CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

Tocilizumab and Sarilumab: Evidence Review and Appraisal

This report is current as of February 25, 2021.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the coronavirus disease 2019 (COVID-19) pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

This report reviews the current scientific evidence on the potential benefits and harms of tocilizumab and sarilumab.

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Table of Contents

Abbreviations 6
Key Findings 7
Introduction 9
Regulatory Status 9
Clinical Evidence 9
Literature Search Methods 9
Selection Criteria 10
Literature Search Results 10
Study Results 30
Appraisal of the Included Trials 59
Discussion 60
Summary of Available Evidence 60
Conclusions 65
Appendix 1: Patient Disposition of Published Trials 66
Appendix 2: Baseline Characteristics 70
Appendix 3: Harms Data 80
Appendix 4: Summary of Appraisal 87
References 93

Tables

Table 1: Selection Criteria 10
Table 2: Characteristics of the Included RCTs 11
Table 3: Characteristics of the Included RCTs 15
Table 4: Characteristics of the Included RCTs 17
Table 5: Clinical Outcomes for REMAP-CAP 37
Table 6: Clinical Outcomes for CORIMUNO-TOC 39
Table 7: Clinical Outcomes for RECOVERY 40
Table 8: Clinical Outcomes for Lescure et al. 41
Table 9: Clinical Outcomes for COVACTA 43
Table 10: Clinical Outcomes for EMPACTA 45
Table 11: Clinical Outcomes for Salvarani et al. 46
Table 12: Clinical Outcomes for Stone et al. 48
Table 13: Clinical Outcomes for TOCIBRAS 50
Table 14: Clinical Outcomes for Wang et al. 52
Table 15: Clinical Outcomes for Zhao et al. 52
Table 16: Summary of Harms 57
Table 17: Summary of Harms 58
Table 18: Patient Disposition for REMAP-CAP 66
Table 19: Patient Disposition for CORIMUNO-TOC 66
Table 20: Patient Disposition for RECOVERY 66
Table 21: Patient Disposition for Lescure et al. 67
Table 22: Patient Disposition for COVACTA 67
Table 23: Patient Disposition for EMPACTA 68
Table 24: Patient Disposition for Salvarani et al. 68
Table 25: Patient Disposition for Stone et al. 68
Table 26: Patient Disposition for TOCIBRAS 69
Table 27: Patient Disposition for Wang et al. 69
Table 28: Patient Disposition for Zhao et al. 69
Table 29: Demographic and Clinical Characteristics at Baseline for REMAP-CAP 70
Table 30: Demographic and Clinical Characteristics at Baseline for CORIMUNO-TOC 71
Table 31: Demographic and Clinical Characteristics at Baseline for RECOVERY 71
Table 32: Demographic and Clinical Characteristics at Baseline for Lescure et al. 72

Table 33: Demographic and Clinical Characteristics at Baseline for COVACTA....74
Table 34: Demographic and Clinical Characteristics at Baseline for EMPACTA....75
Table 35: Demographic and Clinical Characteristics at Baseline for Salvarani et al. 76
Table 36: Demographic and Clinical Characteristics at Baseline for Stone et al.....76
Table 37: Demographic and Clinical Characteristics at Baseline for TOCIRBAS....77
Table 38: Demographic and Clinical Characteristics at Baseline for Wang et al.....78
Table 39: Demographic and Clinical Characteristics at Baseline for Zhao et al.....79
Table 40: Harms Outcomes for REMAP-CAP....80
Table 41: Harms Outcomes for CORIMUNO-TOC 80
Table 42: Harms Outcomes for Lescure et al....81
Table 43: Harms Outcomes for COVACTA....82
Table 44: Harms Outcomes for EMPACTA....83
Table 45: Harms Outcomes for Salvarani et al. 83
Table 46: Harms Outcomes for Stone et al. 84
Table 47: Harms Outcomes for TOCIBRAS....85
Table 48: Harms Outcomes for Wang et al. 86
Table 49: Harms Outcomes for Zhao et al. 86
Table 50: Threats to Internal and External Validity 87

Abbreviations

CI	confidence interval
COVID-19	coronavirus disease 2019
CrI	credible interval
HR	hazard ratio
ICU	intensive care unit
IL-6	interleukin-6
IQR	interquartile range
ITT	intention to treat
mITT	modified intention to treat
OR	odds ratio
RCT	randomized controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
WHO-CPS	World Health Organization Clinical Progression Scale

The following version control table will be updated as changes are made to the report.

Version	Date	Summary of revisions
1.0	February 4, 2021	First report.
2.0	February 25, 2021	Addition of preliminary study results of RECOVERY trial from the pre-print by RECOVERY Collaborative Group[1] REMAP-CAP and COVACTA were published on February 25, 2021 (originally preprints)

Key Findings

Tocilizumab (Actemra) (Hoffmann-La Roche Limited) and sarilumab (Kevzara) (Sanofi, Regeneron Pharmaceuticals) are humanized monoclonal antibodies against the interleukin-6 (IL-6) receptor used in rheumatology that have emerged as potential candidates to treat COVID-19. This report summarizes the current scientific evidence on the potential benefits and harms of tocilizumab and sarilumab for the treatment of COVID-19.

The evidence for this review is based on 8 published randomized controlled trials (RCTs)[2-9] and 3 preprint RCTs.[1,10,11] Of the 10 RCTs that included tocilizumab, 1 study, REMAP-CAP, also included sarilumab. The study by Lescure et al. investigated different doses of sarilumab. The study by Zhao et al. included favipiravir as an active comparator. While most RCTs have been terminated or completed, REMAP-CAP is still recruiting patients and the published results used in this report are those of a preliminary analysis. The RECOVERY trial ended recruitment in the tocilizumab arm and pre-published preliminary results are included in this report. Two studies, CORIMUNO-TOC and EMPACTA, are active trials but no longer recruiting patients. Two trials were terminated early: TOCIBRAS, because of an increase in the number of deaths with tocilizumab, and Salvarani et al., because of futility.

The RCTs included phase II, phase III, and phase IV trials and only 4 were double-blinded.[3,6,8,10] All trials were multi-centre, although some were conducted in 1 country only. COVACTA and the study by Lescure et al. included Canadian study sites. The follow-up periods ranged from 14 days to 60 days. Sample sizes ranged from 26 patients to 4,116 patients. All RCTs were conducted in adult patients and most were men. The RCTs enrolled patients who were either critically ill or had moderate or severe disease with different requirements for respiratory support at baseline. In most trials, tocilizumab was administered as 1 dose of 8 mg/kg, up to a maximum dose of 800 mg by IV infusion, with the option to administer a second dose if the patient did not improve. In REMAP-CAP, sarilumab was administered as 1 dose of 400 mg via IV infusion. In the study by Lescure et al., sarilumab was administered as either a 200 mg or 400 mg by IV infusion with the option for a second dose.

In REMAP-CAP, sarilumab was better than no treatment for the following outcomes: number of organ support–free days, hospital survival, 90-day survival, time to intensive care unit (ICU) discharge, and time to hospital discharge. Conversely, the study by Lescure et al. found no significant difference in time to improvement of at least 2 points on a 7-category ordinal scale and the proportion of patients alive at 29 days for each sarilumab-dose group (200 mg or 400 mg) compared with the placebo group. The results of REMAP-CAP should be interpreted carefully, as the trial is still ongoing.

While REMAP-CAP did not report the number of patients experiencing an adverse event, no patients in the sarilumab group experienced a serious adverse event. In the study by Lescure

et al., the proportion of patients experiencing a treatment-emergent adverse event was similar between each sarilumab-dose group (200 mg or 400 mg) and the placebo group, whereas the proportion of patients experiencing a treatment-emergent serious adverse event was higher in each sarilumab-dose group (200 mg and 400 mg) compared with the placebo group.

The efficacy results for tocilizumab ranged. REMAP-CAP found the number of organ support–free days was better with tocilizumab compared with no treatment. REMAP-CAP, RECOVERY, CORIMUNO-TOC and COVACTA reported a decrease in the time to hospital discharge, whereas 4 RCTs[3,5,6,11] reported no difference for these outcomes between tocilizumab and the control groups. The outcome of mechanical ventilation or death was in favour of tocilizumab in 4 RCTs,[1-3,9] but not in the study by Stone et al. Patients' clinical status was not improved in any of the 4 trials[3,4,6,8] that assessed this outcome. The study by Wang et al. and Zhao et al., respectively, found no difference in cure rate or lung remission between the tocilizumab and control groups. While RECOVERY found a significant difference in mortality in favour of the tocilizumab group compared to the usual care group, 5 RCTs[3-6,8] found no differences in mortality between the tocilizumab group and the placebo or standard care group. The results of REMAP-CAP and RECOVERY should be interpreted carefully, as these are preliminary results and REMAP-CAP is still ongoing.

CORIMUNO-TOC, COVACTA, and EMPACTA had a higher proportion of patients who experienced an adverse event in the control group than in the treated group. This was also true for serious adverse events, with a higher proportion of patients experiencing a serious adverse event in the control group. However, in TOCIBRAS, Salvarani et al., and Wang et al., more patients experienced an adverse event with tocilizumab compared with the control groups. Salvarani et al. and Stone et al. reported a comparable proportion of patients with a serious adverse event. In Zhao et al., combination therapy (tocilizumab with favipiravir) resulted in more patients with an adverse event compared with either treatment alone. RECOVERY reported a similar proportion of patients with major cardiac arrhythmia in the tocilizumab plus usual care group and usual care group, and found no difference in cause-specific mortality between the tocilizumab plus usual care group and usual care group. EMPACTA reported that no patients withdrew from treatment due to adverse events. None of the other trials reported whether any patients had withdrawn from treatment due to an adverse event.

Of note, the inclusion criteria, baseline patient characteristics, delivery of standard care, primary outcomes and corresponding definitions, and trial location (single country versus international) differed across the RCTs, which limits the direct comparison of results across studies. Three trials that were published in preprints have not been peer reviewed. Furthermore, several study limitations affect the interpretation of the results, including the small sample size in 5 trials,[2,4,5,7,11] the lack of any sample size calculation in REMAP-CAP, and the lack of control for type I error in 8 RCTs.[1,2,4,5,7-9,11] All but 4 trials were open label, which may have favoured tocilizumab.

Despite the availability of 10 RCTs on tocilizumab, the place in therapy of tocilizumab is still unclear. It may offer some benefit in reducing the need for mechanical ventilation, as 4 of 5 RCTs showed a difference between treatment groups in favour of tocilizumab compared with control groups. Of note, RECOVERY — a large RCT — showed a significant reduction in mortality in favour of tocilizumab compared with usual care; however, the results are preliminary.

Introduction

Tocilizumab (Actemra) (Hoffmann-La Roche Limited) and sarilumab (Kevzara) (Sanofi and Regeneron Pharmaceuticals) are humanized monoclonal antibodies against the IL-6 receptor that are used in rheumatology and have emerged as potential candidates to treat COVID-19.[12] Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection experience inflammation due to a cytokine storm that is triggered by the immune system.[13] Among the inflammatory markers released in the cytokine storm are IL-6, a pleiotropic comprising lymphocytes, monocytes, and fibroblasts.[12] Elevated levels of IL-6 in the plasma may result in adverse outcomes, such as acute respiratory distress syndrome.[13] Tocilizumab and sarilumab work by inhibiting IL-6 from interacting with the IL-6 receptor and the subsequent release of cytokines and inflammation that follows.[14]

Regulatory Status

In Canada, tocilizumab is indicated for rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome.[15] Sarilumab is indicated for rheumatoid arthritis in Canada.[16] Neither drug is approved specifically for the treatment of COVID-19.

The objective of this report is to summarize the current scientific evidence on the potential benefits and harms of tocilizumab and sarilumab for the treatment of COVID-19 and does not include a detailed critical appraisal of the study findings.

Clinical Evidence

Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[17]

This report is an update of a literature search strategy developed for previous CADTH reports.[18,19] Published literature was identified by searching the following bibliographic databases: Ovid MEDLINE and Ovid Embase. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tocilizumab and sarilumab for COVID-19. No filters were applied to limit the retrieval by study type. The initial searches were limited to English-language documents published between January 1, 2019 and July 20, 2020.

For the current report, database searches were rerun on January 14, 2021 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since July 20, 2020. Retrieval was limited to English-language documents. Conference abstracts were excluded from the search. Database alerts will update the search weekly until the project is discontinued.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[20] Health Technology Assessment (HTA) Agencies, Drug and Device Regulatory Approvals, Advisories and Warnings, and Databases (Free). The following clinical trial registries were

searched: the Health Canada Clinical Trials Database, the US National Institutes of Health's clinicaltrials.gov, the EU Clinical Trials Register, and the WHO's International Clinical Trials Registry Platform (ICTRP). Preprints (unpublished manuscripts) were also searched.

Selection Criteria

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. Studies of interest were selected for review according to the criteria outlined in Table 1.

Non-randomized studies, single-arm trials, case series, case reports, conference reports, editorials, letters to the editor, and press releases were excluded from the evidence review.

Table 1: Selection Criteria

Population	Patients with a confirmed diagnosis of COVID-19
Intervention	Interleukin-6 receptor monoclonal antibodies: tocilizumab and sarilumab
Comparators	• Placebo • Standard care/usual care • Other pharmacotherapies
Outcomes	Efficacy and safety
Study design	Randomized controlled trials (published and preprints)

Literature Search Results

The initial literature search identified 5 RCTs that met the inclusion criteria: CORIMUNO-TOC by Hermine et al.,[2] EMPACTA by Salama et al.,[3] Salvarani et al.,[5] Stone et al.,[6] and Zhao et al.[7] TOCIBRAS by Veiga et al.[4] was identified in a database alert.

Four RCTs were identified by searching preprints: REMAP-CAP by Gordon et al.,[21] RECOVERY by Horby et al.,[1]COVACTA by Rosas et al.,[22] and the trial by Lescure et al.[10] Two preprints have now been published on February 25, 2021: REMAP-CAP [9] and COVACTA.[8] One additional preprint RCT by Wang et al.[11] was identified through collaboration with the Department of Health Research Methods, Evidence, and Impact at McMaster University[23] that completed a living systematic review and network meta-analysis on drug treatments for COVID-19.

Eleven RCTs met the inclusion criteria. Of the ten RCTs that included tocilizumab, 1 RCT also included sarilumab, and 1 RCT included different doses of sarilumab. Of note, REMAP-CAP and RECOVERY had preliminary results. Two trials were terminated early: TOCIBRAS, because of an increase in the number of deaths with tocilizumab, and Salvarani et al., because of futility. For Salvarani et al., the trial was stopped at the interim analysis stage; therefore, only interim results are included in this report.

Ongoing trials of tocilizumab and sarilumab are presented in CADTH's *Ongoing Trials for Drugs in the Prevention and Treatment of COVID-19* study characteristics.[24]

The characteristics of the studies of interest to this report are summarized in Table 2, Table 3, and Table 4.

Table 2: Characteristics of the Included RCTs

		REMAP-CAP	CORIMUNO-TOC	RECOVERY	Lescure et al.
DESIGNS AND POPULATIONS	**NCT Number**	NCT02735707	NCT04331808	NCT04381936	NCT04327388
	Status	Recruiting	Active, no recruiting	RECOVERY still recruiting; however, no longer including patients in the treatment arm with tocilizumab	Completed
	Study completion date	December 2023	December 31, 2021	December 2031	September 2, 2020
	Funding	various international funders	Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, AP-HP Foundation and the Reacting program	UK Research and Innovation (Medical Research Council), National Institute for Health Research, Wellcome, Bill and Melinda Gates Foundation, Department for International Development, Health Data Research UK, Medical Research Council Population Health Research Unit, NIHR Clinical Trials Unit Support Funding, and the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections	Sanofi and Regeneron Pharmaceuticals, Inc.
	Study design	Phase IV, MC, OL, multifactorial adaptive platform	Phase II, MC, OL	Phase II and phase III, MC, OL, platform	Phase III, MC, adaptive, DB, PC
	Locations	13 countries however 6 countries across113 sites were specific to the immune modulation therapy study population	France (9 centres)	UK (131 centres)	45 sites in 11 countries, including Canada
	Randomized, N	353	131	4,116	420
	Inclusion criteria	• critically ill patients • aged >18 years • suspected or confirmed COVID-19 • admitted to an ICU • receiving respiratory[a] or cardiovascular organ support[b]	• patients not requiring ICU at admission • confirmed SARS-CoV-2 infection • moderate, severe, or critical pneumonia	• hospitalized adult patients • clinically suspected or laboratory-confirmed SARS-CoV-2 infection • hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy)	• hospitalised patients ≥ 18 years • laboratory-confirmed SARS-CoV-2 infection • 2 weeks prior to randomization • evidence of pneumonia by chest imaging or chest auscultation

	REMAP-CAP	CORIMUNO-TOC	RECOVERY	Lescure et al.
		• WHO-CPS score of 5 with O_2 levels of 3 L/ minute or higher without noninvasive ventilation or mechanical ventilation	• evidence of systemic inflammation (CRP ≥ 75 mg/L) • no medical history that might • put the patient at significant risk if they were to participate in the trial	• severe disease[d] or critical disease[e]
Exclusion criteria	• death is imminent • prior participation in REMAP-CAP within 90 days • baseline platelet count < 50 x 10^9 / L • baseline ALT or AST > 5 ULN	• known hypersensitivity to TCZ • pregnancy • current documented • bacterial infection • laboratory results out of ranges: absolute neutrophil count 1.0 ×10^9 /L or less or platelets less 50 G /L	• known hypersensitivity to TCZ • evidence of active • TB infection or clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)	• low probability of surviving 48 hours or remaining at the investigational site >48 hours, or dysfunction of ≥ 2 organ systems or need for extracorporeal support or renal replacement therapy at screening • ANC < 2000/mm^3 • AST or ALT > 5-fold ULN at screening • platelets < 50,000/mm^3 at screening known active, incompletely treated, suspected, or known extrapulmonary TB • prior or concurrent use ofimmunosuppressants at screening (e.g., IL-6 inhibitors or JAK inhibitors) within 30 days of baseline • anti-CD20 agents, IL-1 receptor antagonist (anakinra), abatacept, TNF-alpha inhibitors, cyclophosphamide, cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, IV immunoglobulin, or • systemic chronic corticosteroids for a condition not related to COVID-19 at doses higher than prednisone 10 mg/day or equivalent

		REMAP-CAP	CORIMUNO-TOC	RECOVERY	Lescure et al.
					• suspected or known active systemic bacterial or fungal infections within 4 weeks of screening
DRUGS	**Intervention(s)**	Tocilizumab 8 mg/ kg (max 800 mg) IV; repeat 12 to 24 hours at discretion of clinician Sarilumab 400 mg IV one dose	Tocilizumab 8 mg/ kg IV on day 1 + usual care. Additional fixed dose of 400 mg IV on day 3 if oxygen requirement not decreased by 50% (decision left to the treating physician)	Tocilizumab 400 mg to 800 mg IV (based on body weight: 800mg if weight > 90kg; 600 mg if weight > 65 and ≤ 90 kg; 400 mg if weight > 40 and ≤ 65 kg; and 8 mg/kg if weight ≤ 40 kg) + usual care Additional dose 12 hours to 24 hours later if condition not improved	Sarilumab 200 mg IV or Sarilumab 400 mg IV. A second dose within 24 hours to 48 hours could be administered after the first dose as determined by the investigator.
	Comparator(s)	No immune modulation	Usual care (antibiotic, antiviral, corticosteroids, vasopressors, anticoagulants)	Usual care	Placebo
DURATION	**Phase**				
	Treatment duration	one day	up to three days	Up to 2 days	up to 2 days
	Follow-up	21 days	28 days	28 days	29 days and 60 days
OUTCOMES	**Primary end point**	respiratory and cardiovascular organ support-free days up to day 21	• the proportion of patients dead or needing non-invasive/ high flow oxygen or mechanical ventilation on day 4 (> 5 on the WHO-CPS) • survival with no need for non-invasive or mechanical ventilation at day 14	All-cause mortality	time from baseline to clinical improvement of ≥ 2 points on a 7-point ordinal scale[f]
	Secondary end points	• hospital mortality/survival • 90-day survival • respiratory support-free days • cardiovascular support-free days	• clinical status assessed with the WHO-CPS at day 7 and day 14 • overall survival	• time to discharge alive from hospital • composite of invasive mechanical ventilation	Key secondary outcome • proportion of patients alive at day 29

		REMAP-CAP	CORIMUNO-TOC	RECOVERY	Lescure et al.
		• time to ICU discharge • time to hospital discharge • WHO ordinal scalec at day 14 • progression to invasive mechanical ventilation, ECMO, or death among those not ventilated at baseline	• time to discharge • time to oxygen supply independency • biological factors such as CRP levels • adverse events	(including ECMO) or death among patients not receiving invasive mechanical ventilation at randomization Prespecified subsidiary clinical outcomes: • use of non-invasive respiratory support (defined as high-flow nasal oxygen, continuous positive airway pressure, or non-invasive ventilation) • time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days) • use of renal dialysis or hemofiltration Safety	Other secondary outcomes • differences in time-to-event end points by treatment (e.g., time to improvement of ≥1 point on the 7-point scale, fever resolution, or discharge from hospital), • score changes at specific time points (e.g., proportion with 1-point improvement/ worsening) • event durations (e.g., mechanical ventilation, hospitalisation) • clinical laboratory parameters • safety
Notes	**Publications**	Gordon et al.; preliminary results	Hermine et al.	RECOVERY Collaborative Group (preprint); preliminary results	Lescure et al. (preprint)

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP-HP = Assistance Publique – Hôpitaux de Paris; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DB = double blind; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IL-1 = interleukin-1; JAK = Janus kinase; MC = multi-centre; OL = open label; PB = placebo controlled; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; TCZ = tocilizumab; TNF = tumour necrosis factor; ULN = upper limit of normal; WHO = World Health Organization; WHO-CPS = World Health Organization Clinical Progression Scale.

[a] Respiratory support is defined as invasive or non-invasive mechanical ventilation including via-high flow nasal cannula if flow rate > 30 L/min and FIO2 > 0.4. If non-invasive ventilation would normally be provided but is being withheld, due to infection control concerns associated with aerosol-generating procedures, then the patient still meets the severe disease state criteria.

[b] Cardiovascular organ support defined as the intravenous infusion of any vasopressor or inotrope.

[c] WHO ordinal scale; range is 0 to 8, where 0 = no illness, 1 to 7 = increasing level of care, and 8 = death

[d] Severe disease defined as administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device.

[e] Critical disease defined as need for supplemental oxygen delivered by non-rebreather mask of high-flow nasal cannula, use of invasive or noninvasive ventilation, or treatment in an ICU.

[f] 1 = death; 2 = hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3 = hospitalized, on noninvasive ventilation or high-flow oxygen devices; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise); 6 = hospitalized, not requiring supplemental oxygen, no longer requiring ongoing medical care; 7 = not hospitalized. Discharge prior to day 29 was considered a 2-point improvement.

Table 3: Characteristics of the Included RCTs

		COVACTA	EMPACTA	Salvarani et al.
DESIGNS AND POPULATIONS	**NCT number**	NCT04320615	NCT04372186	NCT04346355
	Status	Completed	Active, not recruiting	Terminated
	Study completion date	July 28, 2020	December 1, 2021	June 6, 2020
	Funding	Hoffmann-LaRoche	Genentech Inc.	Azienda Unità Sanitaria Locale Reggio Emilia
	Study design	Phase III, MC, DB, PB	Phase III, MC, DB, PB	Phase II, MC, OL
	Locations	62 study locations (US, UK, Canada, Spain, France, Gernamny, Italy, Denmark and Netherlands)	61 study locations (US, Brazil, Kenya, Mexico, Peru, South Africa)	Italy (24 centres)
	Randomized, N	452	389	126
	Inclusion criteria	• Hospitalized patients 18 years and older • Confirmed severe COVID-19 pneumonia with evidence of bilateral chest infiltrates • Blood oxygen saturation ≤ 93% or partial pressure of oxygen or fraction of inspired oxygen < 300 mm Hg	• Hospitalized patients 18 years and older • Confirmed COVID-19 pneumonia • Blood oxygen saturation < 94% while breathing ambient air	• Hospitalized patients • 18 years and older • Confirmed COVID-19 pneumonia • Acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio between 200 mm Hg and 300 mm Hg • An inflammatory phenotype defined by a temperature > 38°C during the last 2 days or serum CRP ≥ 10 mg/dL and CRP level increased to at least twice the admission measurement
	Exclusion criteria	• Death is imminent within 24 hours • Active TB • Bacterial, fungal, or viral infection other than SARS-CoV-2	• Death is imminent within 24 hours • Receiving continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation • Active TB • Bacterial, fungal, or viral infection other than SARS-CoV-2 • Patients with coexisting conditions that preclude safe participation in the trial	• ICU admission • Known hypersensitivity to tocilizumab • Any condition preventing future admission to ICU

		COVACTA	EMPACTA	Salvarani et al.
Drugs	**Intervention(s)**	Tocilizumab 8 mg/kg (max. 800 mg) IV; if patient did not improve or worsen, a second dose was administered 8 to 24 hours after the first dose	Tocilizumab 8 mg/kg (max. 800 mg) IV plus standard care, according to local practice. If patient did not improve or worsen, a second dose was administered 8 to 24 hours after the first dose	Tocilizumab 8 mg/kg (max. 800 mg) IV followed by a second dose after 12 hours
	Comparator(s)	Placebo plus standard care	Placebo plus standard care according to local practice	Standard care
Duration	**Phase**			
	Treatment duration	One day	One day	One day
	Follow-up	• 28 days (primary analysis) • 60 days (final study visit)	• 28 days (efficacy analysis) • 60 days total follow-up	14 days
Outcomes	**Primary end point**	Clinical status on a 7-category ordinal scale at day 28	• Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28 (results of the primary efficacy analysis evaluated according to age, race, or ethnic group; geographic region; glucocorticoid use; antiviral use; and the number of doses of tocilizumab or placebo received)	Clinical worsening within 14 days since randomization[a]
	Secondary end points	• Clinical status at day 14 on the 7-category ordinal scale • Mortality at day 28 • Ventilator-free days to day 28 • Time to improvement from baseline in ≥ 2 categories on the 7-category ordinal scale • Time to hospital discharge • Time to clinical failure • Incidence of mechanical ventilation • Incidence of ICU transfer	• The time to hospital discharge or readiness for discharge as assessed with the use of a 7-category ordinal scale • Time to at least a 2-category improvement in clinical status relative to baseline on the 7-category ordinal scale • Time to clinical failure • Death • Safety	• Efficacy of early versus late administration of tocilizumab • Admission to ICU with mechanical ventilation • Mortality • Toxicity of tocilizumab

		COVACTA	EMPACTA	Salvarani et al.
		• Duration of ICU stay • Safety		
NOTES	**Publications**	Rosas et al.	Salama et al.	Salvarani et al.

COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DB = double blind; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; max. = maximum; MC = multi-centre; OL = open label; PaO_2 = partial pressure of oxygen; PB = placebo controlled; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis.

[a] Defined by any 1 of the following events: admission to ICU with mechanical ventilation; death; PaO_2:FiO_2 ratio less than 150 mm Hg in 1 of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination.

Table 4: Characteristics of the Included RCTs

		Stone et al.	TOCIBRAS	Wang et al.	Zhao et al.
DESIGNS AND POPULATIONS	**Clinical trial number**	NCT04356937	NCT04403685	Chinese Clinical Trial Registry (ChiCTR 2000029765)	NCT04310228 Chinese Clinical Trial Registry (ChiCTR 2000030096)
	Status	Completed	Terminated	Completed	Completed
	Study completion date	August 27, 2020	July 21, 2020	March 13, 2020	March 15, 2020
	Funding	Genentech	Hospitals and research institutes in Brazil; laboratory analysis by Fleury Laboratory, São Paulo, Brazil	Department of Science and Technology of Anhui Province and Health Commission of Anhui Province and the China National Center for Biotechnology Development	Chinese COVID-19 scientific research emergency project, China Mega-Project for Infectious Diseases and China Mega-Project for Innovative Drugs
	Study design	Phase III, MC, DB, PC	Phase III, MC, OL	Phase IV, MC, OL	MC, OL
	Locations	US (7 centres)	Brazil (9 centres)	China (6 centres)	China (4 centres)
	Randomized, N	243	129	65	31

	Stone et al.	TOCIBRAS	Wang et al.	Zhao et al.
Inclusion criteria	• Patients 19 to 85 years old • Confirmed SARS-CoV-2 infection • Severe COVID-19 with 2 of the following signs: fever (body temperature > 38°C) within 72 hours before enrolment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation > 92% • One of the following laboratory parameters: CRP level > 50 mg/L ferritin level > 500 ng/L, D-dimer level > 1,000 ng/L, or lactate dehydrogenase level > 250 U/L	• Hospitalized patients aged 18 years or older • Confirmed diagnosis of SARS-CoV-2 infection 2 • Severe or critical COVID-19 • Evidence of pulmonary infiltrates confirmed with chest computed tomography or radiography • Receiving supplemental oxygen to maintain oxygen saturation > 93% or receiving mechanical ventilation less than 24 hours before the randomization • Two or more of the following criteria: D-dimer > 2.74 nmol/L; CRP > 50 mg/L; ferritin > 300 mcg/L; lactate dehydrogenase > ULN	• Patients 18 to 85 years old • A confirmed diagnosis of COVID-19 • Moderate or severe disease • Elevated IL-6 plasma levels	• Patients older than 18 years • Confirmed COVID-19 • Increased IL-6 levels
Exclusion criteria	• Supplemental oxygen > 10 L/min • Recent history of treatment with biologic drugs or small molecule immunosuppressive therapy • Receiving other immunosuppressive therapy that placed them at higher risk for an infection • Diverticulitis	• Active uncontrolled infection • AST or ALT > 5 times the ULN • Renal disease with an estimated glomerular filtration of < 30 mL/min/1.72 m^2	• Woman who is pregnant or lactating • ALT or AST > 5 times the ULN • Neutropenia < 0.5 × 10^9/L • Platelet < 50 × 10^9/L • Diagnosis of rheumatism and immunity-related diseases, cancer, and other related diseases • Taking antirejection or immunomodulatory drugs • Allergy to TCZ or any excipients • Active hepatitis and TB, associated with specific bacterial and fungal infection • Organ transplantation • Mental disorders	• Allergy to FAV or TCZ • Woman who is pregnant or lactating • ALT or AST > 5 times the ULN • Active hepatitis, TB, and definite bacterial or fungal infections

		Stone et al.	TOCIBRAS	Wang et al.	Zhao et al.
Drugs	**Intervention(s)**	TCZ 8 mg/kg (max. 800 mg) IV within 3 hours after informed consent obtained	TCZ 8 mg/kg (max. 800 mg) IV once plus standard care	TCZ 400 mg IV plus standard care. A second dose was given if patient remained febrile for 24 hours following the first dose	• TCZ 4 mg/kg to 8 mg/kg (recommended 400 mg) IV. If still febrile within 24 hours of first dose, 1 additional dose was given • Plus FAV 1,600 mg b.i.d. on first day and 600 mg b.i.d. on day 2 to day 7; after day 7, treatment was continued at the discretion of the investigator
	Comparator(s)	Placebo	Standard care	Standard care	• TCZ monotherapy • FAV monotherapy
Duration	**Phase**				
	Treatment duration	One day	One day	One day	One day
	Follow-up	29 days	28 days	NR	NR
Outcomes	**Primary end point**	Intubation (or death, for patients who died before intubation)	Clinical status (7-level ordinal scale) at 15 days	Cure rate	Cumulative lung lesion remission rate
	Secondary end points	• Clinical worsening based ordinal clinical improvement scale • Discontinuation of supplemental oxygen among patients who had been receiving it at baseline • Other (tertiary) outcomes: time-to-event analyses (e.g., improvement, discharge, or death), analyses of duration (supplemental oxygen use, receipt of mechanical ventilation), and binary outcomes (admission to the ICU or death)	• All-cause mortality at day 28 • In-hospital mortality • Sequential organ failure assessment score at 8 and 15 days • Clinical status at 8 days assessed using a 6-level ordinal scale and at 29 days using a 7-level ordinal scale • Ventilator-free days within 29 day • Time to independence from supplemental oxygen within 29 days	• Recovery rate of hypoxia over 14 days • Worsening rate of hypoxia during hospitalization • Duration of hospital stay • Time to negative virus load • Safety	• Improvement in clinical symptoms • Changes in blood routine test and IL-6 level • Change in oxygen therapy • Safety

		Stone et al.	TOCIBRAS	Wang et al.	Zhao et al.
			• Duration of hospital stay • Safety • Pre-specified exploratory outcomes: levels of serum inflammatory markers and cytokines		
NOTES	**Publications**	Stone et al.	Veiga et al.	Wang et al. (preprint)	Zhao et al.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; b.i.d. = twice daily; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DB = double blind; FAV = favipiravir; ICU = intensive care unit; IL-6 = interleukin-6; MC = multi-centre; max. = maximum; min = minute; NR = not reported; OL = open label; PB = placebo controlled; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; TCZ = tocilizumab; ULN = upper limit of normal.

Study Design Characteristics

REMAP-CAP

REMAP-CAP was a phase IV, randomized, embedded, multifactorial, adaptive, platform, international, multi-centre study that compared tocilizumab and sarilumab to control.[25] The trial remains ongoing and results published so far are preliminary as data are not yet available for 11 outcomes. Under its adaptive design, REMAP-CAP evaluated multiple treatment interventions across multiple therapeutic areas. While the immune modulation therapy domain included 5 interventions, this report includes results pertaining to IL-6 receptor monoclonal antibodies — tocilizumab and sarilumab — and the control group (no immune modulation). A blinded international trial steering committee and unblinded independent data- and safety-monitoring board overlooked the trial. Although the trial was conducted across 13 countries, 6 countries across 113 sites included patients who were randomized to the immune modulation therapy domain (tocilizumab group, sarilumab group, or control group). [9]

Patients aged 18 years and older who were critically ill with suspected or confirmed COVID-19 who received respiratory or cardiovascular organ support in an ICU were eligible for enrolment. Patients with previous participation in REMAP-CAP within 90 days, or if death was deemed to be imminent, were excluded. Patients with the following laboratory values were excluded: a baseline alanine aminotransferase or an aspartate aminotransferase that exceeds 5 times the upper limit of normal and a baseline platelet count of less than 50×10^9/L. Inclusion and exclusion criteria details are provided in Table 2.

In REMAP-CAP, patients were randomly assigned in a 1:1:1 ratio to receive treatment with tocilizumab or sarilumab or control via a centralized computer program. Although patients were randomized to receive either tocilizumab or sarilumab or control, they could also be randomized to other interventions within other therapeutic domains. Although blinding was not maintained during the randomization of patients, neither the clinical staff nor members of the international trial steering committee received any information about aggregate patient outcomes. An interim analysis was conducted on October 20, 2020 by the independent data and safety monitoring board, which showed that tocilizumab met the predefined statistical criteria for efficacy (posterior probability, 99.75%; odds ratio [OR] = 1.87, 95% credible interval 1.20 to 2.76). On November 19, 2020, randomization to the control group closed and randomization resumed among other interventions in the immune modulation therapy domain. Tocilizumab 8 mg/kg (maximum total dose of 800 mg) was administered by IV infusion and repeated in 12 to 24 hours at the discretion of the clinician. Sarilumab 400 mg was administered by IV infusion as 1 dose.

The primary outcome was respiratory and cardiovascular organ support–free days calculated up to day 21. In this composite outcome, a score of −1 was assigned to the worst outcome of death. A minimum clinically important difference was defined as 1.5 days. Additional study outcomes are described in Table 2.

A Bayesian cumulative logistic model was applied for the primary analysis, which calculated posterior probability distributions for the primary outcome. There was no maximum sample size for the REMAP-CAP study and study power is not known. For time-to-event secondary outcomes, a hazard ratio (HR) and 95% confidence interval (CI) were reported.

CORIMUNO-TOC

CORIMUNO-TOC was a phase II, open-label, multi-centre RCT that compared patients who received tocilizumab plus usual care versus usual care alone.[2,26]

The enrolled patients had moderate or severe pneumopathy according to the World Health Organization (WHO) criteria of severity of COVID pneumopathy not requiring admission at the ICU. Moderate cases were defined as "showing fever and respiratory symptoms with radiological findings of pneumonia and requiring between 3L/min and 5L/min of oxygen to maintain an oxygen saturation (SaO2) of 97% or more" (p. 2).[2] Severe cases were defined as meeting any of the following criteria: "respiratory distress (30 breaths/min or more); oxygen saturation of 93% or less at rest in ambient air or oxygen saturation of 97% or less with O2 > 5L/min; a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2)" (p. 2).[2]

Patients were excluded if they had known hypersensitivity to tocilizumab, pregnancy, presence of bacterial infection or abnormal laboratory values for neutrophils or platelets. Inclusion and exclusion criteria details are provided in Table 2.

Patients were randomized in a 1:1 ratio (stratified according to site and block sizes of 2 and 4) to receive tocilizumab plus usual care or usual care alone via a centralized, web-based secure system. The trial follow-up was 28 days. Data-quality monitoring was performed under the supervision of representation from the study's sponsor, Assistance Publique – Hôpitaux de Paris and the contract research organization. Tocilizumab was administered as 8 mg/kg by IV infusion on day 1 in combination with usual care. An additional fixed dose of tocilizumab 400 mg by IV infusion on day 3 was suggested if the oxygen requirement had not decreased by more than 50%. This decision was left to the treating physician. Usual care was defined as treatment provided to the patient at the discretion of the clinician and included any of the following: supplemental oxygen, noninvasive and invasive ventilation, antibiotic drugs, antiviral drugs, corticosteroids, vasopressor support, anticoagulants, renal-replacement therapy, and extracorporeal membrane oxygenation.

The co-primary outcomes of the trial were the following: proportion of patients who had a World Health Organization Clinical Progression Scale (WHO-CPS) score higher than 5 on day 4 and survival with no need for noninvasive or mechanical ventilation measured on day 14. A protocol amendment was made on April 6, 2020 to both primary outcomes to include high-flow oxygen in noninvasive ventilation to be consistent with the core outcome set proposed by WHO. Pre-specified secondary outcomes included the following: clinical status assessed with the WHO-CPS at day 7 and day 14, overall survival, time to discharge, and time to oxygen supply independency. Additional study outcomes are described in Table 2.

The study was determined to have a "power of 97.2% to detect a decrease in event rate from 0.50 to 0.20, and 73.9% to detect a decrease in event rates from 0.50 to 0.30"(p. 3).[2] For the outcome assessed at day 4, the treatment effect was an absolute risk difference and HR for the outcome at day 14. Posterior probabilities of an absolute risk difference of less than −5.5% and an HR of less than 0.85 were classified as a "reasonable effect under the assumption of a 50% event rate at the time of analysis"(p. 4).[2]

RECOVERY

RECOVERY was a phase II and phase III, platform, open-label, multi-centre RCT that compared tocilizumab plus usual care with usual care.[27] The study was conducted across 131 sites in the UK. RECOVERY was sponsored by the Nuffield Department of Population Health at the University of Oxford and the results published so far are preliminary.[1]

Patients hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection, hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy), and evidence of systemic inflammation (CRP ≥ 75 mg/L) were enrolled in the trial. Patients were excluded from the trial if they exhibited hypersensitivity to tocilizumab; and if they showed evidence of active tuberculosis infection or active bacterial, fungal, viral, or other infection not related to COVID-19. Inclusion and exclusion criteria details are provided in Table 2.

Under its platform design, the RECOVERY trial included a main randomization component that consisted of the following three parts: "part 1 no additional treatment vs. either dexamethasone, lopinavir-ritonavir, hydroxychloroquine, azithromycin, or colchicine; part 2 no additional treatment vs. either convalescent plasma or REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-117 CoV-2 spike protein); and part 3 no additional treatment vs. aspirin"[1] (p. 6). On April 14, 2020, tocilizumab versus no additional treatment were added as treatment arms in the second randomization component. Following 21 days from the main randomization component, patients who met the study inclusion criteria were randomized in a 1:1 ratio via a web-based randomization scheme with allocation concealment to receive either tocilizumab by IV infusion plus usual care or usual care. Randomization was not stratified. Both study staff and patients were not blinded during treatment assignment. Study investigators, the steering committee, and other members of the RECOVERY trial were blinded to the trial data. The steering committee determined a priori that if all-cause mortality assessed at 28 days in the usual care group exceeded 25%, then a sample size of approximately 4, 000 patients would provide the study "90% power at a two-sided P = 0.01 resulting in a proportional one-fifth reduction"[1] (p. 10) in all-cause mortality at 28 days. On January 24, 2021, the steering committee ended recruitment in the tocilizumab arm, as more than 4, 000 patients had already been randomized. The dose of tocilizumab was 8 mg/kg up to 800 mg total dose and was administered by IV infusion. A second dose of tocilizumab was available 12 hours to 24 hours after the patient received the first dose of tocilizumab at the discretion of the treating clinician, provided the patient's condition did not show any improvement. Usual care was delivered according to each study site.

The primary outcome was all-cause mortality. The secondary outcomes in the trial were time to hospital discharge and a composite outcome of mechanical ventilation or death assessed among patients not receiving invasive mechanical ventilation at randomization. Additional study outcomes are described in Table 2.

Outcomes were assessed at 28 days of follow-up and a prespecified analysis will be conducted at 6 months. For the primary outcome, a log-rank test and Kaplan-Meier survival curve was conducted. Rate ratios and 95% CIs were calculated. Data for the primary outcome was based on 92% of randomized patients. All patients will have completed 28 days of follow-up by February 25, 2021. Prespecified subgroup analyses were performed for the primary outcome according to the following characteristics: age, sex, ethnicity, level of respiratory support, days since symptom onset, and use of systemic corticosteroids (including dexamethasone).

Lescure et al.

Lescure et al. reported the findings of a phase III, adaptive, randomized, double-blind, placebo-controlled, multi-centre, international trial that compared 200 mg sarilumab administered by IV infusion and 400 mg sarilumab administered by IV infusion with placebo.[28] The trial was conducted in 11 countries, including Canada.[10]

Patients aged 18 years and older who were hospitalized with confirmed SARS-CoV-2 infection with pneumonia were enrolled in the trial. Patients had either severe disease defined as needing "administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device" (p. 5)[10] or critical disease, which involved the "need for supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, use of invasive or noninvasive ventilation, or treatment in an intensive care unit" (p. 5).[10] Patients were excluded at screening if they had at least 2 dysfunctional organs, concomitant use of immunosuppressants, required extracorporeal life support or renal-replacement therapy, had an absolute neutrophil count of less than 2,000/mm^3, had aspartate aminotransferase or alanine aminotransferase levels above 5 times the upper limit of normal, platelets less than 50,000/mm^3, or tuberculosis. Inclusion and exclusion criteria details are provided in Table 2.

Patients were randomized in a 2:2:1 ratio (stratified according to severity of disease and use of systemic corticosteroids) to receive 1 dose of sarilumab 200 mg or 400 mg by IV infusion or placebo. A centralized randomized scheme was implemented along with permuted blocks of 5 via an interactive response technology system. The pharmacist was unblinded while preparing and dispensing sarilumab and placebo, whereas both patients and study investigators were blinded during treatment assignment and the duration of the study. On April 8, 2020, an amendment was made to the protocol to allow an optional second dose of sarilumab within 24 hours to 48 hours of the first dose at the discretion of the study investigator. A matching placebo was administered on day 1 by IV infusion, with an optional matching placebo within 24 hours to 48 hours following the first dose. The study design, data collection, data analysis, and data interpretation were conducted by Sanofi.

The primary outcome was a time to clinical improvement of at least 2 points from baseline defined on a 7-category ordinal scale as follows: 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; and 7 = death. The key secondary outcome was the proportion of patients alive at day 29. Of note, an amendment was made to the original protocol on April 8, 2020 for these phase III primary and secondary outcomes. Additional study outcomes are described in Table 2.

At 29 days of follow-up, a primary analysis was planned followed by a final analysis at day 60. A sample size of approximately 400 patients comprising 160 patients each in the sarilumab 400 mg group and sarilumab 200 mg group and 80 patients in the placebo group was determined to provide at least 90% power for each pairwise comparison between treatment groups, based on a log-rank test of superiority with a 2-sided significance level of 5%. For the primary outcome, a stratified log-rank test was applied and a Cox proportional-hazards model used treatment as a covariate. A Cochran-Mantel-Haenszel test estimated the difference in proportion of patients alive at 29 days of follow-up between the sarilumab-

dose groups and placebo group. A hierarchical testing strategy was conducted and multiplicity was taken into account for the primary and key secondary outcomes.

COVACTA

COVACTA was a phase III, randomized, double-blind, placebo-controlled, international, multi-centre study that compared tocilizumab versus placebo plus standard care.[29] The trial was conducted in 62 study locations, including Canada.[8]

The patients enrolled in the trial were aged 18 years or older and were hospitalized with confirmed severe COVID-19 pneumonia as well as a blood oxygen saturation of 93% or less, or a partial pressure of oxygen or fraction of inspired oxygen of less than 300 mm Hg. Patients were excluded if death was imminent and inevitable within 24 hours or they had active tuberculosis or a bacterial, fungal, or viral infection other than SARS-CoV-2. Inclusion and exclusion criteria details are provided in Table 3.

Patients were randomized in a 2:1 ratio (stratified according to geographic region and mechanical ventilation) to receive tocilizumab or placebo plus standard care via an interactive voice or web-based response system and permuted block randomization. Tocilizumab was administered as 8 mg/kg (maximum 800 mg) by IV infusion. If the patient did not improve or worsen, a second dose was administered 8 to 24 hours following the first dose. Standard care was defined according to local practice, which included the following: antiviral treatment, low-dose glucocorticoids, convalescent plasma, and supportive care.

The primary outcome was clinical status assessed at 28 days, defined on a 7-category ordinal scale as follows: 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. Key secondary efficacy outcomes included clinical status assessed at day 14 on the 7-category ordinal scale, mortality at day 28, ventilator-free days to day 28, time to improvement from baseline in at least 2 categories on the 7-category ordinal scale, and time to hospital discharge. Additional study outcomes are described in Table 3.

The primary analysis was conducted based on 28 days of follow up. The primary outcome was assessed based on a non-parametric van Elteren test and a proportional odds model. A Cochran-Mantel-Haenszel test was conducted to determine differences in mortality, incidence of mechanical ventilation, and ICU transfer. A log-rank test was applied for time-to-event secondary outcomes. A sample size of 450 patients was calculated to determine a power of 90% for the primary outcome associated with an OR = 2 on the ordinal scale. Based on hierarchical testing, if significance was met for clinical status, then mortality at 28 days was assessed

EMPACTA

EMPACTA was a phase III, randomized, double-blind, placebo-controlled, international, multi-centre study that compared tocilizumab versus placebo plus standard care.[30] The trial was conducted across 61 study locations.[3]

Hospitalized patients aged 18 years and older with confirmed COVID-19 pneumonia and a blood oxygen saturation of less than 94% while breathing ambient air were enrolled in this trial. Patients receiving continuous positive airway pressure, bilevel positive airway

pressure, or mechanical ventilation were excluded, as were those presenting with tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2 and coexisting conditions that preclude safe participation in the trial. Inclusion and exclusion criteria details are provided in Table 3.

Patients were randomized in a 2:1 ratio (stratified according to country and age) to receive tocilizumab plus standard care or placebo plus standard care via an interactive voice or web-based response system and permuted block randomization. The pharmacist was unblinded while preparing and labelling tocilizumab and placebo, whereas the remainder of the trial staff and patients were blinded to treatment assignment. Patients were followed up for 60 days with efficacy outcomes assessed by day 28 and safety by day 60. Tocilizumab was administered as 8 mg/kg (maximum 800 mg) by IV infusion. If the patient did not improve or worsen, a second dose was administered 8 to 24 hours following the first dose. Placebo consisted of an unaltered saline infusion bag. Standard care was delivered according to local practice.

The primary outcome was mechanical ventilation or death by day 28. Key secondary outcomes included the following: time to hospital discharge assessed according to the 7-category ordinal scale, time to improvement in clinical status, time to clinical failure, and death. Additional study outcomes are described in Table 3.

A hierarchy testing strategy was applied for the primary and secondary outcomes "to control the overall trial-wide type I error rate using a 5% significance level"(p. 4).[3] If the primary outcome reached significance using the 2-sided 5% significance level, testing of the key secondary outcomes proceeded in the following order: time to hospital discharge, time to improvement in clinical status, time to clinical failure, and death.

Salvarani et al.

Salvarani et al. conducted a phase II, open-label, parallel, randomized, multi-centre study that assessed the efficacy and safety of tocilizumab compared with standard care.[31] The trial was conducted in Italy across 24 centres.[5]

Hospitalized patients18 years and older with confirmed COVID-19 pneumonia who had "acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio of between 200 mm Hg and 300 mm Hg" (p. 2)[5] were enrolled in the study. In addition, patients were eligible for the trial if they had "an inflammatory phenotype defined by a temperature greater than 38°C during the last 2 days, or serum C-reactive protein (CRP) levels of at least 10 mg/dL or higher, and/ or a CRP level increased to at least twice the admission measurement"(p.2).[5] Patients admitted to the ICU having a known hypersensitivity to tocilizumab or any condition preventing future admission to the ICU were excluded from the study. Inclusion and exclusion criteria details are provided in Table 3.

Patients were randomized in a 1:1 ratio (stratified according to the centre) to receive tocilizumab plus standard care or standard care via telephone access to Azienda USL-IRCCS. Allocation concealment was performed using a centralized randomization list that was not available to clinicians. Permuted block randomization of different sizes was conducted. An independent data safety and monitoring committee was established to oversee the conduct of the trial and the safety and efficacy outcomes as well as to provide updates about the status of the study. The Azienda USL-IRCCS of Reggio Emilia collected study data, monitored the conduct of the trial, and performed the statistical analyses. Patients were followed up for 14 days and a minimum of 30 days to assess secondary

outcomes. Tocilizumab was administered as 8 mg/kg (maximum 800 mg) by IV infusion followed by a second dose after 12 hours. Standard care was delivered according to the protocol at each study centre. All drugs were permitted except IL-1 blockers, Janus-kinase inhibitors, and tumour necrosis factor inhibitors. Steroids were allowed if already taken prior to hospitalization. In the event a patient was admitted to the ICU or experienced any clinical worsening, treatment with steroids was available to patients in the tocilizumab plus standard care group soon after leaving the study and patients in the standard care group could receive tocilizumab.

The primary outcome was clinical worsening within 14 days since randomization. Key secondary outcomes included efficacy of early versus late administration of tocilizumab, admission to ICU with mechanical ventilation, mortality, and toxicity of tocilizumab.

Although the original protocol did not include a pre-specified interim analysis, AIFA, the regulatory authority overseeing tocilizumab in Italy introduced interim analyses in all ongoing trials. The proposed amendment which was formally submitted on May 18, 2020 included "an interim analysis for futility at one-third of the planned sample size (132 patients)" (p. 4).[5] On June 2, 2020 a statistical report was submitted to the data safety and monitoring committee that included data from 124 patients with 2 weeks of follow-up. Upon review, the study was terminated for futility on June 11, 2020 and the final sample size included 126 patients.

Stone et al.

Stone et al. was a phase III, prospective, randomized, double-blind, placebo-controlled, multi-centre study that compared tocilizumab plus standard care versus placebo.[32] The study was conducted in the US across 7 centres.[6]

Patients aged 19 to 85 years old with confirmed SARS-CoV-2 infection were enrolled in the study. Patients were required to have "at least 2 of the following signs: fever (body temperature > 38°C) within 72 hours before enrolment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation great than 92%" (p.2).[6] In addition, patients were required to have " at least 1 of the following laboratory parameters: a CRP level greater than 50 mg/L, a ferritin level greater than 500 ng/L, a D-dimer level greater than 1,000 ng/L, or a lactate dehydrogenase level of greater than 250 U/L" (p. 2).[6] Patients with a recent history of treatment with biologic drugs or small molecule immunosuppressive therapy, or if they received immunosuppressive therapy that the investigator deemed put the patient at a higher risk of an infection, were excluded from the study. Inclusion and exclusion criteria details are provided in Table 4.

Patients were randomized in a 2:1 ratio (stratified according to site) and permuted block randomization in blocks of 3 and 6 to receive tocilizumab plus standard care or placebo. Genentech funded the study and provided tocilizumab treatment to patients; however, it did not contribute toward the data analysis, data interpretation, or writing of the manuscript. Patients were followed up for 29 days. Tocilizumab was administered as 8 mg/kg (maximum 800 mg) by IV infusion. It is unclear how standard care was defined.

The primary outcome was intubation, or death for those patients who died prior to intubation. There were 2 secondary outcomes. The first secondary outcome included clinical worsening assessed according to an ordinal scale as follows: 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; and 7 = death. The second secondary outcome was discontinuation of supplemental oxygen among patients who had been receiving it at baseline and assessed at 29 days. Additional study outcomes are described in Table 4.

A log-rank test (stratified by site) compared the tocilizumab group and placebo group for primary and secondary outcomes. A stratified Cox proportional-hazards model provided HRs and 95% CIs to estimate the differences between the tocilizumab group and placebo group. A Bonferroni-Holm correction was applied for the secondary outcomes in order to obtain an overall 2-sided significance level of less than 5%.

TOCIBRAS

TOCIBRAS was a prospective, open-label, superiority, randomized controlled study that compared tocilizumab plus standard care with standard care.[33] The study was conducted in Brazil across 9 hospitals.[4]

Hospitalized patients aged 18 years or older with a confirmed diagnosis of SARS-CoV-2 infection with symptoms that lasted greater than 3 days and severe or critical COVID-19, including "evidence of pulmonary infiltrates confirmed with chest computed tomography (CT) or radiography" (p. 2)[4], were eligible for enrolment. Patients were eligible for the study if they were receiving supplemental oxygen to maintain an oxygen saturation greater than 93%, or receiving mechanical ventilation less than 24 hours before the randomization, and they had 2 or more of the following criteria: "D-dimer greater than 2.74 nmol/L, CRP greater than 50 mg/L, ferritin greater than 300 mcg/L, and lactate dehydrogenase greater than the upper limit of normal" (p. 2).[4] The original trial protocol was amended on June 4, 2020 upon study initiation to allow patients receiving mechanical ventilation under 24 hours to be included. On June 7, 2020, an additional amendment was made to allow X-ray evidence of COVID-19 in addition to CT. Patients with active uncontrolled infection were excluded.[4] Inclusion and exclusion criteria details are provided in Table 4.

Patients were randomized in a 1:1 ratio (stratified according to age and sex) and block randomization in blocks of 2, 4, 6, and 8 to receive tocilizumab plus standard care or standard care. Allocation concealment was maintained by a central web access system. An independent data-monitoring committee overlooked the trial. Hospital staff were unblinded to treatment assignment and collected patient data. Patients discharged on or after day 15 were contacted by an interviewer who was uninformed of treatment assignment to assess patients' vital status and return to daily activities. Tocilizumab was administered once as 8 mg/kg (maximum 800 mg) by IV infusion. Standard care was defined according to local guidelines for the treatment of patients with COVID-19 and included the concomitant administration of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics.[4]

The primary outcome was clinical status, defined on a 7-category ordinal scale as follows: 1 = discharged or ready for discharge; 2 = in non–ICU hospital ward, not requiring supplemental oxygen; 3 = in non–ICU hospital ward, requiring supplemental oxygen; 4 = in ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5 = in ICU, requiring intubation and mechanical ventilation; 6 = in ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7 = death. Some secondary outcomes included all-cause mortality at day 28, in-hospital mortality, and

ventilator-free days within 29 days.[4] Additional pre-specified secondary and exploratory outcomes are described in Table 4.

The study was terminated by the data safety and monitoring committee following enrolment of 129 patients due to an increased number of deaths at 15 days reported in the tocilizumab group compared with the standard care group. Although ordinal logistic regression was initially planned to analyze the primary outcome, the assumption of odds proportionality was not met (Brant test P = 0.04). Therefore, the 7-category ordinal scale was collapsed into a binary outcome with levels 1 to 5 defined as "alive and not receiving mechanical ventilation" and levels 6 to 7 defined as "receiving mechanical ventilation" (p. 3).[4]

Wang et al.

Wang et al. was a phase IV, open-label, randomized, controlled, multi-centre study that compared tocilizumab in combination with standard care versus standard care alone.[11,34] The study was conducted in China across 6 hospitals.

Patients aged 18 to 85 years old with a confirmed diagnosis of moderate or severe COVID-19 positive for SARS-CoV-2 infection and elevated IL-6 plasma levels were enrolled in the study. The diagnosis of moderate or severe COVID-19 was determined based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (fifth or updated version) sponsored by the National Health Commission of The People's Republic of China. Moderate was defined as "fever or other respiratory symptoms and bilateral pulmonary lesions confirmed by chest imaging" (p. 8).[11] The presence of any of the following criteria constituted severe disease: "a respiratory rate of 30 breaths per minute or more, an oxygen saturation of 93% or more while breathing room air, or a ratio of partial pressure of oxygen to fraction of inspired oxygen of 300 mm Hg or less"(p. 8).[11] Patients who were pregnant or breastfeeding were excluded. Inclusion and exclusion criteria details are provided in Table 4.

Patients were randomized in a 1:1 ratio and computer-generated block randomization to receive tocilizumab plus standard care or standard care alone. Since tocilizumab was approved in the *Diagnosis and Treatment Protocol for Severe COVID-19* (seventh edition) in China, any patient randomized to the standard care group who experienced disease progression within 3 days of randomization was transferred to the tocilizumab group. The investigator for each sub-site enrolled patients consecutively until the total number of cases allotted to the site was maximized. A competitive recruitment approach was followed for study enrolment. Tocilizumab was administered as 400 mg by IV infusion. A second dose was given provided the patient remained febrile for 24 hours following the first dose. Standard care was delivered based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (fifth or updated version).

The primary outcome was cure rate. Cure was defined as "fever attenuated continuously for 7 days, 2 negative COVID-19 nucleolus acid detections, and a CT scan showing that chest effusion had been absorbed by more than 50% as of the patient's discharge from hospital"(p.9).[11] Secondary outcomes included recovery rate of hypoxia over 14 days, the worsening rate of hypoxia during hospitalization, the duration of hospital stay, and the time to negative virus load. Hypoxia was defined as "when inhaling room air, the peripheral oxygen saturation was less than 93%" (p. 9).[11] Hypoxia recovery required "the patient's fingertip oxygen saturation [to be] ≥ 93% when inhaling room air" (p. 9).[11] Hypoxia worsening was defined as the need for "the patient's inhaling oxygen concentration [to be] upregulated so as to maintain normal oxygen saturation levels" (p. 9).[11]

A Chi-square test or Fisher's exact test was conducted for the primary and secondary outcomes. The study was designed to have a 30% cure rate, and 10% cure rate in the tocilizumab plus standard care group and standard care alone group, respectively.

Zhao et al.

Zhao et al. was an open-label, randomized, controlled, multi-centre study that compared tocilizumab in combination with favipiravir, favipiravir monotherapy, and tocilizumab monotherapy.[7,35] The study was conducted in China across 4 hospitals.

Patients older than 18 years with confirmed COVID-19 according to Chinese guidelines and increased IL-6 levels were enrolled in the study. Patients with an allergy to favipiravir or tocilizumab as well as patients who were pregnant or breastfeeding were excluded from the study. A clinical classification of disease severity was recorded for each patient based on the Chinese COVID-19 guidelines (seventh edition). The details of the inclusion and exclusion criteria are provided in Table 4.

Patients were randomized in a 1:1:3 ratio to receive tocilizumab monotherapy, favipiravir monotherapy, or tocilizumab plus favipiravir. Tocilizumab was administered as 4 mg/kg to 8 mg/kg (recommended amount of 400 mg) by IV infusion. If the patient remained febrile within 24 hours of the first dose, 1 additional dose was given. Favipiravir was administered as 1,600 mg twice daily on the first day and 600 mg twice daily on days 2 to 7. After day 7, treatment was continued at the discretion of the investigator.

The primary outcome was the cumulative lung lesion remission rate, which was determined when the "lung CT examination indicated absorption of lung inflammation" (p. 2).[7] Some secondary outcomes included improvement in clinical symptoms and changes in oxygen therapy. Other secondary outcomes are listed in Table 3.

A log-rank (Mantel-Cox) test was conducted for the primary outcome.

Study Results

Patient Disposition

REMAP-CAP

The patient disposition of REMAP-CAP is summarized in Appendix 1. Of the 2,046 patients who were randomized in at least 1 therapeutic domain of the REMAP-CAP trial, 895 patients were randomized in the immune modulation therapy domain. (There were 366 patients in the tocilizumab group, 48 patients in the sarilumab group, 412 patients in the control group, and 69 patients received another intervention). The results related to 69 patients assigned to another intervention are not included in this report. There were 13 patients who withdrew consent in the tocilizumab group and 10 patients who withdrew consent in the control group. Primary outcome data were not available for 3 patients in each of the tocilizumab and sarilumab groups and 5 patients in the control group. The intention-to-treat (ITT) population included 353 patients in the tocilizumab group, 48 patients in the sarilumab group, and 402 patients in the control group.

CORIMUNO-TOC

The patient disposition of CORIMUNO-TOC is summarized in Appendix 1. Of the 131 patients who were screened in CORIMUNO-TOC, 64 patients were randomized in the tocilizumab and usual care group versus 67 patients in the usual care group. In the

tocilizumab plus usual care group, 8 patients were lost to follow-up at day 28, leaving 56 patients who completed the trial through day 28. There were 3 patients who did not receive the assigned treatment. In the usual care group, 3 patients were lost to follow-up at day 28, leaving 64 patients in the usual care group.

RECOVERY

The patient disposition of RECOVERY is summarized in Appendix 1. Of the 4,116 patients enrolled across 131 study sites that offered tocilizumab, 2,022 patients were randomized to the tocilizumab group and 2,094 patients were randomized to receive usual care. Although 1,602 patients completed follow-up in the tocilizumab plus usual care group, there were 83.2% of patients who received treatment with tocilizumab. The reasons why 16.8% of patients did not receive treatment with tocilizumab was not reported. Three patients each withdrew consent in the tocilizumab plus usual care group and usual care group, respectively.

Lescure et al.

The patient disposition of Lescure et al. is summarized in Appendix 1. Of the 431 patients who were screened in the study, 161 patients were randomized to receive 200 mg of sarilumab, 173 patients were randomized to receive 400 mg of sarilumab, and 86 patients were randomized to the placebo group. Two patients in each of the 200 mg sarilumab group and placebo group, respectively, did not receive assigned treatment. Of the 2 patients who did not receive the assigned 200 mg of sarilumab, 1 patient improved and 1 patient withdrew consent. Of the 2 patients who did not receive placebo, 1 patient was randomized twice and 1 patient had a suspected bacterial infection.

COVACTA

The patient disposition of COVACTA is summarized in Appendix 1. Of the 479 patients who were screened in COVACTA, 452 patients underwent randomization (301 patients in the tocilizumab group versus 151 patients in the tocilizumab plus placebo group). In the tocilizumab group, 57 patients died, 7 patients were lost to follow-up, 7 patients discontinued from the study based on their decision, 4 patients discontinued the study due to physician decision, and 2 patients discontinued the study due to other reasons. In the placebo plus standard care group, 29 patients died, 5 patients were lost to follow-up, 4 patients discontinued the study due to patient decision and 4 due to physician decision, and 1 patient discontinued the study due to other reasons. The modified intention-to-treat population (mITT) population included 294 patients in the tocilizumab group and 144 patients in the placebo plus standard care group. The safety population included 295 and 143 patients in the tocilizumab group and placebo plus standard care group, respectively. Note that 1 patient randomly assigned to the placebo plus standard care group was treated with tocilizumab and included in the tocilizumab group for the safety population.

EMPACTA

The patient disposition of EMPACTA is summarized in Appendix 1. Of the 445 patients who were screened in EMPACTA, 259 patients were randomized in the tocilizumab plus standard care group versus 129 patients in the placebo plus standard care group. In the tocilizumab plus standard care group, 24 patients died, 8 patients withdrew, and 1 patient discontinued the study due to withdrawal by physician. In the placebo plus standard care group, 11 patients died, 2 patients transferred to another facility, and 1 patient discontinued the study due to withdrawal by physician. The mITT population included 249 patients in the

tocilizumab plus standard care group and 128 patients in the placebo plus standard care group. The safety population included 250 and 127 patients in the tocilizumab plus standard care group and placebo plus standard care group, respectively.

Salvarani et al.

The patient disposition for the study by Salvarani et al. is summarized in Appendix 1. Of the 126 patients who were screened in the study, 60 patients were randomized in the tocilizumab group versus 66 patients in the standard care group. In the standard care group, 6 patients did not receive assigned treatment, 3 patients discontinued from the study before day 30, and 3 patients withdrew consent. The ITT population included 60 patients in the tocilizumab group and 63 patients in the standard care group.

Stone et al.

The patient disposition for the study by Stone et al. is summarized in Appendix 1. Of the 1,560 patients who were screened in the study, 161 patients were randomized in the tocilizumab group versus 82 patients in the placebo group. The ITT population included 161 patients in the tocilizumab group and 82 patients in the placebo group. The mITT population included 161 patients in the tocilizumab group and 81 patients in the placebo group. One patient was intubated prior to receiving placebo and excluded from the mITT population; however, they were included in the safety population.

TOCIBRAS

The patient disposition for the study by Veiga et al. is summarized in Appendix 1. Of the 129 patients who were randomized in the study, 64 patients were randomized in the tocilizumab plus standard care group versus 64 patients in the standard care group. While 64 patients were assigned to the standard care group, 2 patients received treatment with tocilizumab at the discretion of the investigator. Therefore, the safety population included 67 patients in the tocilizumab plus standard care group and 62 patients in the standard care group. The analysis of the primary and secondary outcomes included 65 patients in the tocilizumab plus standard care group and 64 patients in the standard care alone group.

Wang et al.

The patient disposition for the study by Wang et al. is summarized in Appendix 1. Of the 65 patients who were screened in the study, 33 patients were randomized in the tocilizumab plus standard care group versus 32 patients in the standard care alone group. In the standard care alone group, 1 patient transferred to the tocilizumab group when their condition worsened. Both the ITT and safety populations included 34 patients in the tocilizumab group and 31 patients in the standard care alone group.

Zhao et al.

The patient disposition for the study by Zhao et al. is summarized in Appendix 1. Of the 31 patients who were screened in the study, 14 patients were randomized in the tocilizumab plus favipiravir group, 5 patients in the tocilizumab group and 7 patients in the favipiravir group. The ITT and safety populations included 14 patients in the tocilizumab plus favipiravir group, 5 patients in the tocilizumab group, and 7 patients in the favipiravir group.

Baseline Characteristics

REMAP-CAP

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The mean age of patients in the tocilizumab group was 61.5 years (standard deviation [SD] = 12.5), 63.4 years (SD = 13.4) in the sarilumab group, and 61.1 years (SD = 12.8) in the control group. The percentage of males was similar in the tocilizumab and control group (73.9% and 70.4%, respectively) versus 81.3% in the sarilumab group. In the study population, more than 70% of patients were White. Diabetes mellitus was the most prevalent pre-existing condition, affecting 35.2% in the tocilizumab group and 37.4% in the control group. In the sarilumab group, the most prevalent pre-existing condition was respiratory disease in 31.3% patients.

The median time to enrolment from hospital admission was 1.2 days (interquartile range [IQR] = 0.8 to 2.8) each in the tocilizumab and control group versus 1.4 days (IQR = 0.9 to 2.8) in the sarilumab group. The median time to ICU admission in the tocilizumab, sarilumab, and control groups was 13.1 hours (IQR = 6.6 to 19.0), 16.0 hours (IQR = 11.4 to 20.8) and 14.0 hours (IQR = 6.8 to 19.5), respectively. Noninvasive ventilation was the most common acute respiratory support that occurred in 41.6% of patients in the tocilizumab group, 47.9% of patients in the sarilumab group, and 42.0% of patients in the control group.

CORIMUNO-TOC

The baseline demographic and clinical characteristics of patients are presented in Appendix 2. The median age of patients in the tocilizumab plus usual care group was 64.0 years (IQR = 57.1 to 74.3), and 63.3 years (IQR = 57.1 to 72.3) in the usual care group. The percentage of males was similar in the tocilizumab plus usual care and usual care alone groups (70% and 66%, respectively). Diabetes and chronic cardiac disease were the most prevalent pre-existing conditions, affecting 33% in the tocilizumab plus usual care group. Similarly, in the usual care group, diabetes was the most prevalent pre-existing condition, affecting 34% of patients.

The median time from symptom onset to randomization was 10 days each in the tocilizumab plus usual care group (IQR = 7 to 13) and usual care group (IQR = 8 to 13). The median time from hospital admission to randomization was 1 day each in the tocilizumab plus usual care group (IQR = 1 to 4) and usual care group (IQR = 1 to 2).

RECOVERY

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The mean age of patients in the tocilizumab plus usual care group was 63.3 years (SD = 13.7) and 63.9 years (SD = 13.6) in the usual care group. The percentage of males was similar in the tocilizumab plus usual care group and usual care group (66% and 69%, respectively). Diabetes was the most prevalent pre-existing condition, affecting 28% in the tocilizumab plus usual care group and 29% in the usual care group. There were 82% of patients each in the tocilizumab plus usual care group and usual care group, respectively, who reported using systemic corticosteroids. Following the main randomization, 41% of patients each in the tocilizumab plus usual care group and usual care group, respectively, reported receiving non-invasive respiratory support (i.e., high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation). The proportion of patients with no

ventilator support was comparable in the tocilizumab plus usual care group and usual care group (46% and 45%, respectively).

Lescure et al.

The baseline demographic and clinical characteristics of patients are presented in Appendix 2. While the median age of patients was 58.0 years in both the 200 mg sarilumab group (IQR = 51.0 to 67.0) and 400 mg sarilumab group (IQR = 48.0 to 67.0), in the placebo group, the median age was 60.0 years (IQR = 53.0 to 69.5). The percentage of males was 67.9%, 57.2%, and 64.3% in the 200 mg sarilumab group, 400 mg sarilumab group, and placebo group, respectively. Hypertension was the most prevalent comorbidity, affecting 42.8% in the 200 mg sarilumab group, 40.5% in the 400 mg sarilumab group, and 46.4% in the placebo group. The study was racially diverse, yet 77.2% of patients were White. A total of 42.0% of patients were obese (body mass index of 30 kg/m^2 or greater). Severe disease was noted in 57.9% of patients in the 200 mg sarilumab group, 60.7% of patients in the 400 mg sarilumab group, and 65.5% of patients in the placebo group. The use of systemic corticosteroids prior to dosing was highest in the 400 mg sarilumab group (24.3%) compared with 15.7% in the 200 mg sarilumab group and 19.0% in the placebo group.

COVACTA

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The mean age of patients in the tocilizumab group was 60.9 years (SD = 14.6) and 60.6 years (SD = 13.7) in the placebo plus standard care group. The percentage of males was similar in the tocilizumab and placebo plus standard care group (69.7% and 70.1%, respectively). The COVACTA study was racially diverse, yet more than 50% of patients were White. Hypertension was the most prevalent comorbidity, affecting 60.5% in the tocilizumab group and 65.3% in the placebo plus standard care group. In each of the tocilizumab group and placebo plus standard care group, 37% of patients were on mechanical ventilation. The administration of glucocorticoids for systemic use until the initiation of tocilizumab or placebo was lower in the tocilizumab group compared with the placebo plus standard care group (19.4% versus 28.5%). The administration of antiviral treatment until the initiation of tocilizumab or placebo was reported for 24.1% of patients in the tocilizumab group and 29.2% of patients in the placebo plus standard care group. The administration of convalescent plasma treatment until the initiation of tocilizumab or placebo was similar in the tocilizumab group (1.47) and placebo plus standard care group (0.7%).

EMPACTA

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The mean age of patients in the tocilizumab group was 56.0 years (SD = 14.3) and 55.6 years (SD = 14.9) in the placebo plus standard care group. The percentage of males was similar in the tocilizumab and placebo plus standard care groups (60.2% and 57.0%, respectively). The EMPACTA study was ethnically diverse, with 57.4% and 53.1% of patients identifying as Hispanic or Latino in the tocilizumab plus standard care group and placebo plus standard care group, respectively. In the tocilizumab plus standard care group, 64.7% of patients had an ordinal scale score of 3 at baseline, defined as being in a non–ICU hospital ward and not requiring supplemental oxygen. Similarly, in the placebo plus standard care group, 63.3% of patients had an ordinal scale score of 3 at baseline.

Salvarani et al.

The baseline demographic and clinical characteristics of patients are presented in Appendix 2. The median age of patients in the tocilizumab plus standard care group was 61.5 years (IQR = 51.5 to 73.5) and 60.0 years (IQR = 54.0 to 69.0) in the standard care group. The percentage of males was higher in the tocilizumab plus standard care versus the standard care group (66.7% versus 56.1%). Hypertension was the most prevalent coexisting condition, affecting 45.0% in the tocilizumab plus standard care group and 43.9% in the standard care alone group. The use of hydroxychloroquine was reported among 88.3% of patients in the tocilizumab plus standard care group compared with 93.9% of patients in the standard care group.

Stone et al.

The baseline demographic and clinical characteristics of patients are presented in Appendix 2. The median age of patients in the tocilizumab plus standard care group was 61.6 years (IQR = 46.4 to 69.7) and 56.5.0 years (IQR = 44.7 to 67.8) in the placebo group. The percentage of males was higher in the tocilizumab plus standard care versus placebo group (60% versus 55%). There were 43% and 48% of patients classified as Hispanic or Latino in the tocilizumab plus standard care group and placebo group, respectively. Diabetes was the most prevalent comorbidity, affecting 28% in the tocilizumab plus standard care group and 37% in the placebo group. In the tocilizumab plus standard care group, 83% of patients had an ordinal scale score of 3 at baseline defined as being in a non–ICU hospital ward and not requiring supplemental oxygen whereas in the placebo group, 74% of patients had an ordinal scale score of 3 at baseline.

TOCIBRAS

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The mean age of patients in the tocilizumab plus standard care group was similar to the standard care group (57.4 years [SD = 15.7] versus 57.5 years [SD = 13.5], respectively). The percentage of males was similar in the tocilizumab plus standard care group and standard care group (68% and 69%). Hypertension was the most prevalent coexisting condition, affecting 46% in the tocilizumab plus standard care group and 53% in the standard care group. In the tocilizumab plus standard care group, 60% of patients had an ordinal scale score of 4 at baseline defined as admitted to hospital, receiving supplemental oxygen. Similarly, in the standard care group, 44% of patients had an ordinal scale score of 4 at baseline.

Wang et al.

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The median age of patients was 63 years old each in the tocilizumab plus standard care group (IQR 58 to 71) and standard care group (IQR 54 to 69). The percentage of males was similar in the tocilizumab plus standard care group and standard care group (52.94% and 48.39%, respectively). There were 58.8% and 54.8% of patients with moderate disease severity at baseline in the tocilizumab plus standard care group and standard care group, respectively. There were 41.2% and 45.2% of patients with severe disease at baseline in the tocilizumab plus standard care group and standard care group, respectively. Hypertension was the most prevalent coexisting condition, affecting 29.4% in the tocilizumab plus standard care group and 32.3% in the standard care group.

Zhao et al.

The patient baseline demographic and clinical characteristics are presented in Appendix 2. The median age of patients was 75 years old in the tocilizumab plus favipiravir group (range 34 to 81 years), 71 years old in the tocilizumab group (range 48 to 77 years), and 70 years old (range 45 to 89 years) in the favipiravir group. The percentage of males was lowest in the tocilizumab plus favipiravir group (43%) compared with 60% and 71% in the tocilizumab group and favipiravir group, respectively. A total of 35.7% of patients in the tocilizumab plus favipiravir group exhibited severe-type clinical classification compared with 60.0% and 71.4% of patients in the tocilizumab group and favipiravir group, respectively. Hypertension was the most prevalent concomitant disease, affecting 42.9% each in the tocilizumab plus favipiravir group and favipiravir group, respectively, whereas coronary heart disease was the most prevalent concomitant disease, affecting 60.0% of patients in the tocilizumab group.

Efficacy

REMAP-CAP

The clinical efficacy results for REMAP-CAP are reported in Table 5.

- Organ support–free days:
  - Compared with the control group, the median adjusted odds ratios (primary model) for respiratory and cardiovascular organ support–free days measured at day 21 were 1.64 (95% credible interval [CrI], 1.25 to 2.14) for the tocilizumab group and 1.76 (95% CrI, 1.17 to 2.91) for the sarilumab group, yielding greater than 99.9% and 99.5% posterior probabilities of superiority.
- 90-day survival (time to event):
  - Compared with the control group, the median adjusted HRs for 90-day survival were 1.59 (95% CrI, 1.24 to 2.05) for the tocilizumab group and 1.82 (95% CrI, 1.22 to 3.38) for the sarilumab group, yielding greater than 99.9% and 99.8% posterior probabilities of superiority.
- Time to ICU discharge:
  - Compared with the control group, the median adjusted HRs for time to hospital discharge were 1.42 (95% CrI, 1.18 to 1.70) for the tocilizumab group and 1.64 (95% CrI, 1.21 to 2.45) for the sarilumab group, yielding greater than 99.9% and 99.9% posterior probabilities of superiority.
- Time to hospital discharge:
  - Compared with the control group, the median adjusted HRs were 1.41 (95% CrI, 1.18 to 1.70) for tocilizumab and 1.60 (95% CrI, 1.17 to 2.40) for the sarilumab group, yielding greater than 99.9% and 99.8% posterior probabilities of superiority.

Table 5: Clinical Outcomes for REMAP-CAP

REMAP-CAP[9a]	Tocilizumab n = 353	Sarilumab n = 48	Control n = 402
Organ support–free days up to day 21[b]			
Median (IQR)	10 (−1 to 16)	11 (0 to16)	0 (−1 to 15)
Adjusted OR, mean (SD)	1.65 (0.23)	1.83 (0.44)	1
Median (95% CrI)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Subcomponents of organ support–free days[b]			
In-hospital death, n/N (%)	98/350 (28)	10/45 (22)	142/397 (36)
Organ support–free days in survivors, median (IQR)	14 (7 to 17)	15 (6 to 17)	13 (4 to 17)
Primary in-hospital survival			
Adjusted OR, mean (SD)	1.66 (0.31)	2.25 (0.96)	1
Median (95% CrI)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
90-day survival (time to event)			
Adjusted HR, mean (SD)	1.60 (0.21)	1.94 (0.56)	1
Median (95% CI)	1.59 (1.24 to 2.05)	1.82 (1.22 to 3.38)	1
Respiratory support–free days			
Adjusted OR, mean (SD)	1.74 (0.25)	2.04 (0.53)	1
Median (95% CrI)	1.73 (1.31 to 2.27)	1.94 (1.27 to 3.32)	1
Cardiovascular support–free days			
Adjusted OR, mean (SD)	1.70 (0.26)	1.95 (0.53)	1
Median (95% CrI)	1.68 (1.25 to 2.24)	1.85 (1.20 to 3.30)	1
Time to ICU discharge			
Adjusted HR, mean (SD)	1.43 (0.13)	1.69 (0.32)	1
Median (95% CrI)	1.42 (1.18 to 1.70)	1.64 (1.21 to 2.45)	1
Time to hospital discharge			
Adjusted HR, mean (SD)	1.42 (0.13)	1.65 (0.31)	
Median (95% CrI)	1.41 (1.18 to 1.70)	1.60 (1.17 to 2.40)	
WHO scale at day 14[c]			
Adjusted OR, mean (SD)	1.85 (0.26)	1.91 (0.43)	
Median (95% CrI)	1.83 (1.40 to 2.41)	1.86 (1.22 to 2.91)	
Progression to invasive mechanical ventilation, ECMO, or death, restricted to those not intubated at baseline			
Free from invasive mechanical ventilation at baseline, n	242	37	273
Progression to intubation, ECMO, or death, n/N (%)	100/242 (41.3)	13/37 (35.1)	144/273 (52.7)
Adjusted OR, mean (SD)	1.72 (0.33)	1.82 (0.55)	1

REMAP-CAP[9a]	Tocilizumab n = 353	Sarilumab n = 48	Control n = 402
Median (95% CrI)	1.69 (1.17 to 2.42)	1.74 (1.01 to 3.14)	1

COVID-19 = coronavirus disease 2019; CrI = credible interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ICU = intensive care; IQR = interquartile range; OR = odds ratio; SD = standard deviation; WHO = World Health Organization.

[a] All models are structured such that a higher OR HR is favourable.

[b] The primary analysis of organ support–free days and in-hospital mortality used data from all participants enrolled in the trial who met COVID-19 severe state criteria and who were randomized within at least 1 domain (n = 1,928), adjusting for age, sex, time period, site, region, domain, and intervention eligibility and intervention assignment.

[c] The WHO scale ranges from 0 (no disease) to 8 (death).

CORIMUNO-TOC

The clinical efficacy results for CORIMUNO-TOC are reported Table 6.

- WHO-CPS score higher than 5 on day 4:
  - On day 4, 12 patients (19%) randomized to tocilizumab plus usual care versus 19 patients (28%) in the usual care alone group had a WHO-CPS score higher than 5 (median posterior absolute risk difference = −9%; 95% CrI, −23.3 to 5.5)
- First event of noninvasive ventilation or high-flow oxygen, mechanical ventilation, or death on day 14:
  - On day 14, 15 patients in the tocilizumab plus usual care (cumulative incidence of event = 24%; 95% CI, 13 to 35) versus 24 patients in the usual care group (cumulative incidence of event = 36%; 95% CI, 33 to 58) reported at least 1 event of noninvasive ventilation or high-flow oxygen, mechanical ventilation, or death. The posterior median HR was 0.58 (95 CI%, 0.30 to 1.11).
- Overall survival on day 28:
  - In the tocilizumab plus usual care group, there were 7 deaths as of day 28 compared with 8 deaths in the usual care group (adjusted HR = 0.92; 95% CI, 0.33 to 2.53).
- Oxygen supply dependency on day 28:
  - The adjusted HR for weaning off oxygen in the tocilizumab plus usual care group compared with the usual care alone group was 1.41 (95% CI, 0.98 to 2.01).
- Discharge by day 28:
  - In the tocilizumab plus usual care group, the cumulative incidence of discharge was 83% (95% CI 70 to 90%) compared to 73% (95% CI 61 to 82) in the usual care group. The adjusted HR was 1.52; 95% CI, 1.02 to 2.27).

Table 6: Clinical Outcomes for CORIMUNO-TOC

CORIMUNO-TOC[2]	Tocilizumab (n = 63)	Usual care (n = 67)
WHO-CPS score higher than 5 on day 4		
n (%)	2 (19)	19 (28)
ARD (95% CI)	−9% (−23.3 to 5.5)	
Noninvasive ventilation or high-flow oxygen, mechanical ventilation, or death by day 14		
n	15	24
Cumulative incidence, % (95% CI)	24 (13 to 34)	36 (23 to 46)
Difference	−12 (−28 to 4)	
First event, n		
Noninvasive ventilation or high-flow oxygen	8	13
Mechanical ventilation	3	8
Death or DNR order	4	3
Mechanical ventilation or death by day 14		
% (95% CI)	17 (8 to 26)	27 (15 to 37)
Difference	−9 (−24 to 5)	
First event, n		
Mechanical ventilation	5	14
Death or DNR order	6	4
Discharge by day 28		
Cumulative % (95% CI)	83 (70 to 90)	73 (61 to 82)
Adjusted HR, 95% CI	1.52 (1.02 to 2.27)	
Deaths		
At day 14, n	7	6
Survival, % (95% CI)	89 (81 to 97)	91 (84 to 98)
At day 28	7	8
Survival, % (95% CI)	89 (81 to 97)	88 (80 to 96)

ARD = absolute risk difference; CI = confidence interval; DNR = do not resuscitate; HR = hazard ratio; WHO-CPS = World Health Organization Clinical Progression Scale.

RECOVERY

The clinical efficacy results for RECOVERY are reported in Table 7.

- All-cause mortality at 28 days:
  - At 28 days of follow-up, there were 596 patients (29%) who died in the tocilizumab plus usual care group compared to 694 patients (33%) who died in the usual care group.
  - There was a significant difference in all-cause mortality at 28 days in favour of the tocilizumab plus usual care group compared to the usual care group (rate ratio 0.86, 95% CI, 0.77 to 0.96, P = 0.0066).
- Discharged alive from hospital within 28 days:
  - At 28 days of follow-up, the median time to being discharged alive was 20 days in the tocilizumab plus usual care group compared to more than 28 days in the usual care group.

- At 28 days follow-up, there were 54% of patients in the tocilizumab plus usual care group discharged alive from the hospital compared to 47% of patients in the usual care group (rate ratio 1.22, 95% CI, 1.12 to 1.34, P < 0.0001).

- Mechanical ventilation or death:
  - There was a difference in receipt of invasive mechanical ventilation or death at 28 days in favour of the tocilizumab plus usual care group compared to the usual care group (rate ratio 0.85, 95% CI, 0.78 to 0.93, P = 0.0005).

Table 7: Clinical Outcomes for RECOVERY

RECOVERY[1]	TCZ n = 2,022	UC n = 2,094
All-cause 28-day mortality		
n (%)	596 (29)	694 (33)
RR (95% CI)	0.86 (0.77 to 0.96)	
P value	0.0066	
Time to discharge alive		
Median days	20	> 28
Discharged alive from hospital within 28 days		
n (%)	1,093 (54)	990 (47)
RR (95% CI)	1.22 (1.12 to 1.34)	
P value	< 0.0001	
Receipt of invasive mechanical ventilation or death[a]		
n/N (%)	571/1,754 (33)	687/1,800 (38)
RR (95% CI)	0.85 (0.78 to 0.93)	
P value	0.0005	
Receipt of ventilation[b]		
n/N (%)	233/935 (25)	242/933 (26)
RR (95% CI)	0.96 (0.82 to 1.12)	
P value	0.61	
Successful cessation of invasive mechanical ventilation[c]		
n/N (%)	91/1,268 (34)	94/294 (32)
RR (95% CI)	1.07 (0.80 to 1.43)	
P value	0.64	
Use of hemodialysis or hemofiltration[d]		
n/N (%)	103/2,003 (5)	142/2,075 (7)
RR (95% CI)	0.75 (0.59 to 0.96)	
P value	0.02	

CI = confidence interval; RR = rate ratio; TCZ = tocilizumab; UC = usual care.

[a] Analyses include only those on no ventilator support or non-invasive ventilation at second randomization.

[b] Analyses include only those on no ventilator support at second randomization.

[c] Analyses restricted to those on invasive mechanical ventilation at second randomization.

[d] Analyses exclude those on hemodialysis or hemofiltration at second randomization.

Lescure et al.

The clinical efficacy results are reported in Table 8.

- Time to at least a 2-point improvement as of day 29:
  - The time to an improvement in clinical status of at least 2 points on the 7-category ordinal scale by day 29 in the 200 mg sarilumab group was 10 days (95% CI, 9 to 12) versus 12 days in the placebo group (95% CI, 9 to 15).
  - There was no significant difference in time to an improvement in clinical status of at least 2 points on the 7-category ordinal scale by day 29 between the 200 mg sarilumab group and placebo group (HR = 1.03; 95% CI, 0.75 to 1.40; P = 0.96).
  - The time to improvement in clinical status of at least 2 points on the 7-category ordinal scale by day 29 in the 400 mg sarilumab group was 10 days (95% CI, 9 to 13) versus 12 days in the placebo group (95% CI, 9 to 15).
  - There was no significant difference in time to an improvement in clinical status of at least 2 points on the 7-category ordinal scale by day 29 between the 400 mg sarilumab group and placebo group (HR = 1.14; 95% CI, 0.84 to 1.54; P = 0.34).
- Proportion of patients alive at day 29:
  - There was no significant difference in the proportion of patients alive at day 29 in the 200 mg sarilumab group (89.9%) compared with placebo group (91.7%) (difference = –1.7; 95% CI, –9.3 to 5.8; P = 0.63).
  - There was no significant difference in the proportion of patients alive at day 29 in the 400 mg sarilumab group (91.9%) compared with the placebo group (91.7%) (difference = 0.2; 95% CI, –6.9 to 7.4; P = 0.85).

Table 8: Clinical Outcomes for Lescure et al.

Lescure et al. (mITT)[10a]	SAR 200 mg n = 159	SAR 400 mg n = 173	PB n = 84
Time to ≥ 2-point improvement on the ordinal 7-point clinical status scale			
Kaplan-Meier estimates, median days (95% CI)[b]	10.0 (9.0 to 12.0)	10.0 (9.0 to 13.0)	12.0 (9.0 to 15.0)
P value[c]	0.96	0.34	NA
HR versus PB, (95% CrI)[d]	1.03 (0.75 to 1.40)	1.14 (0.84 to 1.54)	NA
Patients alive at day 29			
n (%)[e]	143 (89.9)	159 (91.9)	77 (91.7)
Difference versus PB, 95% CI[f]	–1.7 (–9.3 to 5.8)	0.2 (–6.9 to 7.4)	NA
P value versus PB[g]	0.63	0.85	NA
Patients alive at day 60			
n (%)	142 (89.3)	155 (89.6)	75 (89.3)
Difference versus PB, 95% CI[f]	0 (–8.2 to 8.2)	0.3 (–7.7 to 8.3)	NA
P value versus PB[g]	0.99	0.81	NA
Patients discharged due to recovery, n (%)			
Day 29	126 (79.2)	137 (79.2)	70 (83.3)
Day 60	135 (84.9)	144 (83.2)	73 (86.9)

Lescure et al. (mITT)[10a]	SAR 200 mg n = 159	SAR 400 mg n = 173	PB n = 84
Initiation of mechanical ventilation, noninvasive ventilation, or use of high-flow nasal cannula			
n (%)	26 (20.5)	33 (23.4)	13 (19.1)
Difference versus PB, (95% CI)[f]	1.4 (–10.3 to 13.0)	4.3 (–7.4 to 16.0)	NA
P value[g]	0.81	0.61	NA
Patients with need for ICU care during study (not in ICU at baseline)[h]			
n (%)	11 (11.2)	17 (14.9)	7 (12.5)
Difference versus PB (95% CI)[f]	–1.3 (–12.0 to 9.4)	2.4 (–8.4 to 13.3)	NA
P value[g]	0.98	0.54	NA
Hospitalization among patients alive at day 60[i]			
LS mean days (SE)[j]	15.6 (1.0)	16.1 (0.9)	15.9 (1.3)
Difference versus PB (95% CI)	–0.2 (–3.5 to 3.0)	0.2 (–3.0 to 3.0)	NA
P value	0.87	0.87	NA

CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; LS = least squares; mITT = modified intention to treat; NA = not applicable; PB = placebo; SAR = sarilumab; SE = standard error.

[a] Stratified by severity of illness and use of systemic corticosteroids as entered in the interactive response system.

[b] Two-sided 95% CI is computed by Brookmeyer and Crowley method (log-log transformation).

[c] P value based on log-rank test.

[d] Cox proportional hazard model. HR > 1 indicates greater chance of improvement for SAR compared with placebo.

[e] One death in the SAR 200 mg group was included in the "all patients" summary but not in either the "severe" or "critical" categories, as the patient had multi-organ failure.

[f] Based on asymptomatic confidence limits.

[g] P value based on Cochran-Mantel-Haenszel test.

[h] Even when ICU not available.

[i] Days of hospitalization since the first dose was counted.

[j] The analysis of the end point was performed using the analysis of covariance (ANCOVA) model with treatment group and randomization strata as fixed effects.

COVACTA

The clinical efficacy results for COVACTA are reported in Table 9.

- Clinical status at day 28:
  - The odds of improvement in clinical status on the 7-category ordinal scale were not significantly different in the tocilizumab group compared with the placebo plus standard care group at day 28 (odds ratio [OR] = 1.19; 95% CI, 0.81 to 1.76, P = 0.31).
- Clinical status at day 14:
  - The odds of improvement in clinical status on the 7-category ordinal scale were not different in the tocilizumab group compared with the placebo plus standard care group at day 14 (OR = 1.42; 95% CI, 0.99 to 2.05).
- Mortality at day 28:
  - By day 28, there was no difference in mortality in patients who received tocilizumab versus placebo plus standard care (difference 0.3; 95% CI, −7.6 to 8.2).

- Time to hospital discharge:
  - The median time to hospital discharge was longer in the placebo plus standard care group (28 days; 95% CI, 20 to not estimable) versus the tocilizumab group (20 days; 95% CI, 17 to 27) (HR = 1.35; 95% CI, 1.02 to 1.79, P = 0.04).

Table 9: Clinical Outcomes for COVACTA

COVACTA[8]	Tocilizumab n = 294	Placebo n = 144
Clinical status based on a 7-category ordinal scale[a] at day 28		
Median (95% CI)[a]	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[b]	0.31	
OR (95% CI)[c]	1.19 (0.81 to 1.76)	
Clinical status based on a 7-category ordinal scale[a] at day 14		
Median (95% CI)[a]	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)
Difference (95% CI)	–1.0 (–2.0 to 0.5)	
Mortality at day 28		
n (%)	58 (19.7)	28 (19.4)
95% CI	15.2 to 24.3	13.0 to 25.9
Weighted difference, % (95% CI)[d]	0.3 (–7.6 to 8.2)	
P value	0.94	
Time to hospital discharge		
Days, median (95% CI)	20.0 (17.0 to 27.0)	28 (20.0 to NE)
HR (95 CI)[f]	1.35 (1.02 to 1.79)	
Time to improvement of ≥ 2 categories on a 7-cateogry ordinal scale of clinical status		
Days, median (95% CI)	14.0 (12.0 to 17.0)	18.0 (15.0 to 28.0)
HR (95 CI)[f]	1.26 (0.97 to 1.64)	
Duration of ICU stay		
Days, median (95% CI)	9.8 (7.0 to 15.7)	15.5 (8.7 to 25.5)
Difference (95% CI)	–5.8 (–15.0 to 2.9)	
P value[b]	0.05	
Incidence of ICU stay by patients not in ICU at baseline		
n/N (%)	27/127 (21.3)	23/64 (35.9)
Weighted difference, % (95% CI)[g]	–14.8 (–28.6 to –1.0)	
P value	0.01	
Ventilator-free days to day 28		
Days, median (95% CI)	22.0 (18.0 to 28.0)	16.5 (11.0 to 26.0)
Difference (95% CI)	5.5 (–2.8 to 13.0)	

COVACTA[8]	Tocilizumab n = 294	Placebo n = 144
Incidence of mechanical ventilation of patients not on mechanical ventilation at randomization		
n/N (%)	51/183 (27.9)	33/90 (36.7)
Weighted difference, % (95% CI)[g]	–8.9 (–20.7 to 3.0)	
Clinical failure[h] of patients not on mechanical ventilation at randomization		
n/N (%)	53/183 (29.0)	38/90 (42.2)
HR (95% CI)[i]	0.61 (0.40 to 0.94)	

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ICU = intensive care unit; NE = not estimable; OR = odds ratio.

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

[b] P value based on van Elteren test stratified by region and mechanical ventilation at randomization.

[c] OR based on ordinal logistic regression analysis adjusted for region and mechanical ventilation at randomization.

[d] P value based on extended Cochran-Mantel-Haenszel test stratified by region and mechanical ventilation at randomization.

[e] P value based on log-rank test stratified by region and mechanical ventilation at randomization.

[f] Cox proportional-hazards model stratified by region and mechanical ventilation at randomization.

[g] Weighted difference in percentages calculated using the Cochran-Mantel-Haenszel test stratified by region at randomization.

[h] Death, withdrawal during hospitalization, transfer to ICU, or requirement for invasive mechanical ventilation within 28 days of baseline.

[i] Stratified log-rank test for P value and Cox proportional-hazards model for HR, including stratification by region at randomization.

EMPACTA

The clinical efficacy results for EMPACTA are reported in Table 10.

- Mechanical ventilation or death by day 28:
  - The proportion of patients on mechanical ventilation or dead by day 28 was 12% in the tocilizumab plus standard care group (95% CI 8.5 to 16.9) and 19.3% in the placebo plus standard care group (95% CI 13.3 to 27.4).
  - The risk of mechanical ventilation or death was significantly lower in the tocilizumab plus standard care group compared with the placebo plus standard care group (HR = 0.56; 95% CI, 0.33 to 0.97; P = 0.04).
- Time to hospital discharge or readiness for discharge by day 28:
  - The median time to hospital discharge by day 28 in the tocilizumab plus standard care group was 6 days (95% CI, 6 to 7) versus 7.5 days in the placebo plus standard care group (95% CI, 7 to 9).
  - There was no significant difference in the median time to hospital discharge by day 28 between the tocilizumab plus standard care and placebo plus standard care group (HR = 1.16; 95% CI, 0.91 to 1.48).
- Time to improvement in clinical status by day 28:
  - The time to improvement in clinical status by day 28 in the tocilizumab plus standard care group was 6 days (95% CI, 6 to 7) versus 7 days in the placebo plus standard care group (95% CI, 6 to 9).
  - There was no significant difference in clinical status by day 28 between the tocilizumab plus standard care group and placebo plus standard care group (HR = 1.15; 95% CI, 0.90 to 1.48).

- Time to clinical failure by day 28:
  - The time to clinical failure could not be estimated in either the tocilizumab plus standard care group or the placebo plus standard care group.
- Death by day 28:
  - In the tocilizumab plus standard care group, there were 26 deaths (10.4%; 95% CI, 7.2 to 14.9) compared with 11 deaths (8.6%; 95% CI, 4.9 to 14.7) reported in the placebo plus standard care group (weighted difference 2.0 points, 95% CI, –5.2 to 7.8).

Table 10: Clinical Outcomes for EMPACTA

EMPACTA (mITT)[3]	Tocilizumab n = 249	Placebo n = 128
Mechanical ventilation or death by day 28[a,b]		
% (95% CI)	12.0 (8.5 to 16.9)	19.3 (13.3 to 27.4)
HR (95% CI)	0.56 (0.33 to 0.97)	
P value	0.04	
Time to hospital discharge or readiness for discharge by day 28[c]		
Days, median (95% CI)	6.0 (6.0 to 7.0)	7.5 (7.0 to 9.0)
HR (95% CI)	1.16 (0.91 to 1.48)	
Time to improvement in clinical status by day 28[c,d]		
Days, median (95% CI)	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)
HR (95% CI)	1.15 (0.90 to 1.48)	
Time to clinical failure by day 28[d]		
Days, median (95% CI)	NE	NE
HR (95% CI)	0.55 (0.33 to 0.93)	
Death by day 28[e,f]		
n (%)	26 (10.4)	11 (8.6)
95% CI	7.2 to 14.9	4.9 to 14.7
Weighted difference (95% CI)	2.0 (–5.2 to 7.8)	

CI = confidence interval; HR = hazard ratio; mITT = modified intention to treat; NE = not estimable.

[a] The P value was calculated with the log-rank test. Significance testing was performed hierarchically to control the trial-wide type I error rate at a 5% significance level.

[b] The cumulative percentages of patients were estimated with the Kaplan-Meier method and compared with the use of the stratified log-rank test, with age group (≤ 60 years or > 60 years) as a stratification factor. The stratified Cox proportional-hazards model with age group (≤ 60 or > 60 years) as a stratification factor was used to estimate the HR and 95% CI.

[c] The median time to a secondary outcome event was estimated with the Kaplan-Meier approach.

[d] Improvement in clinical status was determined with the use of the 7-category ordinal scale.

[e] The Wilson method was used to estimate the 95% CI for the observed proportion. The Cochran-Mantel-Haenszel weighting approach with the age group (≤ 60 years or > 60 years) as the stratification factor was used to calculate the weighted difference in percentages. The Newcombe method was used to estimate the 95% CI for the weighted difference. Deaths by day 28 included all deaths reported from ordinal scale scoring, adverse events reporting, and public death records during the hospital stay and after hospital discharge.

[f] The weighted difference is expressed as percentage points.

Salvarani et al.

- The clinical efficacy results are reported in Table 11.
- Clinical worsening at 14 days:
  - There was no significant difference in clinical worsening within 14 days since the randomization between the tocilizumab plus standard care group versus the standard care alone group (rate ratio 1.05; 95% CI, 0.59 to 1.86).
- Admission to ICU at 14 days:
  - 10.0% patients in the tocilizumab plus standard care group were admitted to the ICU compared with 7.9% in the standard care alone group (rate ratio 1.26; 95% CI, 0.41 to 3.91).
- Death at 14 days:
  - There was no difference in deaths between the tocilizumab plus standard care group and the standard care alone group (rate ratio 1.05; 95% CI, 0.07 to 16.4).

Table 11: Clinical Outcomes for Salvarani et al.

Salvarani et al.[5]	Tocilizumab n = 60	Standard Care n = 63
Clinical worsening[a] at 14 days		
n (%)	17 (28.3)	17 (27.0)
RR (95% CI)	1.05 (0.59 to 1.86)	
P value	0.87	
Admissions to ICU at 14 days		
n (%)	6 (10.0)	5 (7.9)
RR (95% CI)	1.26 (0.41 to 3.91)	
Deaths at 14 days		
n (%)	1 (1.7)	1 (1.6)
RR (95% CI)	1.05 (0.07 to 16.4)	
Discharges at 14 days		
n (%)	34 (56.7)	36 (57.1)
RR (95% CI)	0.99 (0.73 to 1.35)	
Admissions to ICU at 28 days		
n (%)	6 (10.0)	5 (7.9)
RR (95% CI)	1.26 (0.41 to 3.91)	
Deaths at 28 days		
n (%)	2 (3.3)	1 (1.6)
RR (95% CI)	2.10 (0.20 to 22.6)	
Discharges at 28 days		
n (%)	54 (90.0)	58 (92.1)
RR (95% CI)	0.98 (0.87 to 1.09)	

CI = confidence interval; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; PaO_2 = partial pressure of oxygen; RR = rate ratio.

[a] One patient in the standard care group was admitted to the ICU without a PaO_2:FiO_2 ratio of less than 150 mm Hg.

Stone et al.

- The clinical efficacy results are reported in Table 12.
- Mechanical ventilation or death at 28 days:
  - The proportion of patients who had mechanical ventilation or were dead within 28 days was lower in the tocilizumab group (10.6%; 95% CI, 6.7 to 16.6) compared with the placebo plus standard care group (12.5%; 95% CI, 6.9 to 22.0).
  - The risk of mechanical ventilation or death was not significantly different between the tocilizumab group compared with the placebo plus standard care group (HR = 0.83; 95% CI, 0.38 to 1.81).
- Clinical worsening at 28 days:
  - The risk of worsening in clinical status on the 7-category ordinal scale was not significantly different between the tocilizumab group compared with the placebo plus standard care group (HR = 1.11; 95% CI, 0.59 to 2.10).
- Death:
  - There was no difference in the risk of death between the tocilizumab group compared with the placebo plus standard care group (HR = 1.52; 95% CI, 0.41 to 5.61).
- Discontinuation of supplemental oxygen:
  - There was no significant difference in discontinuation of supplemental oxygen among the patients receiving it at baseline in the tocilizumab group and the placebo plus standard care group (HR = 0.94; 95% CI, 0.67 to 1.30).

Table 12: Clinical Outcomes for Stone et al.

Stone et al. (mITT)[6a,b]	Tocilizumab n = 161	Placebo n = 81
Mechanical ventilation or death		
Patients with events within 28 days, n	17	10
Patients with event at day 14, % (95% CI)	9.9 (6.2 to 15.7)	10.0 (5.1 to 18.9)
Patients with event at day 28, % (95% CI)	10.6 (6.7 to 16.6)	12.5 (6.9 to 22.0)
HR (95% CI)	0.83 (0.38 to 1.81)	
Log-rank P value	0.64	
Clinical worsening on ordinal scale[c]		
Patients with events within 28 days, n	31	14
Patients with event at day 14, % (95% CI)	18.0 (12.9 to 24.9)	14.9 (8.7 to 24.7)
Patients with event at day 28, % (95% CI)	19.3 (14.0 to 26.2)	17.4 (10.7 to 27.7)
HR (95% CI)	1.11 (0.59 to 2.10)	
Log-rank P value	0.73	
Mechanical ventilation[d]		
Patients with events within 28 days, n	11	8
Patients with event at day 14, % (95% CI)	6.8 (3.6 to 11.4)	10.0 (4.6 to 17.7)
Patients with event at day 28, % (95% CI)	6.8 (3.6 to 11.4)	10.0 (4.6 to 17.7)
HR (95% CI)	0.65 (0.26 to 1.62)	
Death		
Patients with events within 28 days, n	9	3
Patients with event at day 14, % (95% CI)	4.4 (2.1 to 8.9)	1.3 (0.2 to 8.7)
Patients with event at day 28, % (95% CI)	5.6 (3.0 to 10.5)	3.8 (1.2 to 11.3)
HR (95% CI)	1.52 (0.41 to 5.61)	
Discontinuation of supplemental oxygen of patients receiving it at baseline		
Patients with events within 28 days, n	114	56
Patients with event at day 14, % (95% CI)	75.4 (67.9 to 82.2)	78.8 (68.3 to 87.7)
Patients with event at day 28, % (95% CI)	82.6 (75.9 to 88.4)	84.9 (75.2 to 92.2)
Time to event, median days (95% CI)	5.0 (3.8 to 7.6)	4.9 (3.8 to 7.8)
HR (95% CI)	0.94 (0.67 to 1.30)	
Log-rank P value	0.69	
Clinical improvement on ordinal scale[c]		
Patients with events within 28 days, n	147	72
Patients with event at day 14, % (95% CI)	86.3 (80.6 to 91.1)	81.5 (72.4 to 89.0)
Patients with event at day 28, % (95% CI)	91.3 (86.3 to 95.1)	88.9 (81.0 to 94.5)
Time to event, median days (95% CI)	6.0 (5.0 to 6.0)	5.0 (4.0 to 7.0)
HR (95% CI)	1.06 (0.80 to 1.41)	

Stone et al. (mITT)[6a,b]	Tocilizumab n = 161	Placebo n = 81
Initial discharge		
Patients with events within 28 days, n	147	72
Patients with event at day 14, % (95% CI)	86.3 (80.6 to 91.1)	81.5 (72.4 to 89.0)
Patients with event at day 28, % (95% CI)	91.3 (86.3 to 95.0)	88.9 (81.0 to 94.5)
Time to event, median days (95% CI)	6.0 (4.0 to 7.0)	6.0 (5.0 to 6.0)
HR (95% CI)	1.08 (0.81 to 1.43)	
Duration of receipt of supplemental oxygen		
Median days (IQR)[e]	4.0 (1.8 to 11.6)	3.9 (1.1 to 9.2)
Duration of mechanical ventilation[f]		
Median days (IQR)	15.0 (12.6 to NR)	27.9 (16.3 to NR)
Admission to ICU or death		
Patients, %	15.9	15.8
RR (95% CI)	0.97 (0.50 to 1.88)	

CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; mITT = modified intention to treat; NR = not reached; RR = relative risk.

[a] The mITT population included the 242 patients (161 in the tocilizumab group and 81 in the placebo group) who underwent randomization and received either tocilizumab or placebo before intubation or death.

[b] Percentages were estimated from the Kaplan-Meier curve.

[c] Worsening was defined as an increase in score on the ordinal clinical improvement scale by at least 1 point among patients receiving supplemental oxygen at baseline or at least 2 points among those not receiving supplemental oxygen at baseline. Improvement was defined as an increase in score of at least 2 points.

[d] Results for the time-to-event analysis of mechanical ventilation were obtained with the use of competing-risks analyses with death treated as a competing event. The percentage of patients with an event was estimated from the cumulative incidence function for the event of interest (mechanical ventilation). The cause-specific HR is reported.

[e] Patients who did not receive supplemental oxygen were assigned a value of 0. Patients who died before discontinuation of supplemental oxygen were assigned a value equal to the number of days from when supplemental oxygen began until the end of the 28-day follow-up period.

[f] The median and IQR for duration of mechanical ventilation were estimated from Kaplan-Meier curves generated for patients who received mechanical ventilation (11 in the tocilizumab group and 8 in the placebo group). Data for patients who died without discontinuation of mechanical ventilation were censored at 28 days.

TOCIBRAS

The clinical efficacy results for TOCIBRAS are reported in Table 13.

- Clinical status at day 15:
  - The 7-category ordinal scale was collapsed into a binary outcome. There was no significant difference in the odds of being alive and not receiving mechanical ventilation (scale of 1 to 5) or receiving mechanical ventilation or dead (scale 6 to 7) by day 15 in the tocilizumab plus standard care group compared with the standard care group (OR = 1.54; 95% CI, 0.66 to 3.66).
- Receiving mechanical ventilation or dead by day 15:
  - The proportion of patients receiving mechanical ventilation was higher in the tocilizumab plus standard care group (28%) compared with the standard care group (20%). The OR was 1.54, 95% CI, 0.66 to 3.66, P = 0.32.
- Mortality up to 28 days:
  - Mortality was 21% in the tocilizumab plus standard care group compared with 9% in the standard care group.

- There was no difference in mortality up to 28 days between the tocilizumab plus standard care group versus the standard care group (OR = 2.70; 95% CI, 0.97 to 8.35).

Table 13: Clinical Outcomes for TOCIBRAS

TOCIBRAS[4]	Tocilizumab n = 65	Standard Care n = 64
Receiving mechanical ventilation or dead by day 15[a]		
Patients, n (%)	18 (28)	13 (20)
OR of clinical status levels 1 to 5 versus levels 6 to 7 (95% CI)[a]	1.54 (0.66 to 3.66)	
P value	0.32	
Clinical status (7-level ordinal scale) at day 15, n (%)		
1: Not admitted to hospital, no limitation on activities	32 (49)	26 (41)
2: Not admitted to hospital, limitation on activities	3 (5)	5 (8)
3: Admitted to hospital, not receiving supplemental oxygen	6 (9)	6 (9)
4: Admitted to hospital, receiving supplemental oxygen	6 (9)	10 (16)
5: Admitted to hospital, receiving noninvasive ventilation or high-flow oxygen through nasal cannula	0	4 (6)
6: Admitted to hospital, receiving mechanical ventilation	7 (11)	11 (17)
7: Death	11 (17)	2 (3)
Mortality up to 28 days		
Patients, n (%)	14 (21)	6 (9)
OR (95% CI)	2.70 (0.97 to 8.35)	
P value	0.07	
In-hospital mortality		
Patients, n (%)	14 (21)	6 (9)
OR (95% CI)	2.70 (0.97 to 8.35)	
P value	0.02	
SOFA score at day 15		
Mean score (SD)	4.3 (3.6)	4.3 (3.6)
Mean ratio	0.99 (0.65 to 1.49)	
P value	0.95	
Clinical status (7-level ordinal scale) at day 29, n (%)		
OR of clinical status levels 1 to 5 versus levels 6 to 7 (95% CI)	2.17 (0.88 to 5.60)	
P value	0.10	
1: Not admitted to hospital, no limitation on activities	34 (52)	32 (50)
2: Not admitted to hospital, limitation on activities	8 (12)	16 (25)
3: Admitted to hospital, not receiving supplemental oxygen	4 (6)	2 (3)
4: Admitted to hospital, receiving supplemental oxygen	1 (1)	4 (6)
5: Admitted to hospital, receiving noninvasive ventilation or high-flow oxygen through nasal cannula	0	0
6: Admitted to hospital, receiving mechanical ventilation	4 (6)	4 (6)

TOCIBRAS[4]	Tocilizumab n = 65	Standard Care n = 64
7: Death[b]	14 (21)	6 (9)
Ventilator-free days within 29 days[c]		
Days, mean (SD)	19.4 (12.0)	20.5 (10.8)
RR (95% CI)	1.12 (0.86 to 1.99)	
P value	0.53	
Time to supplemental oxygen independence within 29 days		
Days, median (IQR)	6 (5 to 12)	10 (8 to 14)
HR (95% CI)	1.37 (0.92 to 2.04)	
P value	0.12	
Duration of hospital stay		
Days, mean (SD)	11.3 (8.0)	14.7 (8.2)
RR (95% CI)	0.70 (0.55 to 0.87)	
P value	0.001	

CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; IQR = interquartile range; RR = rate ratio; SD = standard deviation; SOFA = sequential organ failure assessment.

[a] The primary outcome, clinical status measured at 15 days using 7-level ordinal scale, was analyzed as a composite of death or mechanical ventilation as pre-specified in the statistical analysis plan because the assumption of proportional odds, necessary to analyze the original 7-level ordinal scale, did not hold.

[b] Death before day 29; ventilator-free days considered to be 0.

[c] Nineteen deaths were associated with COVID-19 related acute respiratory failure or multiple organ dysfunction and 1 death with COVID-19 related cerebral hemorrhage.

Wang et al.

- The clinical efficacy results are reported in Table 14.
- Cure rate:
  - The cure rate among patients in the tocilizumab plus standard care group was 94.12% (32/34) compared with 87.10% (27/31) of patients in the standard care group; however, the difference between these 2 groups was not statistically significant (P = 0.4133).
- Hypoxia recovery at day 14:
  - The proportion of patients who experienced hypoxia recovery at day 14 was higher in the tocilizumab plus standard care group compared with the standard care group [22/24 (91.67%) versus 12/20 (60.00%), P = 0.0328].
- Length of hospitalization:
  - The median length of hospitalization was longer in the tocilizumab plus standard care group (26 days; IQR, 17 to 27) compared with the standard care group (24 days; IQR, 15 to 28), P = 0.7311.
- Time to negative virus load:
  - The median time to negative virus load was similar in the tocilizumab plus standard care group (17 days; IQR, 12 to 20) compared with the standard care group (16 days; IQR, 12 to 21.5), P = 0.9022 .

Table 14: Clinical Outcomes for Wang et al.

Wang et al.[11]	Tocilizumab n = 34	Standard care n = 31
Cure rate		
Patients, n/N (%)	32/34 (94.12)	27/31 (87.10)
P value	0.4133	
Rate of hypoxia recovery at day 14		
Patients, n/N (%)	22/24 (91.67)	12/20 (60.00)
P value	0.0328	
Length of hospitalization		
Days, median (IQR)	26 (17 to 27)	24 (15 to 28)
P value	0.7311	
Time to negative virus load		
Days, median (IQR)	17 (12 to 20)	16 (12 to 21.5)
P value	0.9022	

IQR = interquartile range.

Zhao et al.

The clinical efficacy results are reported in Table 15.

- Primary outcome cumulative lung lesion remission rate at day 14:
  - The risk of cumulative lung remission at day 14 was higher in the favipiravir group compared with the tocilizumab plus favipiravir group (HR = 2.66; 95% CI, 1.08 to 6.53).
  - There was no difference in the risk of cumulative lung remission at day 14 between the favipiravir group compared with the tocilizumab group (HR = 3.16; 95% CI, 0.62 to 16.10).

Table 15: Clinical Outcomes for Zhao et al.

Zhao et al.[7]	Tocilizumab plus favipiravir n = 14	Tocilizumab n = 5	Favipiravir n = 7
Cumulative lung lesion remission rate at day 14			
Tocilizumab versus tocilizumab plus favipiravir, HR (95% CI)	1.28 (0.39 to 4.23)		
P value	0.575		
Favipiravir versus tocilizumab plus favipiravir, HR (95% CI)	2.66 (1.08 to 6.53)		
P value	0.019		
Favipiravir versus tocilizumab, HR (95% CI)	3.16 (0.62 to 16.10)		
P value	0.034		
Mortality or incidence of invasive mechanical ventilation			
Patients, n (%)	0	0	2 (28.5)
Relief of symptoms			
Fever, P value	0.002	NS	0.029
Cough, P value	0.041	NS	NS
Dyspnea, P value	0.023	NS	NS
Change in laboratory values			
Neutrophils, mean %			

Zhao et al.[7]	Tocilizumab plus favipiravir n = 14	Tocilizumab n = 5	Favipiravir n = 7
Before treatment	63.5	69.8	NR
After treatment	56.7	55.5	NR
P value	0.022	0.032	0.073
Lymphocytes, mean %			
Before treatment	25.3	19.2	NR
After treatment	31.2	30.3	NR
P value	0.043	0.019	0.120
Interleukin-6, median pg/mL			
Before treatment	10.5	27.5	NR
After treatment	61.6	61.8	NR
P value	0.005	0.19	0.290

CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not significant.

Harms

REMAP-CAP

The percentage of patients who experienced adverse events and serious adverse events is detailed in Table 16. The details for the outcome of harms are available in Appendix 3.

There were 9 patients (2.5%) who experienced a serious adverse event in the tocilizumab group compared with 11 patients (2.7%) in the control group. The most common serious adverse event that occurred in the tocilizumab group was bleeds among 5 patients (1.4%), whereas thrombosis was the most common serious adverse event reported in 7 patients (1.7%) in the control group. Patients in the sarilumab group did not report any serious adverse events. Most deaths occurred in the control group, 35.8% of patients, compared with 28.0% and 22.2% in the tocilizumab group and sarilumab group, respectively.

CORIMUNO-TOC

The percentage of patients who experienced adverse events and serious adverse events are detailed in Table 16. The details for the outcome of harms are available in Appendix 3.

There were 28 patients (44%) who experienced at least 1 adverse event in the tocilizumab plus usual care group compared with 36 patients (54%) in the usual care group. Patients with at least 1 serious adverse event was reported for 20 patients (32%) in the tocilizumab plus usual care group compared with 29 patients (43%) in the usual care group. There were 9 deaths in the tocilizumab plus usual care group compared with 23 deaths in the usual care group.

RECOVERY

Cause-specific mortality and major cardiac arrhythmia were pre-specified as safety outcomes. The proportion of any major cardiac arrhythmia was similar in the tocilizumab plus usual care group and usual care group (5% and 6%, respectively). There was no difference in the cause-specific mortality between the tocilizumab plus usual care group and usual care group. There were 3 serious adverse reactions reported in the tocilizumab plus usual care group (1 each of otitis externa, *Staphylococcus aureus* bacteremia, and lung abscess). These serious adverse reactions were resolved with treatment.

Lescure et al.

The percentage of patients who experienced treatment-emergent adverse events and treatment-emergent serious adverse events are detailed in Table 16. The details for the outcome of harms are available in Appendix 3.

There were 103 patients (64.8%) and 121 patients (69.9%) in the 200 mg sarilumab group and 400 mg sarilumab, respectively, who experienced at least 1 treatment-emergent adverse event compared with 55 patients (65.5%) in the placebo group. Patients with at least 1 treatment-emergent serious adverse event was reported for 42 patients (26.4%) in the 200 mg sarilumab group, 51 patients (29.5%) in the 400 mg sarilumab group, and 20 patients (23.8%) in the placebo group. A treatment-emergent adverse event leading to death occurred in 17 patients (10.4%), 18 patients (10.4%), and 9 patients (10.7%) in the 200 mg sarilumab group, 400 mg sarilumab group, and placebo group, respectively.

COVACTA

The percentage of patients who experienced adverse events and serious adverse events are detailed in Table 166. The details for the outcome of harms are available in Appendix 3.

At the clinical cut-off date (June 24, 2020), there were 237 patients (80.3%) who had experienced at least 1 adverse event in the tocilizumab group compared with 118 patients (82.5%) in the placebo plus standard care group. The most common adverse events of special interest were serious infections, which occurred in 70 patients (23.7%) and 41 patients (28.7%) in the tocilizumab group and placebo plus standard care group, respectively. Patients with at least 1 serious adverse event was reported for 113 patients (38.3%) in the tocilizumab group compared with 62 patients (43.4%) in the placebo plus standard care group. There were 70 deaths in the tocilizumab group compared with 33 deaths in the placebo plus standard care group. COVID-19 pneumonia was the most common cause of death.

EMPACTA

The percentages of patients who experienced adverse events, serious adverse events, and withdrawals due to adverse events are detailed in Table 16. The details for the outcome of harms are available in Appendix 3.

The proportion of patients who experienced at least 1 adverse event by day 60 was similar in the tocilizumab plus standard care group and placebo plus standard care group (50.8% versus 52.8%). Serious adverse events by day 60 were reported in 38 patients (15.2%) in the tocilizumab group compared with 25 patients (19.7%) in the placebo plus standard care group. By day 60, serious infections were reported in 13 patients (5.2%) and 9 patients (7.1%) in the tocilizumab and placebo plus standard care group, respectively. There were 29 deaths in the tocilizumab plus standard care group compared with 15 deaths in the placebo plus standard care group.

Salvarani et al.

The percentages of patients who experienced adverse events and serious adverse events are detailed in Table 17. The details for the outcome of harms are available in Appendix 3.

Fourteen patients (23.3%) in the tocilizumab plus standard care group experienced an adverse event compared with 7 patients (11.1%) in the standard care group. The most common adverse events reported were increased alanine aminotransferase level and

decreased neutrophil count. Serious adverse events were reported in 1 patient in the tocilizumab plus standard care group compared with 2 patients in the standard care group. By day 60, there were 2 deaths in the tocilizumab plus standard care group compared with 1 death in the standard care group.

Stone et al.

The percentages of patients who experienced adverse events and serious adverse events are detailed in Table 17. The details for the outcome of harms are available in Appendix 3.

Serious adverse events were reported in 28 patients (17.4%) in the tocilizumab plus standard care group compared with 12 patients (14.6%) in the placebo group. Serious infections of grade 3 or higher occurred in 13 patients (8.1%) and 14 patients (17.1%) in the tocilizumab plus standard care group and placebo group, respectively. Deep venous thrombosis was the most common serious adverse event, occurring in 3 patients in the placebo group, whereas pulmonary embolism, stroke and deep venous thrombosis were the most common serious adverse events in the tocilizumab plus standard care group, experienced by 2 patients each. There were 9 deaths in the tocilizumab plus standard care group compared with 4 deaths in the placebo group.

TORCIBRAS

The percentages of patients who experienced adverse events and serious adverse events are detailed in Table 17. The details for the outcome of harms are available in Appendix 3.

There were 29 patients (43%) who experienced adverse events in the tocilizumab plus standard group compared with 21 patients (34%) in the standard care group. A serious adverse event was reported in 11 patients (16%) in the tocilizumab plus standard care group compared with 7 patients (11%) in the standard care group. The most common serious adverse event reported was elevated alanine aminotransferase, aspartate aminotransferase, or bilirubin levels among 7 patients (10%) and 3 patients (5%) in the tocilizumab plus standard care group and standard care group, respectively. At 15 days, there were 11 deaths in the tocilizumab plus standard care group compared with 2 deaths in the standard care group.

Wang et al.

The percentages of patients who experienced adverse events and serious adverse events are detailed in Table 17. The details for the outcome of harms are available in Appendix 3.

There were 20 patients (58.8%) who experienced adverse events in the tocilizumab plus standard group compared with 4 patients (12.9%) in the standard care group. Abnormal hepatic function was the most common adverse event, reported among 6 patients (17.6%) in the tocilizumab group. One patient in the standard care group reported a serious adverse event. Of note, 1 patient in the standard care group who experienced a severe reaction within 3 days of randomization was transferred to the tocilizumab plus standard care group.

Zhao et al.

The percentages of patients who experienced adverse events and serious adverse events are detailed in Table 17. The details for the outcome of harms are available in Appendix 3.

Nine patients (64.3%) experienced adverse events in the tocilizumab plus favipiravir group compared with 2 patients (40.0%) each in the tocilizumab group and favipiravir group, respectively, and 4 patients (12.9%) in the standard care group. The most common adverse event reported was increased alanine aminotransferase, which was reported for 3 patients (21.4%) in the tocilizumab plus favipiravir group. In the tocilizumab group, 1 patient (20.0%) reported increased alanine aminotransferase and 1 reported increased aspartate aminotransferase. No deaths occurred in the treatment groups.

Table 16: Summary of Harms

	REMAP-CAP [9]			CORIMUNO-TOC [2]		Lescure et al. [10a,b]			COVACTA [8]		EMPACTA [3]	
	TCZ (n = 353)	SAR (n = 48)	Control (n = 402)	TCZ (n = 63)	UC (n = 67)	SAR 200 mg	SAR 400 mg	PB	TCZ (n = 295)	PB (n = 143)	TCZ (n = 250)	PB (n = 127)
Adverse events, n (%)												
Number of patients with an adverse event	NR	NR	NR	28 (44)	36 (54)	103 (64.8)	121 (69.9)	55 (65.5)	228 (77.3)	116 (81.1)	127 (50.8)	67 (52.8)
Serious adverse events, n (%)												
Number of patients with a serious adverse event	9 (2.5)	0	11 (2.7)	20 (32)	29 (43)	42 (26.4)	51 (29.5)	20 (23.8)	113 (38.3)	62 (43.4)	38 (15.2)	25 (19.7)
Withdrawals due to adverse events, n (%)												
Withdrawal from trial because of adverse event	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
Deaths, n (%)	98/350 (28.0)	10/45 (22.2)	142/397 (35.8)	9 (7)	23 (34.3)	17 (10.7)	18 (10.4)	9 (10.7)	58 (19.7)	28 (19.6)	29 (11.6)	15 (11.8)

NR = not reported; PB = placebo; SAR = sarilumab; TCZ = tocilizumab; UC = usual care.

[a] Treatment-emergent adverse events and treatment-emergent serious adverse events reported for Lescure et al.

[b] Any treatment-emergent adverse event leading to death are reported for Lescure et al.

Table 17: Summary of Harms

	Salvarani et al.[5]		Stone et al.[6]		TOCIBRAS[4]		Wang et al.[11]		Zhao et al.[7]		
	TCZ (n = 60	SC (n = 63)	TCZ (n = 161)	PB (n = 82)	TCZ (n = 67)	SC (n = 62)	TCZ (n = 82)	SC (n = 31)	TCZ plus FAV (n = 14)	TCZ (n = 5)	FAV (n = 7)
Adverse events, n (%)											
Number of patients with an adverse event	14 (23.3)	7 (11.1)	NR	NR	29 (43)	21 (34)	20 (58.8)	4 (12.9)	9 (64.3)	2 (40.0)	2 (40.0)
Serious adverse events, n (%)											
Number of patients with a serious adverse event	1 (1.7)	2 (2.3)	28 (17.4)	12 (14.6)	11 (16)	7 (11)	0	1 (3.2)	0	0	0
Withdrawals due to adverse events, n (%)											
Withdrawal from trial because of adverse event	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Deaths, n (%)	2 (3.3)	1 (1.6)	9 (5.6)	4 (4.9)	11 (17)	2 (3)	NR	NR	0	0	0

FAV = favipiravir; NR = not reported; PB = placebo; SC = standard care; TCZ = tocilizumab.

Appraisal of the Included Trials

Threats to internal and external validity for 11 RCTs are summarized in Appendix 4.

Two trials were terminated early: TOCIBRAS, because of an increase in the number of deaths with tocilizumab, and Salvarani et al., because of futility. For Salvarani et al., the trial was stopped at the interim analysis. Therefore, only interim results are reported in the report. Only 4 RCTs were double-blinded trials.[3,6,8,10] While all trials were multi-centre, 7 RCTs[1,2,4-7,11] were conducted in 1 country only. One RCT[1] included a large sample size, five RCTs[2,4,5,7,11] included small sample sizes and there were no control for type I error in 8 RCTs.[1,2,4,5,7-9,11] Four RCTs[3,8-10] included a racially diverse study population, yet greater than 40% of patients were White and all RCTs enrolled more men.

Discussion

Summary of Available Evidence

Eleven trials were the focus of this review: 8 published RCTs[2-9] and 3 RCTs published as preprints.[1,10,11] Ten RCTs included tocilizumab, 1 study by Lescure et al. investigated different doses of sarilumab, and 1 study, REMAP-CAP, included both sarilumab and tocilizumab. The study by Zhao et al. also included favipiravir as an active comparator. Two trials were terminated early: TOCIBRAS, because of an increase in the number of deaths with tocilizumab, and Salvarani et al., because of futility. Ongoing trials of tocilizumab and sarilumab are presented in the CADTH report, *Ongoing Trials for Drugs in the Prevention and Treatment of COVID-19*.[24]

REMAP-CAP was a phase IV, randomized, embedded, multifactorial, adaptative, platform, international, multi-centre study that enrolled critically ill patients with COVID-19 receiving either respiratory or cardiovascular organ support. Patients were randomly assigned in a 1:1:1 ratio to tocilizumab, sarilumab, or control. The primary outcome was respiratory and cardiovascular organ support–free days assessed up to day 21. The study by Lescure et al. was a phase III, adaptive, randomized, double-blind, placebo-controlled, multi-centre, international trial that enrolled hospitalized patients with confirmed severe or critical SARS-CoV-2 disease. Patients were randomized in a 2:2:1 ratio to 2 different doses of sarilumab or placebo. The primary outcome was time to improvement of at least 2 points on the 7-category ordinal scale.

RECOVERY was a phase II and phase III, platform, open-label, multi-centre, large RCT that randomly assigned patients in a 1:1 ratio to tocilizumab plus usual care or usual care. While disease severity was not specified for trial enrolment, patients had hypoxia and evidence of systemic inflammation. The primary outcome was all-cause mortality assessed at 28 days.

While Stone et al. included patients with severe COVID-19, and CORIMUNO-TOC included patients with moderate, severe and critical COVID-19, in both studies, patients were not receiving supplemental oxygen at enrolment. Stone et al. was a phase III, prospective, randomized, double-blind, placebo-controlled, multi-centre study that randomized patients in a 2:1 ratio to receive tocilizumab plus standard care or placebo. The primary outcome was intubation or death for those patients who died prior to intubation. CORIMUNO-TOC was a phase II, open-label, randomized controlled trial that compared patients who received tocilizumab plus usual care versus usual care alone. Patients were randomized in a 1:1 ratio (to receive tocilizumab plus usual care or usual care). The co-primary end points of the study were the following: proportion of patients who had a WHO-CPS score of at least 5 or greater assessed on day 4, and survival with no need for noninvasive or mechanical ventilation measured on day 14.

COVACTA was a phase III, randomized, double-blind, placebo-controlled, international, multi-centre study that enrolled patients with severe COVID-19. Patients were randomized in a 2:1 ratio to receive tocilizumab or placebo plus standard care.

While EMPACTA and the study by Salvarani et al. did not specify COVID-19 disease severity, patients receiving mechanical ventilation were not enrolled. EMPACTA was a phase III, randomized, double-blind, placebo-controlled, multi-centre study that randomized patients in a 2:1 ratio to receive tocilizumab plus standard care or placebo plus standard care. Salvarani et al. conducted a phase II, open-label, parallel, randomized, multi-centre

study that randomized patients in a 1:1 ratio to receive tocilizumab plus standard care or standard care. The primary efficacy outcome was clinical worsening within 14 days since randomization.

TOCIBRAS was a prospective, open-label, superiority, randomized controlled, multi-centre study that recruited patients with COVID-19 receiving supplemental oxygen or mechanical ventilation. Patients were randomized in a 1:1 ratio to receive tocilizumab plus standard care or standard care.

Wang et al. was a phase IV, open-label, randomized controlled, multi-centre study that randomized patients with moderate or severe COVID-19 in a 1:1 ratio to receive tocilizumab plus standard care or standard care.

Zhao et al. was an open-label, randomized controlled, multi-centre study that included patients with common-type COVID-19 (e.g., fever, respiratory tract, and pneumonia) and severe COVID-19 at baseline. Patients were randomized in a 1:1:3 ratio to receive tocilizumab in combination with favipiravir, favipiravir monotherapy, and tocilizumab monotherapy. The primary outcome was the cumulative lung lesion remission rate, which was determined when the "lung CT examination indicated absorption of lung inflammation" (p. 2).[7]

Tocilizumab 8 mg/kg (up to a maximum dose of 800 mg) was administered by IV infusion in 8 RCTs.[1-6,21,22] In CORIMUNO-TOC, an additional fixed dose of tocilizumab 400 mg by IV infusion on day 3 was to be administered if the oxygen requirement had not decreased by more than 50%. In REMAP-CAP and RECOVERY, the initial dose of tocilizumab could be repeated in 12 to 24 hours at the discretion of the clinician, whereas in COVACTA, a second dose was administered 8 to 24 hours after the first dose. In EMPACTA, a second dose of tocilizumab was administered 8 to 24 hours after the first dose if the patient did not improve or worsen. In Salvarani et al., a second dose of tocilizumab was administered after 12 hours. In the study by Wang et al., tocilizumab was administered as 400 mg by IV infusion. In the study by Zhao et al., 4 mg/kg to 8 mg/kg (400 mg recommended) of tocilizumab was administered by IV infusion. if the patient remained febrile within 24 hours of the first dose, 1 additional dose was given.

In REMAP-CAP, sarilumab 400 mg was administered by IV infusion as 1 dose, whereas in the study by Lescure et al., patients received either 200 mg or 400 mg of sarilumab by IV infusion as 1 dose, with an optional second dose initiated within 24 to 48 hours after the first dose at the discretion of the study investigator.

Efficacy

Respiratory and Cardiovascular Organ Support–Free Days (1 Trial)

Tocilizumab

In REMAP-CAP, the median respiratory and cardiovascular organ support–free days measured at day 21 was better with tocilizumab than control (adjusted OR = 1.64; 95% CrI, 1.25 to 2.14).

Sarilumab

In REMAP-CAP, the median respiratory and cardiovascular organ support–free days measured at day 21 was better with sarilumab than control (adjusted HR = 1.76; 95% CrI, 1.17 to 2.91).

Mechanical Ventilation or Death (5 Trials)

In EMPACTA, the proportion of patients with mechanical ventilation or death by day 28 was significantly lower in the tocilizumab plus standard care than in the placebo plus standard care group (HR = 0.56; 95% CI, 0.33 to 0.97). In addition, RECOVERY found a difference in receipt of invasive mechanical ventilation or death at 28 days in favour of the tocilizumab plus usual care group compared to the usual care group (rate ratio 0.85, 95% CI, 0.78 to 0.93, P = 0.0005). Similarly, in REMAP-CAP, there was a difference in progression to invasive mechanical ventilation, extracorporeal membrane oxygenation, or death among those not intubated at baseline in favour of the tocilizumab group compared to the control group (adjusted OR = 1.69, 95% CrI, 1.17 to 2.42). CORIMUNO-TOC, there was a moderate benefit in the proportion of patients on noninvasive ventilation or high-flow oxygen or mechanical ventilation or who had died by day 14 in favour of the tocilizumab plus usual care group (24%; 95% CI, 13 to 24) compared with the usual care group (36%; 95% CI, 23 to 46). However, Stone et al. found no significant difference in mechanical ventilation or death by day 28 between the tocilizumab group or placebo group.

Clinical Status (5 Trials)

Tocilizumab

In COVACTA, the odds of improvement in clinical status on the 7-point ordinal scale was not significantly different in the tocilizumab group compared with the placebo plus standard care group at day 28 (OR = 1.19; 95% CI, 0.81 to 1.76). This result was consistent with the TOCIBRAS study, which showed no significant difference in clinical status (i.e., receiving mechanical ventilation or death) at day 15 between the tocilizumab plus standard care group versus the standard care group (OR = 1.54; 95% CI, 0.66 to 3.66). Additionally, EMPACTA and the study by Stone et al. found no difference in the median time to improvement in clinical status on the 7-point ordinal scale by day 28 in the tocilizumab plus standard care group versus the placebo group.

Sarilumab

In the study by Lescure et al., there was no significant difference in time to an improvement of at least 2 points on the 7-category ordinal scale between the 200 mg sarilumab group and placebo group (HR = 1.03; 95% CI, 0.75 to 1.40) and between the 400 mg sarilumab group and placebo group (HR = 1.14; 95% CI, 0.84 to 1.54).

Clinical Worsening (2 Trials)

Salvarani et al. found no difference in clinical worsening at 14 days between the tocilizumab plus standard care group and the standard care group (rate ratio 1.05; 95% CI, 0.59 to 1.86). Similarly, Stone et al. found no difference in clinical worsening on the 7-category ordinal scale between the tocilizumab plus standard care group compared with the placebo group (HR = 0.83; 95% CI, 0.38 to 1.81).

Clinical Failure (2 Trials)

In EMPACTA, there was a difference in median time to clinical failure in favour of the tocilizumab plus standard care group compared with the placebo plus standard care group (HR = 0.55; 95% CI, 0.33 to 0.93). COVACTA showed that the risk of clinical failure among patients not on mechanical ventilation at randomization was lower in the tocilizumab group compared with the placebo plus standard care group (HR = 0.61; 95% CI, 0.40 to 0.94).

Time to ICU Discharge or Hospital Discharge (8 Trials)

Tocilizumab

In REMAP-CAP, the median time to ICU discharge and hospital discharge was shorter with the tocilizumab group than with the control group (adjusted HR = 1.42; 95% CrI, 1.18 to 1.70 and adjusted HR = 1.41; 95% CrI, 1.18 to 1.70, respectively). Similarly, RECOVERY, CORIMUNO-TOC and COVACTA found a difference in favour of the tocilizumab group compared with the control group for the outcome of time to hospital discharge. However, EMPACTA and Wang et al. found no difference in the time to hospital discharge between the tocilizumab plus standard care group compared with the placebo or standard care group. Likewise, Salvarani et al. found no difference between the tocilizumab group and tocilizumab plus standard care group at 14 days in overall admissions to ICU and discharges, respectively (rate ratio 1.26; 95% CI, 0.41 to 3.91; and rate ratio 0.99; 95% CI, 0.73 to 1.35, respectively). There remained no difference in overall admissions to ICU and discharges at 30 days. Furthermore, Stone et al. found no difference between the tocilizumab plus standard care and placebo group for time to discharge.

Sarilumab

In REMAP-CAP, the median time to ICU discharge was shorter with sarilumab than control (adjusted HR = 1.64; 95% CrI, 1.21 to 2.45). In REMAP-CAP, the median time to hospital discharge was shorter in the sarilumab group compared with the control group (adjusted HR = 1.60; 95% CrI, 1.17 to 2.40).

Mortality-Related Outcomes (8 Trials)

RECOVERY found a significant difference in mortality at 28 days in favour of the tocilizumab plus usual care group compared to the usual care group (rate ratio 0.86, 95% CI, 0.77 to 0.96, P = 0.0066), whereas 5 RCTs[3-6,22] found no differences in mortality between the tocilizumab group and placebo or the standard care group.

In CORIMUNO-TOC, the hazard of death was lower in the tocilizumab plus usual care group compared to the usual care group (adjusted HR = 0.92, 95% CI, 0.33 to 2.53).

REMAP-CAP found a difference in hospital survival in favour of the tocilizumab group compared to control (median adjusted OR = 1.65, 95% CrI, 1.14 to 2.35)

Other Reported End Points

In the study by Lescure et al., there was no significant difference in the proportion of patients alive at 29 days between the 200 mg sarilumab group compared with the placebo group (difference = −1.7; 95% CI, −9.3 to 5.8), nor with the 400 mg sarilumab group compared with the placebo group (difference = 0.2; 95% CI, −6.9 to 7.4). At 60 days of follow-up, there remained no difference in the proportion of patients alive between each sarilumab-dose group (200 mg or 400 mg) compared with the placebo group.

In the study by Wang et al., there was no statistically significant difference in cure rate between the tocilizumab plus standard care group compared with standard care group.

In the study by Zhao et al., the risk of cumulative lung remission at day 14 was higher in the favipiravir group compared with the favipiravir plus tocilizumab group (HR = 2.66; 95% CI, 1.08 to 6.53). There was no difference in the risk of cumulative lung remission at day 14 between the favipiravir group compared with the tocilizumab group (HR = 3.16; 95% CI, 0.62 to 16.10).

The RCTs differed across inclusion criteria, administration of tocilizumab, delivery of standard care, primary outcomes and corresponding definitions, and trial location (single country versus international), which limits the direct comparison of results across studies. The study by Salvarani et al. was terminated by the scientific committee for futility with the enrolment capped at 126 patients. In addition, TORCIBRAS was terminated early with enrolment stopped at 129 patients due to an increased number of deaths reported at 15 days in the tocilizumab plus standard care group versus the standard care group. While RECOVERY had a large sample size, the results available so far are preliminary. As the preliminary results are based on the ITT population, the effect sizes reported may not be a true representation of treatment with tocilizumab, as 17% of patients in the tocilizumab plus usual care group did not receive treatment with tocilizumab. The sample sizes were very small in the study by Zhao et al., which limits the conclusions that can be made regarding the efficacy of tocilizumab. The standard care delivered to patients varied across countries and study sites. Moreover, the concomitant use of drugs (e.g., hydroxychloroquine, corticosteroids, antiretrovirals, and azithromycin) available as part of standard care while receiving treatment with tocilizumab may involve possible interaction effects with IL-6 receptor monoclonal antibodies. The results reported for RECOVERY, Lescure et al. and Wang et al. were available in preprints and have not been peer reviewed. Therefore, the results of these studies should be interpreted with caution.

Harms

Tocilizumab

CORIMUNO-TOC, COVACTA, and EMPACTA had a higher proportion of patients who experienced an adverse event in the control group than in the tocilizumab group. This was also true for serious adverse events, with a higher proportion of patients experiencing a serious adverse event in the control group. However, in TOCIBRAS, Salvarani et al., and Wang et al., more patients experienced an adverse event in the tocilizumab group compared with the placebo or standard care group. Salvarani et al. and Wang et al. reported a comparable proportion of patients with a serious adverse event. In Zhao et al., more patients in the tocilizumab plus favipiravir group experienced an adverse event compared with either treatment alone (64.3% versus 40% each). RECOVERY reported a similar proportion of patients with major cardiac arrhythmia in the tocilizumab plus usual care group and usual care group, and found no difference in cause-specific mortality between the tocilizumab plus usual care group and the usual care group. EMPACTA reported that no patients withdrew from treatment due to adverse events. None of the other trials reported whether patients had withdrawn from treatment due to an adverse event.

Sarilumab

While REMAP-CAP did not report the number of patients experiencing an adverse event, no patients in the sarilumab group experienced a serious adverse event compared with 2.5% of patients in the tocilizumab group. In the study by Lescure et al., the proportion of patients who reported at least 1 treatment-emergent adverse event was similar across the 200 mg sarilumab group, 400 mg sarilumab group, and placebo group, whereas the proportion of patients with at least 1 serious treatment-emergent adverse event was higher in each sarilumab-dose group (200 mg or 400 mg) compared with the placebo group.

Conclusions

RECOVERY, REMAP-CAP, CORIMUNO-TOC, COVACTA, EMPACTA, TOCIBRAS, Salvarani et al., Stone et al., Wang et al., and Zhao et al. provided the information to date regarding the efficacy and safety of tocilizumab. Lescure et al. investigated 2 different doses of sarilumab. REMAP-CAP, for which the results are preliminary, included both tocilizumab and sarilumab. Zhao et al. included favipiravir as an active comparator. TOCIBRAS was terminated early, because of an increase in the number of deaths with tocilizumab, as was the trial by Salvarani et al., because of futility. While most trials have been terminated or completed, REMAP-CAP is still recruiting patients and CORIMUNO-TOC and EMPACTA are active trials but no longer recruiting patients. RECOVERY closed recruitment of patients receiving tocilizumab.

The RCTs differed across inclusion criteria, baseline patient characteristics, delivery of standard care, primary outcomes and corresponding definitions, and trial location (single country versus international), which limits the direct comparison of results across studies. Four trials were published in preprints that have not been peer reviewed. Furthermore, study limitations, such as the use of an open-label design, small sample size and lack of control for type I error, affect the interpretation of the results.

In REMAP-CAP, sarilumab was better than no treatment for the following outcomes: number of organ support–free days, hospital survival, 90-day survival, time to ICU discharge, and time to hospital discharge. Conversely, the study by Lescure et al. found no significant difference in time to improvement of at least 2 points on a 7-category ordinal scale, nor in the proportion of patients alive at 29 days for each sarilumab-dose group (200 mg or 400 mg) compared with the placebo group. The results of REMAP-CAP should be interpreted carefully, as the trial is still ongoing.

The efficacy results for tocilizumab ranged, with some trials showing better outcomes with tocilizumab, whereas others showing no difference or worse outcomes with the control group. Similarly, there were more patients with adverse events and serious adverse events with tocilizumab in some but not all trials. Despite the availability of 10 RCTs on tocilizumab, the place in therapy of tocilizumab is still unclear. It may offer some benefit in reducing the need for mechanical ventilation, as 4 of 5 RCTs showed a difference between treatment groups in favour of tocilizumab compared with control. RECOVERY, a large RCT, showed a significant reduction in mortality in favour of tocilizumab compared with usual care, whereas 5 other smaller trials did not.

Appendix 1: Patient Disposition of Published Trials

Table 18: Patient Disposition for REMAP-CAP

	REMAP-CAP [9]		
	Tocilizumab	Sarilumab	Control
Screened, N	3,301		
Randomized, N	366	48	412
Reason for discontinuation, N (%)			
Withdrawal of consent	13 (4)	0	10 (2)
ITT, N	353	48	402
No outcome available	3	3	5
Safety, N	353	48	402

ITT = intention to treat; PP = per protocol.

Table 19: Patient Disposition for CORIMUNO-TOC

	CORIMUNO-TOC [2]	
	Tocilizumab plus usual care	Usual care
Screened, N	131	
Randomized, N	64	67
Completed study through day 28, N (%)	56 (87)	64 (95)
Did not receive assigned treatment, N (%)	3 (5)	NA
Discontinued from study by day 28, N (%)	8 (12)	3 (4)
Reason for discontinuation, N (%)		
Lost to follow-up	8 (12)	3 (4)
ITT, N	64	67
Analyzed, N	63	67

ITT = intention to treat; NA = not applicable.

Table 20: Patient Disposition for RECOVERY

	RECOVERY[1]	
	TCZ	UC
Screened, N	NA	
Randomized, N	2,022	2,094
Received TCZ, n/N (%)	1,333/1,602 (83.2)	44/1,664 (2.6)
Consent withdrawn, N (%)	3 (0.1)	3 (0.1)
ITT, N	2,022	2,094

ITT = intention to treat; NA = not applicable; TCZ = tocilizumab; UC= usual care.

Table 21: Patient Disposition for Lescure et al.

	Lescure et al.[10]		
	Sarilumab 200 mg	Sarilumab 400 mg	Placebo
Screened, N	431		
Randomized, N	161	173	86
Did not receive assigned treatment, N (%)	2	0	2
Randomized twice	0	0	1
Suspected bacterial infection	0	0	1
Improved	1	0	0
Withdrew consent	1	0	0
Received assigned treatment, N (%)	159	173	84
Completed study through day 60, N (%)	141	153	75
mITT, N	159	173	84
Safety, N	159	173	84

mITT = modified intention to treat.

Table 22: Patient Disposition for COVACTA

	COVACTA[8]	
	Tocilizumab	Placebo
Screened, N	479	
Randomized, N	301	151
Completed study through day 28, N (%)	224 (76)	108 (75)
Discontinued from study on or before day 28, N (%)	70 (24)	36 (25)
Reason for discontinuation, N (%)		
Death	57 (19)	29 (19)
Lost to follow-up	7 (2)	5 (3)
Patient decision	7 (2)	4 (3)
Physician decision	4 (1)	4 (3)
Other reasons	2 (1)	1 (1)
ITT, N	301	151
Modified ITT, N	294	144[a]
Safety, N	295[a]	143

ITT = intention to treat.

[a] One patient randomly assigned to the placebo arm was treated with tocilizumab; this patient was included in the tocilizumab group for the safety population and in the placebo group for the modified ITT population.

Table 23: Patient Disposition for EMPACTA

	EMPACTA[3]	
	Tocilizumab	Placebo
Screened, N	445	
Randomized, N	259	129
Completed study through day 28, N (%)	225 (87)	115 (89)
Did not receive assigned treatment, N (%)	10 (4)	1 (< 1)
Discontinued from study before day 28, N (%)	33 (13)	14 (11)
Reason for discontinuation, N (%)		
Death	24 (9)	11 (8)
Transfer to another facility	0	2 (1)
Withdrawal by patient	8 (3)	1 (< 1)
Withdrawal by physician	1 (< 1)	0
mITT, N	249	128
Safety, N	250	127

mITT = modified intention to treat.

Table 24: Patient Disposition for Salvarani et al.

	Salvarani et al.[5]	
	Tocilizumab	Standard care
Screened, N	126	
Randomized, N	60	66
Completed study through day 30, N (%)	60 (100)	63 (95)
Did not receive assigned treatment, N (%)	2 (3)	6 (9)
Discontinued from study before day 30, N (%)	0	3 (4)
Reason for discontinuation, N (%)		
Withdrew consent	0	3 (4)
ITT, N	60	63

ITT = intention to treat.

Table 25: Patient Disposition for Stone et al.

	Stone et al.[6]	
	Tocilizumab	Placebo
Screened, N	1,560	
Randomized, N	161	82
Did not receive assigned treatment, N (%)	0	1 (1)
ITT, N	161	82
mITT, N	161	81
Safety, N	161	82

ITT = intention to treat; mITT = modified intention to treat.

Table 26: Patient Disposition for TOCIBRAS

	TOCIBRAS [4]	
	Tocilizumab	Standard care
Screened, N	NR	
Randomized, N	65	64
Completed study through day 15, N (%)	65	64
Included in analysis, N (%)	65	64
Received tocilizumab (at discretion of investigator), N (%)	2 (3)	NA
Safety, N	67	62

NA = not applicable; NR = not reported.

Table 27: Patient Disposition for Wang et al.

	Wang et al.[11]	
	Tocilizumab plus standard care	Standard care
Screened, N	65	
Randomized, N	33	32
Did not receive assigned treatment, N (%)	0	1[a] (3)
ITT, N	34	31
Safety, N	34	31

ITT = intention to treat.

[a] Transferred to the tocilizumab group when condition worsened.

Table 28: Patient Disposition for Zhao et al.

	Zhao et al.[7]		
	Tocilizumab plus favipiravir	Tocilizumab	Favipiravir
Screened, N	31		
Randomized, N (%)	14	5	7
ITT, N	14	5	7
Safety, N	14	5	7

ITT = intention to treat.

Appendix 2: Baseline Characteristics

Table 29: Demographic and Clinical Characteristics at Baseline for REMAP-CAP

Characteristics	REMAP-CAP[9]		
	Tocilizumab (n = 353)	Sarilumab (n = 48)	Control (n = 402)
Age, mean years (SD)	61.5 (12.5)	63.4 (13.4)	61.1 (12.8)
Men, n (%)	261 (74)	39 (81.3)	283 (70)
Race or ethnicity, n/N (%)			
White	160/228 (70)	29/39 (74)	206/279 (74)
Asian	41/228 (18)	8/39 (21)	47/279 (17)
Black	12/228 (5)	1/39 (3)	9/279 (3)
Mixed	2/228 (1)	0/39 (0)	5/279 (2)
Other	13/228 (6)	1/39 (3)	12/279 (4)
Body mass index, median kg/m^2 (IQR)	30.5 (26.9 to 34.9) (n = 342)	29.2 (26.0 to 33.8) (n = 39)	30.9 (27.1 to 34.9) (n = 377)
Confirmed SARS-CoV-2 infection, n/N (%)	284/345 (82)	44/47 (94)	334/394 (85)
Pre-existing conditions, n/N (%)			
Diabetes mellitus	123/349 (35.2)	13/48 (27.1)	150/401 (37.4)
Kidney disease	30/312 (9.6)	4/45(8.9)	43/372 (11.6)
Respiratory disease	82/349 (23.5)	15/48 (31.3)	98/401 (24.4)
Immunosuppressive disease	8/348 (2.3)	0/48 (0.0)	14/401 (3.5)
Chronic immunosuppressive therapy	3/349 (0.9)	1/48 (2.1)	6/401 (1.5)
Severe cardiovascular disease	34/339 (10.0)	1/48 (2.1)	47/395 (11.9)
Liver cirrhosis or failure	2/339 (0.6)	0/48 (0.0)	1/395 (0.3)
Time to enrolment, median (IQR)			
From hospital admission, days	1.2 (0.8 to 2.8)	1.4 (0.9 to 2.8)	1.2 (0.8 to 2.8)
From ICU admission, hours	13.1 (6.6 to19.0)	16.0 (11.4 to 20.8)	14.0 (6.8 to 19.5)
Acute respiratory support, n/N (%)			
No support or supplemental oxygen only	1/353 (0.3)	0/48 (0.0)	2/402 (0.5)
High-flow nasal cannula	101/353 (28.6)	17/48 (35.4)	110/402 (27.4)
Noninvasive ventilation only	147/353 (41.6)	23/48 (47.9)	169/402 (42.0)
Invasive mechanical ventilation	104/353 (29.5)	8/48 (16.7)	121/402 (30.1)
Vasopressor support, n/N (%)	63/353 (17.9)	4/48 (8.3)	79/402 (19.7)
PaO_2:$Fi0_2$, median (IQR)	115 (89 to 162) (n = 335)	126 (99 to 157) (n = 48)	118 (89 to 169) (n = 354)
C-reactive protein, median mcg/mL (IQR)	150 (85 to 221) (n = 207)	136 (105 to 204) (n = 37)	130 (71to 208) (n = 244)

ICU = intensive care unit; IQR = interquartile range; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Table 30: Demographic and Clinical Characteristics at Baseline for CORIMUNO-TOC

Characteristics	CORIMUNO-TOC[2]	
	Tocilizumab (n = 63)	Usual care (n = 67)
Age, median years (IQR)	64.0 (57.1 to 74.3)	63.3 (57.1 to 72.3)
Men, n/N (%)	44/63 (70)	44/67 (66)
Body mass index, median kg/m^2 (IQR)	27.9 (23.3 to 30.8) (n = 46)	27.4 (24.5 to 31.3) (n = 46)
WHO-CPS score (0 to 10) = 5, n/N (%)	63/63 (100)	67/67 (100)
Confirmed SARS-CoV-2 infection, n/N (%)	56/63 (89)	61/67 (90)
Respiratory rate, median bpm (IQR)	24.0 (22.0 to 30.0) (n = 56)	26.0 (24.0 to 30.0) (n = 57)
SpO_2, median % (IQR)	95.0 (93.0 to 96.0)	95.0 (93.0 to 97.0)
Time from symptoms onset to randomization, median days (IQR)	10 (7 to 13) (n = 62)	10 (8 to 13) (n = 66)
Time from hospital admission to randomization, median days (IQR)	1 (1to 4) (n = 63)	1 (1to 2) (n = 67)
Coexisting conditions, n/N (%)		
chronic cardiac disease	20/61 (33)	20/67 (30.0)
diabetes	20/61 (33)	23/67 (34)
chronic kidney disease (stage 1 to 3) or dialysis	5/61 (8)	13/67 (19)
asthma	5/61 (8)	3/67 (5)
chronic pulmonary disease (not asthma)	3/61 (5)	3/67 (5)
active malignant neoplasm	4/61 (7)	5/67 (8)
C-reactive protein, median mg/L (IQR)	119.5 (74.5 to 219.5) (n = 56)	127.0 (84.0 to 171.0) (n = 63)

bpm = breaths per minute; IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation by pulse oximetry; WHO-CPS = World Health Organization Clinical Progression Scale.

Table 31: Demographic and Clinical Characteristics at Baseline for RECOVERY

Characteristics	RECOVERY[1]	
	TCZ (n = 2,022)	UC (n = 2,094)
Age, mean years (SD)	63.3 (13.7)	63.9 (13.6)
Men, n (%)	1,335 (66)	1,437 (69)
Ethnicity, n(%)		
White	1,356 (67)	1,426 (68)
Black, Asian, Minority Ethnic	341 (17)	357 (17)
Unknown	325 (16)	311 (15)
Time since symptoms onset, median days (IQR)	9 (7 to 13)	10 (7 to 14)
Time since hospitalisation, median days (IQR)	2 (1 to 5)	2 (1 to 5)
Oxygen saturation, % (IQR)	94 (92 to 96)	94 (91 to 95)
Respiratory support at second randomization, n (%)		
No ventilator support	935 (46)	933 (45)
Non-invasive ventilation	819 (41)	867 (41)
Invasive mechanical ventilation	268 (13)	294 (14)
Biochemistry at second randomization, n (%)		

Characteristics	RECOVERY[1]	
	TCZ (n = 2,022)	UC (n = 2,094)
Latest C-reactive protein, median mg/L (IQR)	143 (107 to 203)	144 (106 to 205)
Previous diseases, n (%)		
Diabetes	569 (28)	600 (29)
Heart disease	435 (22)	497 (24)
Chronic lung disease	473 (23)	484 (23)
Tuberculosis	3 (<1)	5 (<1)
HIV	7 (<1)	8 (<1)
Severe liver disease	14 (<1)	10 (<1)
Severe kidney impairment	118 (6)	99 (5)
Any of the above	1,100 (54)	1,163 (56)
Positive SARS-CoV-2 test result, n (%)	1,891 (94)	1,967 (94)
Use of systemic corticosteroids, n (%)		
Yes	1,664 (82)	1,721 (82)
No	357 (18)	367 (18)
Unknown	1 (<1)	6 (<1)

IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; TCZ = tocilizumab; UC = usual care.

Table 32: Demographic and Clinical Characteristics at Baseline for Lescure et al.

Characteristics	Lescure et al.[10]		
	Sarilumab 200 mg (N = 159)	Sarilumab 400 mg (N = 173)	Placebo (N = 84)
Age, median years (IQR)	58.0 (51.0 to 67.0)	58.0 (48.0 to 67.0)	60.0 (53.0 to 69.5)
Men, n (%)	108 (67.9)	99 (57.2)	54 (64.3)
Race, n (%)			
Asian	5 (3.1)	9 (5.2)	6 (7.1)
Black	3 (1.9)	5 (2.9)	1 (1.2)
White	126 (79.2)	128 (74.0)	67 (79.8)
Other[a]	25 (15.7)	31 (17.9)	10 (11.9)
Ethnicity, n (%)			
Hispanic or Latino, n (%)[b]	55 (33.3)	66 (38.2)	31 (36.9)
Body mass index ≥ 30 kg/m^2, n/N (%)	55/133 (41.4)	63/148 (42.6)	29/69 (42.0)
Comorbidities, n (%)			
Hypertension	68 (42.8)	70 (40.5)	39 (46.4)
Diabetes	45 (28.3)	47 (27.7)	18 (21.4)
Obesity	37 (23.3)	37 (21.4)	12 (14.3)
Neoplasm[c]	17 (10.7)	19 (11.0)	6 (7.1)
Dyslipidemia	16 (10.1)	19 (11.0)	6 (7.1)
Coronary artery disease	7 (4.4)	9 (5.2)	6 (7.1)
COPD	4 (2.5)	8 (4.6)	6 (6.7)
Asthma	10 (6.3)	4 (2.3)	3 (3.6)

Characteristics	Lescure et al.[10]		
	Sarilumab 200 mg (N = 159)	Sarilumab 400 mg (N = 173)	Placebo (N = 84)
Chronic kidney disease	7 (4.4)	6 (3.5)	5 (6.0)
Severity of illness			
Severe[d]	92 (57.9)	105 (60.7)	55 (65.5)
Critical[e]	65 (40.9)	68 (39.3)	29 (34.5)
Multisystem organ dysfunction	2 (1.3)	0	0
Clinical status on a 7-point scale			
2: Hospitalized, on invasive mechanical ventilation or ECMO	17 (10.7)	24 (13.9)	9 (10.7)
3: Hospitalized, on noninvasive ventilation or high-flow oxygen	28 (17.6)	21 (12.1)	11 (13.1)
4: Hospitalized, requiring supplemental oxygen	112 (70.4)	128 (74.0)	64 (76.2)
5: Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	2 (1.3)	0	0
Duration of hospitalization before dosing, median days (IQR)	3.0 (1.0 to 4.0)	2.0 (2.0 to 4.0)	4.0 (2.0 to 6.0)
Admitted to ICU before dosing, n (%)	61 (38.4)	59 (34.1)	28 (33.3)
Duration of ICU stay before dosing, median days (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	1.0 (1.0 to 3.5)
SpO_2 to FiO_2 ratio, median (IQR)	230.0 (165.0 to 296.9)	237.5 (172.7 to 293.8)	240.0 (190.0 to 332.1)
Laboratory findings			
SARS-CoV-2 virus detected, n (%)[f]	147 (92.5)	164 (94.8)	80 (95.2)
C-reactive protein, median mg/mL (IQR)	94.1 (44.6 to 176.8)	96.1 (48.1 to 160.6)	95.5 (55.5 to 184.4)
IL-6, median pg/mL (IQR)	11.6 (5.1 to 23.5)	12.7 (5.5 to 26.5)	13.0 (3.6 to 23.5)

COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IL-6 = interleukin-6; IQR = interquartile range; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation by pulse oximetry.

[a] Includes race not reported, other, or unknown.

[b] 136/150 (90.7%) Hispanic or Latino patients were in the White race category.

[c] Includes benign, malignant, and unspecified neoplasms.

[d] Severe disease was defined requiring supplemental oxygen administration by nasal cannula, simple face mask, or another similar device.

[e] Critical disease was defined as requiring 1 of the following: supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, use of invasive or noninvasive ventilation, or treatment in an ICU.

[f] Based on nasopharyngeal or serum PCR samples collected prior to first infusion.

Table 33: Demographic and Clinical Characteristics at Baseline for COVACTA

Characteristics	COVACTA[8]	
	Tocilizumab (n = 294)	Placebo (n = 144)
Age, mean years (SD)	60.9 (14.6)	60.6 (13.7)
Men, n (%)	205 (69.7)	101 (70.1)
Weight, mean kg (SD)	88.9 (23.6)	88.1 (24.3)
Race or ethnicity n (%)		
American Indian or Alaska Native	8 (2.7)	5 (3.5)
Asian	28 (9.5)	10 (6.9)
Black or African American	40 (13.6)	26 (18.1)
Native Hawaiian or other Pacific Islander	3 (1.0)	5 (3.5)
White	176 (59.9)	76 (52.8)
Multiple	0	1 (0.7)
Unknown	39 (13.3)	21 (14.6)
Region, n (%)		
Europe	120 (40.8)	59 (41.0)
North America	174 (59.2)	85 (59.0)
NEWS2, mean (SD)	7.1 (3.0)	7.0 (3.0)
Ordinal scale for clinical status, n (%)		
2	9 (3.1)	6 (4.2)
3	78 (26.5)	44 (30.6)
4	94 (32.0)	39 (27.1)
5	45 (15.3)	15 (10.4)
6	68 (23.1)	40 (27.8)[a]
Interleukin-6, ng/L	n = 233	n = 100
Mean (SD)	201.9 (418.4)	195.4 (368.2)
Median (range)	88.1 (3.1 to 4,020)	71.2 (3.1 to 2, 810)
C-reactive protein, mg/L	n = 237	n = 125
Mean (SD)	168.4 (101.4)	172.6 (114.0)
Median (range)	157.2 (1.1 to 446.6)	150.3 (1.6 to 499.6)
Mechanical ventilation, n (%)	111 (37.8)	54 (37.5)
Days on mechanical ventilation before baseline among patients on mechanical ventilation at randomization		
n	107	51
Mean (SD)	5.1 (5.5)	4.3 (4.5)
Median (range)	3.0 (0.0 to 28.0)	3.0 (0.0 to 20.0)
Comorbidities, n (%)		
≥ 1 comorbidity	231 (78.6)	124 (86.1)
Obesity	63 (21.4)	27 (18.8)
Diabetes	105 (35.7)	62 (43.1)
Cardiovascular impairment	88 (29.9)	35 (24.3)
Hypertension	178 (60.5)	94 (65.3)

Characteristics	COVACTA[8]	
	Tocilizumab (n = 294)	Placebo (n = 144)
Hepatic impairment	6 (2.0)	2 (1.4)
Chronic lung disease	49 (16.7)	22 (15.3)
Days from first COVID-19 symptom	n = 291	n = 143
Mean (SD)	12.1 (6.6)	11.4 (6.9)
Median (range)	11.0 (1.0 to 49.0)	10.0 (2.0 to 50.0)
Glucocorticoids, n (%)[b]	106 (36.1)	79 (54.9)
Antiviral treatment, n (%)[c]	87 (29.6)	51 (35.4)
Convalescent plasma, n (%)[d]	10 (3.4)	6 (4.2)

COVID-19 = coronavirus disease 2019; NEWS2 = National Early Warning Score 2; SD = standard deviation.

[a] Includes a patient who died on study day 1 (baseline ordinal category 7) but who was in category 6 on day 1 before death.

[b] Only systemic use administered during the period from trial day −7 until the initiation of tocilizumab or placebo on day 1.

[c] Antiviral treatment included lopinavir-ritonavir, remdesivir, lopinavir, ritonavir, chloroquine, hydroxychloroquine, and hydroxychloroquine sulphate administered during the period from trial day −7 until the initiation of tocilizumab or placebo on day 1.

[d] Administered during the period from trial day −7 until the initiation of tocilizumab or placebo on day 1.

Table 34: Demographic and Clinical Characteristics at Baseline for EMPACTA

Characteristics (mITT population)	EMPACTA[3]	
	Tocilizumab (n = 249)	Placebo (n = 128)
Age, mean years (SD)	56.0 (14.3)	55.6 (14.9)
Men, n (%)	150 (60.2)	73 (57.0)
Body mass index, mean kg/m^2 (SD)	32.0 (7.9)	33.1 (7.2)
Race or ethnicity, n (%)		
Hispanic or Latino	143 (57.4)	68 (53.1)
American Indian or Alaska Native	33 (13.3)	15 (11.7)
Black	35 (14.1)	21 (16.4)
Non-Hispanic White	28 (11.2)	20 (15.6)
unknown or other	10 (4.0)	4 (3.1)
Country, n (%)		
US	201 (80.7)	103 (80.5)
Mexico, Kenya, South Africa, Peru, and Brazil	48 (19.3)	25 (19.5)
Category on 7-category ordinal scale for clinical status, n (%)[a]		
2	24 (9.6)	11 (8.6)
3	161 (64.7)	81 (63.3)
4	64 (25.7)	36 (28.1)
C-reactive protein, median mg/L (range)	124.50 (2.5 to 2,099.0)	143.40 (9.0 to 3,776.0)

ICU = intensive care unit; mITT = modified intention to treat; SD = standard deviation.

[a] Categories on the 7-category ordinal scale range from 1 to 7, with higher categories indicating a worse condition. Category 1: indicates that the patient was discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate, as well as stable oxygen saturation while breathing ambient air or ≤ 2 litres of supplemental oxygen); 2: hospitalized in a non–ICU hospital ward (or ready for a hospital ward) and not receiving supplemental oxygen; 3: hospitalized in a non–ICU hospital ward (or ready for a hospital ward) and receiving supplemental oxygen; 4: hospitalized in an ICU or non–ICU hospital ward and receiving noninvasive ventilation or high-flow oxygen; 5: hospitalized in an ICU and receiving intubation and mechanical ventilation; 6: hospitalized in an ICU and receiving extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; and 7: died.

Table 35: Demographic and Clinical Characteristics at Baseline for Salvarani et al.

Characteristics	Salvarani et al.[5]	
	Tocilizumab (n = 60)	Standard care (n = 66)
Age, median years (IQR)	61.5 (51.5 to 73.5)	60.0 (54.0 to 69.0)
Men, n (%)	40 (66.7)	37 (56.1)
Days from symptom onset to randomization, median (IQR)	7.0 (4.0 to 11.0)	8.0 (6.0 to 11.0)
Days from hospital admission to randomization, median (IQR)	2 (1 to 3)	2 (1 to 4.2)
Coexisting comorbidities, n (%)		
Diabetes mellitus	10 (16.7)	9 (13.6)
Obesity (BMI ≥ 30)	16 (28.1)	22 (36.1)
Hypertension	27 (45.0)	29 (43.9)
COPD	2 (3.3)	2 (3.0)
Respiratory rate, median bpm (IQR)	20.0 (18.0 to 24.0)	20.0 (18.0 to 24.0)
C-reactive protein, median mg/dL (IQR)	10.5 (5.0 to 14.6)	6.5 (3.2 to 11.8)
PaO_2:FiO_2, median mm Hg (IQR)	262.5 (241.0 to 286.5)	268.2 (244.0 to 290.0)
Interleukin-6, median pg/mL (IQR)	50.4 (28.3 to 93.2)	34.3 (19.0 to 59.3)
Hydroxychloroquine, n (%)	53 (88.3)	62 (93.9)
Heparin and low-molecular-weight heparin, n (%)	41 (68.3)	40 (60.6)
Antiretrovirals, n (%)[a]	21 (35.0)	31 (47.0)
Azithromycin, n (%)	10 (16.7)	16 (24.2)

BMI = body mass index; bpm = breaths per minute; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; PaO_2 = partial pressure of arterial oxygen.

[a] Antiretrovirals included darunavir-cobicistat, darunavir-ritonavir, or lopinavir-ritonavir. No remdesivir was administered.

Table 36: Demographic and Clinical Characteristics at Baseline for Stone et al.

Characteristics	Stone et al.[6]	
	Tocilizumab (n = 161)	Placebo (n = 82)
Age, median years (IQR)	61.6 (46.4 to 69.7)	56.5 (44.7 to 67.8)
Men, n (%)	96 (60)	45 (55)
Race or ethnicity, n (%)		
American Indian or Alaska Native	1 (1)	0
Asian	7 (4)	2 (2)
Black	24 (15)	16 (20)
Native Hawaiian or Pacific Islander	0	1 (1)
White	71 (44)	33 (40)
Other	35 (22)	15 (18)
Unknown	23 (14)	15 (18)
Hispano or Latino ethnic group, n (%)		
Hispanic or Latino	70 (43)	39 (48)
Not Hispanic or Latino	84 (52)	35 (43)
Unknown	7 (4)	8 (10)
Body mass index, median kg/m^2 (IQR)	29.9 (26.0 to 34.2)	30.2 (25.7 to 33.8)
BMI ≥ 30, n (%)	80 (50)	42 (51)

Characteristics	Stone et al.[6]	
	Tocilizumab (n = 161)	Placebo (n = 82)
Days from symptom onset to randomization, median (IQR)	9.0 (6.0 to 13.0)	10.0 (7.0 to 13.0)
Comorbidities, n (%)		
Hypertension	80 (50)	38 (46)
HEART failure	17 (11)	7 (9)
history of myocardial infarction	15 (9)	6 (7)
COPD	15 (9)	7 (9)
Asthma	15 (9)	7 (9)
Diabetes	45 (28)	30 (37)
Chronic kidney disease	29 (18)	13 (16)
History of cancer	22 (14)	8 (10)
Ordinal scale score, n (%) [a]		
2	23 (14)	15 (18)
3	133 (83)	61 (74)
4	5 (3)	5 (6)
5	0	1 (1)
C-reactive protein, median mg/L (IQR)	116.0 (67.1 to 190.6)	94.3 (58.4 to 142.0)
Interleukin-6, median pg/mL (IQR)	23.6 (14.0 to 49.9)	25.4 (14.6 to 40.3)

BMI = body mass index; COPD = chronic obstructive pulmonary disorder; ICU = intensive care unit; IQR = interquartile range.

[a] Scores on the ordinal clinical improvement scale range from 1 to 7, with higher scores indicating worse clinical condition. A score of 2 indicates that the patient was in (or ready for) a non–ICU ward and was not receiving supplemental oxygen; a score of 3, that the patient was in (or ready for) a non–ICU hospital ward and was receiving supplemental oxygen; a score of 4, that the patient was in the ICU or in a non–ICU hospital ward and was receiving noninvasive ventilation or high-flow oxygen; and a score of 5, that the patient was in the ICU, intubated, and receiving mechanical ventilation.

Table 37: Demographic and Clinical Characteristics at Baseline for TOCIRBAS

Characteristics	TOCIRBAS[4]	
	Tocilizumab (n = 65)	Standard care (n = 64)
Age, mean years (SD)	57.4 (15.7)	57.5 (13.5)
Men, n (%)	44 (68)	44 (69)
Days from symptom onset to randomization, mean (SD)	10.0 (3.1)	9.5 (3.0)
Comorbidities, n (%)		
Hypertension	30 (46)	34 (53)
Diabetes	22 (34)	20 (31)
Obesity	15 (23)	16 (25)
Heart failure	4 (6)	3 (5)
Myocardial infarction	4 (6)	3 (5)
COPD	2 (3)	2 (3)
Asthma	4 (6)	1 (2)
Chronic kidney disease	5 (8)	1 (2)
Solid malignancy	4 (6)	5 (8)
Hematological malignancy	1 (1)	0
Previous drug use, n (%)		
None	13 (20)	9 (14)

Characteristics	TOCIRBAS[4]	
	Tocilizumab (n = 65)	Standard care (n = 64)
Corticosteroids (> 5 mg of prednisone for > 30 days)	4 (6)	5 (8)
Other immunosuppressants	5 (5)	2 (3)
Hydroxychloroquine	11 (17)	9 (14)
Azithromycin	23 (35)	31 (48)
Others[a]	41 (63)	38 (59)
Clinical status on a 7-level ordinal scale		
4: Admitted to hospital, receiving supplemental oxygen	36 (60)	28 (44)
5: Admitted to hospital, receiving noninvasive ventilation or high-flow oxygen through nasal cannula	15 (23)	26 (41)
6: Admitted to hospital, receiving mechanical ventilation	11 (17)	10 (16)
SOFA score, mean (SD)	3.4 (1.8)	3.6 (2.1)
Respiratory rate, median rpm (IQR)	20 (18 to 24)	20 (18 to 25)
Peripheral oxygen saturation, median % (IQR)	95 (92 to 96)	95 (93 to 96)
C-reactive protein, mean mg/dL (SD)	160 (104) n = 53	193 (283) n = 63
PaO_2, median mm Hg (IQR)	83 (70 to 105) n = 54	85 (68 to 108) n = 57

COPD = chronic obstructive pulmonary disease; IQR = interquartile range; PaO_2 = partial pressure oxygen; rpm = respirations per minute; SD = standard care; SOFA = sequential organ failure assessment.

[a] Antihypertensive drugs (n = 33), hypoglycemic drugs (n = 22), statins (n = 10), thyroid hormones (n = 5), anticoagulants (n = 4), antidepressants (n = 4), and anticonvulsants (n = 1).

Table 38: Demographic and Clinical Characteristics at Baseline for Wang et al.

Characteristics	Wang et al.[11]	
	Tocilizumab (n = 34)	Standard care (n = 31)
Age, median years (IQR)	63.5 (58 to 71)	63 (54 to 69)
Men, n (%)	18 (52.9)	15 (48.4)
Symptom onset to randomization, median days (IQR)	20 (9 to 29)	24 (19 to 33)
Coexisting conditions, n (%)		
Hypertension	10 (29.4)	10 (32.3)
Diabetes	4 (11.8)	6 (19.4)
Other	8 (23.5)	9 (29.0)
Respiratory rate, median bpm (IQR)	20 (18 to 20)	20 (19 to 20)
C-reactive protein, median mg/L (IQR)	10.0 (3.3 to 23.6)	6.3 (1.2 to 33.7)
Interleukin-6, median pg/mL (IQR)	26.0 (12.8 to 58.0)	24.4 (9.9 to 85.3)
Oxygen support mode, n (%)		
Nasal duct	21 (61.8)	17 (54.8)
Mask	2 (5.9)	2 (6.5)
High flow	3 (8.8)	3 (9.7)
Air	8 (23.5)	9 (29.0)
Disease severity, n (%)		
Moderate	20 (58.8)	17 (54.8)

Characteristics	Wang et al.[11]	
	Tocilizumab (n = 34)	Standard care (n = 31)
Severe	14 (41.2)	14 (45.2)

bpm = breaths per minute; IQR = interquartile range.

Table 39: Demographic and Clinical Characteristics at Baseline for Zhao et al.

Characteristics	Zhao et al.[7]		
	Tocilizumab plus favipiravir (n = 14)	Tocilizumab (n = 5)	Favipiravir (n = 7)
Age, median years (range)	75 (34 to 81)	71 (48 to 77)	70 (45 to 89)
Men, n (%)	6 (43)	3 (60)	5 (71)
Body mass index, median kg/m^2 (range)	24.8 (17.6 to 37.8)	21.5 (20.8 to 26.4)	21.1 (20 to 28)
Interleukin-6, median pg/mL (range)	10.2 (7.4 to 71.9)	27.5 (9.0 to 78.7)	19.8 (9.0 to 222.5)
Concomitant disease, n (%)			
High blood pressure, n (%)	6 (42.9)	2 (40.0)	3 (42.9)
Diabetes, n (%)	1 (7.1)	1 (20.0)	1 (14.3)
Coronary artery disease, n (%)	2 (14.3)	3 (60.0)	1 (14.3)
Clinical classification, n (%)			
Mild type	0	0	0
Common type	8 (57.1)	2 (40.0)	2 (28.6)
Severe type	5 (35.7)	3 (60.0)	5 (71.4)
Critical type	1 (7.1)	0	0

Appendix 3: Harms Data

Table 40: Harms Outcomes for REMAP-CAP

	REMAP-CAP[9]		
	Tocilizumab (n = 353)	Sarilumab (n = 48)	Control (n = 402)
Adverse events, n (%)			
Adverse events	NR	NR	NR
Serious adverse events, n (%)			
Patient with 1 or more serious adverse event	9 (2.5)	0	11 (2.7)
Serious adverse events			
Secondary bacterial infection	1 (0.3)	0	0
Bleeds	5 (1.4)	0	4 (1.0)
Cardiac events	2 (0.6)	0	0
Deterioration in vision	1 (0.3)	0	0
Thrombosis	0	0	7 (1.7)
Deaths, n (%) — hospital mortality	98/350 (28.0)	10/45 (22.2)	142/397 (35.8)

NR = not reported.

Table 41: Harms Outcomes for CORIMUNO-TOC

	CORIMUNO-TOC[2]	
	Tocilizumab (n = 63)	Usual care (n = 67)
Adverse events, n (%)		
Patients with at least 1 adverse event	28 (44)	36 (54)
Patients with multiple adverse events	16 (25)	19 (28)
Number of events	66	86
Serious adverse events, n (%)		
Patients with at least 1 serious adverse event	20 (32)	29 (43)
Patients with multiple serious adverse events	5 (8)	10 (15)
Number of events	26	57
Serious adverse events		
Bacterial sepsis	2 (3)	11 (16)
Neutropenia	4 (6)	0
Atrial fibrillation	0	1 (1.5)
Anemia	1 (1.6)	4 (6.0)
Hyperlipasemia	0	1 (1.5)
Cholestasis	0	2 (3.0)
Hepatic cytolysis	4 (6.4)	4 (6.0)
Fever	2 (3.2)	0
Hyperkalemia	0	1 (1.5)
Hypoglycemia	0	1 (1.5)

	CORIMUNO-TOC[2]	
	Tocilizumab (n = 63)	Usual care (n = 67)
Hypertension	1 (1.6)	0
Acute renal failure	1 (1.6)	2 (3.0)
Arterial ischemia	0	2 (3.0)
Lymphopenia	1 (1.6)	0
Pneumothorax	0	1 (1.5)
Fungal sepsis	0	2 (3.0)
Viral sepsis	0	1 (1.5)
Tetraparesis	0	1 (1.5)
Cough	1 (1.6)	0
Deaths, n (%)		
Acute respiratory distress syndrome	9 (7)	19 (9)
Multiple organ failure	0	1 (1)
Pulmonary embolism	0	3 (1)

Table 42: Harms Outcomes for Lescure et al.

Patients with ≥ 1 event	Lescure et al.[10]		
	Sarilumab 200 mg (n = 159)	Sarilumab 400 mg (n = 173)	Placebo (n = 84)
Adverse events, n (%)			
Any treatment-emergent adverse events	103 (64.8)	121 (69.9)	55 (65.5)
Any adverse events of special interest	53 (33.3)	76 (43.9)	18 (21.4)
ALT increase	48 (30.2)	55 (31.8)	16 (19.0)
Invasive bacterial or fungal infection	8 (5.0)	15 (8.7)	3 (3.6)
Grade ≥ 2 hypersensitivity reaction	1 (0.6)	7 (4.0)	0
Grade 4 neutropenia	3 (1.9)	6 (3.5)	0
Grade ≥ 2 infusion related reaction	1 (0.6)	6 (3.5)	0
Serious adverse events, n (%)			
Any serious treatment-emergent adverse events	42 (26.4)	51 (29.5)	20 (23.8)
Any serious infection	18 (11.3)	22 (12.7)	10 (11.9)
Pneumonia	1 (0.6)	6 (3.5)	0
COVID-19 pneumonia	11 (6.9)	4 (2.3)	2 (2.4)
Bacterial pneumonia	1 (0.6)	3 (1.7)	1 (1.2)
Deaths			
Any treatment-emergent adverse event leading to death	17 (10.7)	18 (10.4)	9 (10.7)

ALT = alanine aminotransferase; COVID-19 = coronavirus disease 2019.

Table 43: Harms Outcomes for COVACTA

	COVACTA[8]	
	Tocilizumab (n = 295)	Placebo (n = 143)
Adverse events, n (%)		
Patients with 1 or more adverse events	228 (77.3)	116 (81.1)
Number of adverse events	778	360
Adverse events of special interest, n (%)		
Infections	126 (42.7)	62 (43.4)
Serious infections	62 (21.0)	37 (25.9)
Opportunistic infections[a]	1 (0.3)	1 (0.7)
Medically confirmed malignancies	1 (0.3)	0
Hypersensitivity[b]	19 (6.4)	4 (2.8)
Anaphylaxis per Sampson criteria	0	1 (0.7)
Hepatic events	5 (1.7)	3 (2.1)
Abnormal liver-function value[c]	6 (2.0)	6 (4.2)
Myocardial infarction	3 (1.0)	2 (1.4)
Stroke	3 (1.0)	2 (1.4)
Bleeding events		
Any	45 (15.3)	16 (11.2)
Serious	13 (4.4)	5 (3.5)
Serious adverse events, n (%)[d]		
Patients with 1 more serious adverse event	113 (38.3)	62 (43.4)
Number of serious adverse events	183	117
Serious infections reported in more than 1% of patients in either treatment arm, n (%)[d]		
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
Deaths, n (%)	58 (19.7)	28 (19.4)

ALT = alanine aminotransferase; COVID-19 = coronavirus disease 2019.

[a] Candida sepsis in the tocilizumab arm and respiratory moniliasis in the placebo arm.

[b] Hypersensitivity reactions include all events that occurred during or within 24 hours after the infusion of tocilizumab or placebo and that were assessed by the nvestigator as being related to the infused agent, regardless of whether the episode was clinically consistent with hypersensitivity

[c] ALT or aspartate aminotransferase levels greater than 3 times the upper limit of normal, with an bilirubin level for either that is twice the upper limit of normal or greater.

[d] Harms outcomes at clinical data cut-off (June 24, 2020)

Table 44: Harms Outcomes for EMPACTA

Harms outcomes through day 60	EMPACTA[3]	
	Tocilizumab (n = 250)	Placebo (n = 127)
Adverse events, n (%)		
Number of adverse events	357	187
Patients with 1 or more adverse events	127 (50.8)	67 (52.8)
Patients with 1 or more grade 3 to 5 adverse events, at greatest intensity	46 (18.4)	31 (24.4)
Patients with 1 more infection	25 (10.0)	16 (12.6)
Serious adverse events, n (%)		
Patients with 1 or more serious adverse events	38 (15.2)	25 (19.7)
Patients with 1 or more serious infections	13 (5.2)	9 (7.1)
Number of serious infections	16	11
Serious infections among more than 1% of patients in either group		
Septic shock	5 (2.0)	3 (2.4)
COVID-19 pneumonia	2 (0.8)	3 (2.4)
Pneumonia not otherwise specified	0	3 (2.4)
Bacterial pneumonia	0	2 (1.6)
Withdrawals due to adverse events, n (%)		
Withdrawal from trial because of adverse event	0	0
Deaths, n (%)		
Total deaths	29 (11.6)	15 (11.8)
Event with fatal outcome	28 (11.2)	13 (10.2)

COVID-19 = coronavirus disease 2019.

Table 45: Harms Outcomes for Salvarani et al.

	Salvarani et al.[5]	
	Tocilizumab (n = 60)	Standard care (n = 63)
Adverse events, n (%)		
Any system	14 (23.3)	7 (11.1)
Gastrointestinal disorders	1 (1.7)	1 (1.6)
Infections and infestations	1 (1.7)	4 (6.3)
Urinary tract infection	1 (1.7)	0
Sepsis	0	2 (3.2)
Esophageal infection	0	1 (1.6)
Bronchial infection	0	1 (1.6)
Fall	1 (1.7)	0
Laboratory abnormalities	8 (13.3)	2 (2.3)
Increased alanine aminotransferase	5 (8.3)	2 (2.3)
Decreased neutrophil count	3 (5.0)	0
Metabolism	2 (3.3)	0

	Salvarani et al.[5]	
	Tocilizumab (n = 60)	Standard care (n = 63)
Hyperglycemia	1 (1.7)	0
Hypokalemia	1 (1.7)	0
Vascular disorders	1 (1.7)	0
Serious adverse events, n (%)		
Serious adverse event	1 (1.7)	2 (2.3)
Severe infection	0	2 (2.3)
Upper gastrointestinal bleeding	1 (1.7)	0
Death, n (%) at day 60	2 (3.3)	1 (1.6)

Table 46: Harms Outcomes for Stone et al.

	Stone et al.[6]	
	Tocilizumab (n = 161)	Placebo (n = 82)
Events, n (%)		
Hypersensitivity reaction to infusion	2 (1.2)	2 (2.4)
Infection grade ≥ 3	13 (8.1)	14 (17.1)
Grade 3	12 (7.5)	14 (17.1)
Grade 4	1 (0.6)	0
Myocardial infarction	0	1 (1.2)
Deep vein thrombosis	2 (1.2)	3 (3.7)
Pulmonary embolism	2 (1.2)	2 (2.4)
Stroke	2 (1.2)	0
Seizure	0	1 (1.2)
Arterial ischemia	1 (0.6)	0
Gastrointestinal perforation	0	0
Demyelinating disorder	0	0
Elevated liver function values		
ALT grade ≥ 3	8 (0.5)	4 (4.9)
Grade 3	8 (0.5)	4 (4.9)
Grade 4	0	0
AST grade ≥ 3	6 (3.7)	3 (3.7)
Grade 3	6 (3.7)	2 (2.4)
Grade 4	0	1 (1.2)
Neutropenia grade ≥ 3	22 (13.7)	1 (1.2)
Grade 3	21 (13.0)	1 (1.2)
Grade 4	1 (0.6)	0
Thrombocytopenia grade ≥ 3	1 (0.6	0
Grade 3	1 (0.6	0
Grade 4	0	0
Bleeding	0	1 (1.2)
Other	21 (13.0)	14 (17.1)

	Stone et al.[6]	
	Tocilizumab (n = 161)	Placebo (n = 82)
Serious adverse events, n (%)		
Number of serious adverse events	36	38
Patients with serious adverse events	28 (17.4)	12 (14.6)
Death, n (%)	9 (5.6)	4 (4.9)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Table 47: Harms Outcomes for TOCIBRAS

	TOCIBRAS[4]	
	Tocilizumab (n = 67)	Standard care (n = 62)
Adverse events, n (%)		
Any adverse events	29 (43)	21 (34)
Any “non-severe” adverse events	24 (36)	15 (24)
“Non-severe” adverse events		
Raised ALT, AST, or bilirubin level	11 (16)	4 (6)
Anemia	7 (10)	10 (16)
Hemorrhage	1 (1)	1 (2)
Neutropenia	1 (1)	0
Thrombocytopenia	4 (6)	0
Neutrophilia	1 (1)	0
Anxiety	1 (1)	0
Lymphopenia	0	1 (2)
Atrial fibrillation	1 (1)	0
Hypoacusis	1 (1)	0
Serious adverse events, n (%)		
Any “severe” adverse events	11 (16)	7 (11)
“Severe” adverse events		
Raised ALT, AST, or bilirubin level	7 (10)	3 (5)
Anemia	3 (4)	3 (5)
Pneumothorax	0	1 (2)
Neutropenia	1 (1)	0
Bleeding	1 (1)	0
Intracranial bleeding	0	1 (2)
Sudden cardiorespiratory collapse	4 (6)	1 (2)
Deaths, n (%)		
Death at day 15[a]	11 (17)	2 (3)
Mortality up to 28 days[a]	14 (21)	6 (9)
In-hospital mortality[a]	14 (21)	6 (9)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[a] Intention-to-treat population.

Table 48: Harms Outcomes for Wang et al.

	Wang et al.[11]	
	Tocilizumab (n = 34)	Standard care (n = 31)
Adverse events, n (%)		
"Non-severe" adverse events	20 (58.8)	4 (12.9)
Liver abnormal	6 (17.6)	1 (3.2)
Leucopenia	5 (14.7)	0
Neutropenia	3 (8.8)	0
Headache	1 (2.9)	0
Insomnia	1 (2.9)	0
Rash	1 (2.9)	0
Constipation	1 (2.9)	0
Hypoglycemia	1 (2.9)	0
Aggravation of pulmonary disease	1 (2.9)	0
Diarrhea	0	1 (3.2)
Arrhythmology	0	1 (3.2)
Anemia	0	1 (3.2)
Serious adverse events, n (%)		
"Severe" adverse event	0	1 (3.2)

Table 49: Harms Outcomes for Zhao et al.

	Zhao et al.[7]		
	Tocilizumab plus favipiravir (n = 14)	Tocilizumab (n = 5)	Favipiravir (n = 7)
Adverse events, n (%)			
Number of adverse events	9 (64.3)	2 (40.0)	2 (28.6)
Increased ALT	3 (21.4)	1 (20.0)	1 (14.3)
Increased AST	2 (14.3)	1 (20.0)	0
Hyperuricemia	1 (7.1)	0	1 (14.3)
Diarrhea	2 (14.3)	0	0
Headache	1 (7.1)	0	0
Serious adverse events, n (%)			
Number of serious adverse events	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Appendix 4: Summary of Appraisal

Table 50: Threats to Internal and External Validity

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
Gordon et al. (REMAP-CAP)	• 1:1:1 ratio • Randomization via centralized computer program • No details available on stratification	NR	Open label	• The use of invasive MV was lowest in the SAR group (17%) vs. TCZ group (29%) and the control group (30%) • Vasopressor support was lowest in the SAR group (8%) vs. TCZ group (18%) and the control group (20%) • Number of patients with severe cardiovascular disease was highest in the TCZ group (10.0%) and control group (11.9%)	Not calculated	Bayesian cumulative logistic model, which determined posterior probability distributions for the primary outcome	• No control for type 1 error • No maximum sample size calculations
Hermine et al. (CORIMUNO-TOC)	• 1:1 ratio • Computer-generated randomization list and permuted block randomization of blocks of varying sizes • Stratified by centre	NR	Open label	Coexisting chronic kidney disease was higher in the UC group (19%) vs. the TCZ plus UC group (8%)	• Trial was designed with "type I error rate of 0.047 if event rates are 50% in each arm, and a power of 97.2% to detect a decrease in event rate from 0.50 to 0.20, and 73.9% to detect a decrease in event rates from 0.50 to 0.30" (p. 7)[2] • Sample size was established to be 120	• ARDs and HRs were reported for the treatment effect at day 4 and 14, respectively • Posterior probabilities of ARD < −5.5% and HR < 0.85 were established, based on a 50% event rate	• UC varied across centres and during the course of the pandemic • At enrolment, patients had to have a WHO-CPS score of ≥ 5, which limits the generalizability of the results outside of patients with moderate, severe, or critical COVID-19 pneumonia • Small sample size • No control for type I error for secondary outcomes
Horby et al. [a] **(RECOVERY)**	• 1:1 ratio • Randomization via web-based computer scheme	Allocation concealment was observed until after randomization; however, no further	Open-label	Balanced	• A sample size of approximately 4,000 patients would "provide the study 90% power at two-sided P = 0.01 to detect a proportional	A log-rank test and Kaplan-Meier survival curves were conducted for the primary outcome	• 17% of patients in the TCZ plus usual care group did not receive treatment with TCZ; therefore, the effect sizes

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
	• Randomization was not stratified	details describing the allocation procedure is provided			reduction"[1] (p.10) of one-fifth in all-cause mortality assessed at 28 days		reported for outcomes may underestimate treatment with tocilizumab • Data for the primary outcome was based on 92% of randomized patients • No control for type I error
Lescure et al.[a]	• 2:2:1 ratio • Central randomization scheme through an interactive response system • Permuted block randomization • Stratified by severity of illness (severe or critical) and use of systemic corticosteroids (yes or no)	NR	Double blind	The proportion of patients with severe disease was lowest in the 200 mg SAR group (57.9%) and the placebo group (65.5%) reported the highest proportion of severe disease	Estimated sample size of 400 patients to provide at least 90% power for pairwise comparisons between each SAR-dose group versus placebo, with log-rank test of superiority using a 2-sided significance level of 5%	Multiplicity was accounted for the primary and key secondary outcomes in the primary analysis conducted at 29 days following a hierarchical testing strategy	• Based on the hierarchical testing strategy, there was no difference in clinical improvement between the 400 mg SAR group vs placebo; however, testing continued for the key secondary outcome of 400 mg SAR vs. placebo • The use of systemic corticosteroids throughout the course of the study may have masked the true efficacy of SAR compared with placebo and produced a non-significant difference for the primary and key secondary outcomes • The trial may have been underpowered, resulting in non-significant differences between each SAR-dose group and placebo groups for the primary outcome

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
Rosas et al. (COVACTA)	• 2:1 ratio • Randomization via interactive voice or web-based response system • Permuted block randomization • Stratified by geographic region (North America, Europe) and MV (yes and no)	NR	Double blind	Patients in the placebo plus SC group (28.5%) reported higher use of glucocorticoids	• Trial had a statistical power of 90% for the primary outcome • Estimated sample size was 450 patients	• Difference in clinical status between treatment groups used a non-parametric van Elteren test • Proportional odds model provided ORs and 95% CIs • Differences in mortality, incidence of mechanical ventilation and ICU transfer between treatment groups were analyzed using the Cochran-Mantel-Haenszel test • Differences in the number of ventilator-free days between treatment groups were assessed using the van Elteren test • Time-to-event secondary outcomes were analyzed using a log-rank test with Kaplan-Meier plots • Based on hierarchical testing, if significance was met for the primary outcome, then mortality was assessed	• SC varied across study sites and countries • While statistical significance for the primary outcome was not met, mortality at 28 days was assessed • No control for type I error
Salama et al. (EMPACTA)	• 2:1 ratio • Randomization via an interactive voice or web-based response system and permuted block randomization • Stratified by country (US, Mexico, Kenya, South Africa, Peru,	NR	Double blind	Diabetes was higher in the TCZ group (42.0%) and obesity was higher in the placebo group (29.9%)	Study was powered 80% to determine a between-group difference in the primary outcome based on a cumulative event rate of 25% in the TCZ group vs. 40% in the placebo group	• Kaplan-Meier method was applied for the primary outcome and stratified log-rank test; • Cox proportional-hazards model was conducted to obtain HRs and 95% CIs • Hierarchy testing was conducted to control the overall trial-wide type I error	Use of systemic glucocorticoids during the study may confound the true effectiveness of TCZ

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
	or Brazil) and age (≤ 60 years or > 60 years)					rate using a 5% significance level. Testing of the secondary outcomes was outlined in a pre-defined order	
Salvarani et al.	• 1:1 ratio • Permuted blocks of different sizes • Conducted by telephone access • Stratified by centre	Centralized randomization list	Open label	Patients with BMI ≥ 30 (36.1%) and antiretroviral use (47.0%) was higher in the standard care group	• Study was powered 80% to detect 50% of patients experiencing clinical worsening using a 2-sided type I error of 5% • Sample size was estimated to be 398 patients	Primary outcome (clinical worsening) and secondary outcomes (admission to the ICU with invasive MV, deaths, and discharges) were analyzed using x^2 test and rate ratio with 95% CI	• While the original protocol did not include any planned interim analysis, the regulatory body introduced interim analyses in all ongoing trials; an amendment was made to conduct an interim analysis for futility based on 132 patients • On June 11, 2020 the scientific committee interrupted the study for futility with 126 patients enrolled; since ICU eligibility criteria were not outlined in the protocol, this may have excluded older patients and those with more severe comorbidities, which may explain the few deaths reported in the study • Secondary outcomes were analyzed according to per protocol and should be interpreted with caution; this is because 14 of the 17 patients who met the primary outcome in the standard care group

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
							received treatment with tocilizumab as rescue therapy • No control for type I error • Small sample size
Stone et al.	• 2:1 ratio • Permuted block randomization of sizes 3 and 6 • Stratified by site	NR	Double blind	No. of patients older than 65 years old was higher in the TCZ plus SC group (37%) vs. placebo (27%)	• Study was powered 80% to detect 30% risk of intubation in placebo group vs. 15% risk of intubation in the TCZ plus SC group using a log-rank test and 2-sided tests and a significance level of 5% • Estimated sample size was 243 patients	• Treatment groups were compared using log-rank tests stratified according to site and differences between treatment groups were reported as HRs and 95% CIs for primary and secondary outcomes • A Bonferroni-Holm correction was applied for secondary outcomes to ensure an overall 2-sided significance level of less than 0.05.	• Standard care practices and strategies to delay intubation evolved during the course of the trial as new drugs became available • No adjustments for multiple comparisons for tertiary and exploratory analyses
Veiga et al. (TOCIBRAS)	• 1:1 ratio • Random blocks of 2, 4, 6, and 8 via computer-generated schedule • Stratified by age (60 years and ≥ 60 years) and sex	Completed via web access system	• Open label • Hospital researchers were unblinded to treatment assignment and collected outcome data • Treatment assignment was known to statisticians who analyzed data	• Use of azithromycin was lower in the TCZ group (35%) vs. SC (48%) • Clinical status at baseline on 7-category ordinal scale of patients admitted to hospital receiving supplemental oxygen was higher in the TCZ group (60%) vs. SC (44%)	Study was powered 80% to detect an OR of 0.44 using a 2-sided significance level of 5% for having the outcome of clinical status on a 7-category ordinal scale	• Clinical status on the 7-category ordinal scale was planned to be assessed using ordinal logistic regression; however, since the assumption of odds of proportionality was not met, the 7-point ordinal scale was collapsed into a binary outcome • Pre-specified subgroup analyses • Sensitivity analyses and post-hoc sensitivity analysis to adjust for imbalance in baseline clinical status	• Death at 15 days was higher in the TCZ plus SC group, which resulted in the early termination of the trial • No control for type I error • Small sample size

	Randomization Method	Allocation concealment	Blinding	Imbalance of baseline characteristics	Power	Statistical tests	Major trial limitations
Wang et al.[a]	• 1:1 ratio • Computer-generated block randomization • Not stratified	NR	Open label	Balanced between TCZ plus SC and SC groups	Study was designed to include 188 patients (94 in the TCZ plus SC group and 94 in the SC group)	Treatment groups were compared using chi-square or Fisher exact tests for primary and secondary outcomes	• No control for type I error • Small sample size • Use of glucocorticoids may confound the true effectiveness of TCZ
Zhao et al.	• 1:1:3 ratio • Randomization scheme NR • Not stratified	NR	Open label	Clinical classification of COVID-19 as “common type” was highest in the FAV plus TCZ group (57.1%) vs. FAV group (28.6%) and TCZ group (40.0%), respectively	No sample size calculation	• A Kruskal-Wallis analysis was applied to compare continuous variables • Categorical variables were assessed using chi-square or Fisher exact tests • Log-rank test (Mantel-Cox) for the comparison between treatment groups in cumulative improvement rate of lung CT imaging	• Small sample size • No control for type I error • Lack of control or placebo group

ARD = absolute risk difference; BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease 2019; CT = computed tomography; FAV = favipiravir; HR = hazard ratio; ICU = intensive care unit; MV = mechanical ventilation; NR = not reported; OR = odds ratio; SAR = sarilumab; SC = standard care; TCZ = tocilizumab; UC = usual care; vs. = versus; WHO-CPS = World Health Organization Clinical Progression Scale.

[a] Prepublication study that has not been peer reviewed.

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