	6 (9.2)
5	10 (9.4)	8 (10.1)	16 (8.5)	6 (9.2)
6	13 (12.3)	7 (8.9)	5 (2.7)	2 (3.1)
7	29 (27.4)	18 (22.8)	29 (15.4)	10 (15.4)

7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward, requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Death or hospital discharge were carried forward, including deaths after withdrawal with any remaining missing data imputed using the last postbaseline observation carried forward method.

Steroids included corticosteroids except topical, inhaled, or dermatologic applications.