“Rolling Collaborative Review” of Covid-19 treatments

TOCILIZUMAB FOR THE TREATMENT OF COVID-19

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| Chapter, page no. | Major changes from version 9.0                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------|
| Summary           | Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab |
|                   | Table 4-8 Ongoing trials of single agent tocilizumab                                          |

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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# LIST OF ABBREVIATIONS

| Abbreviation | Description |
|--------------|-------------|
| AE           | Adverse Event |
| ARR          | Absolute Risk Reduction |
| ATC          | Anatomical Therapeutic Chemical [Classification System] |
| ATMP         | Advanced therapy medicinal product |
| CI           | Confidence Interval |
| CRP          | C-Reactive Protein |
| DOI          | Declaration of interest |
| EUnetHTA     | European Network of Health Technology Assessment |
| GRADE        | Grading of Recommendations, Assessment, Development and Evaluation |
| HR           | Hazard Ratio |
| HRQOL        | Health-related Quality of Life |
| ICD          | International Classification of Diseases |
| ICU          | Intensive Care Unit |
| ITT          | Intention-to-treat |
| MD           | Mean Difference |
| MeSH         | Medical Subject Headings |
| NA           | Not applicable |
| NR           | Not reported |
| OR           | Odds Ratio |
| PP           | Per Protocol |
| RCT          | Randomized Controlled Trial |
| REA          | Relative Effectiveness Assessment |
| RR           | Relative Risk |
| SAE          | Serious Adverse Event |
| SD           | Standard Deviation |
| SMD          | Standardized Mean Difference |
| SmPC         | Summary of product characteristics |
| SoC          | Standard of Care |
| SOP          | Standard Operating Procedure |
| TCZ          | Tocilizumab |
| WP4          | Work Package 4 |
1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA) adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan (“Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning”, published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

| Description       | Project Scope                                                                                                                                 |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Population        | Disease
|                   | SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. |
|                   | ICD-Codes ([https://www.who.int/classifications/icd/covid19/en](https://www.who.int/classifications/icd/covid19/en))
|                   | - An emergency ICD-10 code of ‘U07.1 COVID-19, virus identified’ is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. |
|                   | - An emergency ICD-10 code of ‘U07.2 COVID-19, virus not identified’ is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. |
|                   | - Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. |
|                   | - In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. |
|                   | MeSH-terms
|                   | - COVID-19, Coronavirus Disease 2019 |
|                   | Target population ([https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/](https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)) |
### Asymptomatic or pre-symptomatic Infection
Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.

### Moderate Illness
Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.

### Severe Illness
Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%.

### Critical Illness
Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

### Intervention
Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signalling. Tocilizumab is indicated (EMEA-approved) for the treatment of:

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic arthritis in patients aged ≥2 years
- juvenile idiopathic polyarthritis in patients aged ≥2 years

Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years.

### Comparison
Any active treatment, placebo, or standard of care.

**Rationale:** Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.

### Outcomes
**Main outcome:**
- All-cause Mortality (Survival)

**Additional Outcomes:**

**Efficacy:**
- Length of hospital stay,
- Viral burden (2019-nCoV RT-PCR negativity),
- Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),
- Rates of hospitalization and of patients entering ICU,
- Duration of mechanical ventilation,
- Quality of life.

**Safety:**
- Adverse events (AE),
- Severe adverse events (SAE),
- Withdrawals due to AEs,
- Most frequent AEs,
- Most frequent SAEs.

**Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
**Study design**

| Efficacy: randomised controlled trials (RCT) |
| Safety: observational studies (comparative or single-arm prospective studies and registries) |

### 2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

#### 1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: [find the PROSPERO protocol here](http://find the PROSPERO protocol here). DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

#### Population

People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity.

SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.

#### Intervention

Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.

#### Comparison

Any active treatment, placebo, or standard of care.

#### Outcomes

All-cause mortality

Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.

#### Study design

Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

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EUnetHTA Joint Action 3 WP4
Data extraction, Risk of bias assessment, data synthesis:
Two reviewers from DEPlazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis.
The sources and search methods are described in more detail in Appendix Table 6-2.

| Population   | See project Scope |
|--------------|-------------------|
| Intervention | Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling. |
| Comparison   | Any active treatment, placebo, or standard of care. |
| Outcomes     | See project Scope |
| Study design | Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data |

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).

One researcher of NIPN extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies the Newcastle-Ottawa Scale (NOS) is used to assess the methodological rigor and applicability.

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/
Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of NIPN is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-3.

Data are presented in tabular form.
3 ABOUT THE TREATMENT

3.1 Mode of Action

Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling. IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin [4].

3.2 Regulatory Status

The Market Authorisation Holder of tocilizumab is Roche Pharma. Tocilizumab is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. Tocilizumab is indicated (EMA-approved) for the treatment of:

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic arthritis in patients aged ≥2 years
- juvenile idiopathic polyarthritis in patients aged ≥2 years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years [5].

Tocilizumab is not authorised in Covid-19 patients (EMA, FDA).

3.3 Level of Evidence

Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Patients received either TCZ IV (8 mg/kg) or SC (324 mg); (the optional second dose within 24 hours 52 of 63 patients), and all of the patients received off-label antiretroviral protease inhibitors. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO2/FiO2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison [6].

The phase III COVACTA (NCT04320615) study of tocilizumab did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab. The COVACTA study did not identify any new safety signals for tocilizumab.

The phase III REMDACTA (NCT04409262) has ended, and participants are no longer being treated. REMDACTA did not meet its primary (time from randomization to hospital discharge or “ready for discharge” up to day 28) and key secondary endpoints, which included likelihood of death, likelihood of progression to mechanical ventilation or death, and clinical status. The phase III EMPACTA...
The EMPACTA study showed that patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care were less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]). The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab arm versus 19.3% in the placebo arm. The EMPACTA study did not identify any new safety signals for tocilizumab [28].

A phase III trial involving 243 patients who require hospital but not mechanical ventilation evaluates the effects of tocilizumab compared to placebo. Tocilizumab was not effective for preventing intubation or death, the hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P = 0.64) (HR 0.83;95% confidence interval [CI], 0.38 to 1.81; P = 0.64) [11]. The TOBICRAS phase III randomized clinical trial was terminated early, after 129 patients had been enrolled, because of an increased number of deaths at 15 days in the tocilizumab group [12].

The RECOVERY trial (NCT04381936) is an ongoing randomised trial investigating whether potential treatments for COVID-19 reduce the risk of death. Participants with progressive COVID-19 may undergo an optional subsequent randomisation between tocilizumab and no additional treatment. A total of 2022 patients were randomly allocated to receive tocilizumab by intravenous infusion and were compared with 2094 patients randomly allocated to usual care alone. 82% of patients were taking a systemic steroid such as dexamethasone. Treatment with tocilizumab significantly reduced deaths: 596 (29%) of the patients in the tocilizumab group died within 28 days compared with 694 (33%) patients in the usual care group (rate ratio 0.86; [95% confidence interval [CI] 0.77 to 0.96]; p = 0.007), an absolute difference of 4%. The study also showed that tocilizumab shortens the time until patients are successfully discharged from hospital and reduces the need for a mechanical ventilator (https://www.recoverytrial.net/files/recovery-press-release-tocilizumab_final.pdf).

The ESCAPE Phase II, non-randomized, open label clinical trial (NCT04339712) has ended, results have not been peer-reviewed yet. The aim of this study was to conduct one trial of personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome (MAS) or immune dysregulation (CID). Patients with MAS and CID with increased aminotransferases were assigned to intravenous anakinra; those with CID and normal aminotransferases to tocilizumab. The primary outcome was at least 25% decrease of sequential organ failure assessment (SOFA) score and/or 50% increase of respiratory ratio by day 8; 28-day mortality, change of SOFA score by day 28; serum biomarkers and cytokine production by mononuclear cells were secondary endpoints. The primary study endpoint was met in 58.3% of anakinra-treated patients and in 33.3% of tocilizumab-treated patients (odds ratio 3.11; 95% CIs 1.29-7.73; P = 0.011). No differences were found in mortality and in SOFA score changes. Anakinra increased capacity of mononuclear cells to produce IL-6. Survivors by day 28 who received anakinra were distributed to scales of the WHO clinical progression of lower severity. Greater incidence of secondary infections was found with tocilizumab treatment.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are insufficient data from clinical trials on the use of tocilizumab in patients with COVID-19. The data currently available are presented in Table 4-1, Table 4-2, Table 4-3, Table 4-4 and Table 4-5. The currently available evidence on all-cause mortality, frequency of adverse events, duration of hospitalization, disease severity and hospital discharges is not conclusive, as there is no statistically significant association between these outcomes and the treatment with tocilizumab. For mortality, any adverse events and hospitalization, studies show a trend towards favouring standard of care over tocilizumab, whereas for severe adverse events and the progression of disease, study results tend to favour tocilizumab.
4.2 Safety evidence from observational studies

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab. In two prospective cohort studies with high risk of bias, safety evidence has been reported. In a retrospective analysis of data from 21 patients, no adverse reaction were observed during the treatment [7]. During the 10-day follow-up Toniati et al. 2020 recorded three cases of severe adverse events: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10 [8].

4.3 Ongoing studies

Several RCTs and interventional nRCTs related to tocilizumab alone or in combination therapy are currently ongoing.

4.4 Scientific conclusion about status of evidence generation

High quality evidence from ongoing RCTs are expected to assess effectiveness and safety of tocilizumab in COVID-19 patients.

Future controlled trials in patients with severe illness are needed to confirm or exclude the possibility of treatment benefit with tocilizumab.
Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab

| Outcome                                                                 | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments                                                                 |
|------------------------------------------------------------------------|--------------------------------------|--------------------------|---------------------------------|-----------------------|--------------------------------------------------------------------------|
| All-cause mortality [9]; [10]; [11]; [12]; [13]; [14]; [15]; [18]; [17]| 289 per 1000 (231 to 289)            | RR 0.90 (0.80 to 1.04)   | 6503 (9 RCTs)                   | moderate              | Compared to SoC tocilizumab probably reduces the risk of mortality       |
| Number of patients with any adverse event [9]; [12]; [13]; [14]; [17]; [18]| 505 per 1000 (449 to 702)            | RR 1.12 (0.89 to 1.39)   | 1333 (6 RCTs)                   | very low              | Compared to standard treatment could increase the number of patients with adverse events |
| Number of patients with severe adverse events [9]; [10]; [11]; [12]; [13]; [14]; [15]; [17]; [18]| 146 per 1000 (113 to 161)            | RR 0.92 (0.77 to 1.10)   | 2454 (9 RCTs)                   | moderate              | Compared to SoC tocilizumab probably reduces the risk of severe adverse events |
| Length of stay in hospital [9]; [13]; [15]| Rosas 2020: HR 1.35 [95% CI (1.02; 1.79) Salama 2020: HR 1.16 [95% CI (0.91; 1.48)] REMAP study: HR 1.41 [95% CI (1.18; 1.68)] Cumulative length of hospitalization differs between the two groups in favour of Tocilizumab (HR: 1.32 (95% CI 1.16, 1.49) p <0.0001) | (3 RCTs)              | moderate | Compared to SoC there is no effect on the number of days of hospitalization |
| Length of stay in hospital (mean days) [12]| SMD 0.42 lower (0.77 lower to 0.07 lower) |                         | 129 (1 RCT)                    | low                  | Compared to SoC there is no effect on the number of days of hospitalization |
| Progression of disease severity [10]; [11]; [14]; [16]; [17]| 160 per 1,000 (109 to 144)            | RR 0.79 (0.68 to 0.90)   | 4501 (6 RCTs)                   | moderate              | Compared to SoC tocilizumab probably reduces the risk of progression of disease severity |
| Number of patients discharged [10]; [11]; [16]| 500 per 1,000 (475 to 589)            | RR 1.06 (0.95 to 1.18)   | 4481 (3 RCTs)                   | very low              | Compared to SoC there is no effect on the number of patients discharged  |
| Duration of hospitalization in intensive care [15]| HR 1.42 (IC95% (1.18; 1.71) in favor of tocilizumab |                         | (1 RCT)1                       | moderate              | Compared to SoC tocilizumab probably reduces the number of days of hospitalization in intensive care |
### Outcome

| Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|--------------------------------------|--------------------------|----------------------------------|-----------------------|----------|
| Risk with standard of care           | Risk with tocilizumab    | RR 0.86 (0.72 to 1.04)           | 1868 (1 RCT)          | moderate | Compared to SoC tocilizumab probably reduces the risk of mortality |
| Mortality patients of moderate severity [16] | 217 per 1000 (156 to 225) | RR 0.88 (0.79 to 0.97)           | 310 per 1000 (278 to 342) | RR 0.88 (0.79 to 0.97) | 3008 (4 RCTs) | moderate | Compared to SoC tocilizumab probably reduces the risk of mortality |
| Mortality severe patients [9]; [10]; [15]; [16] | 753 per 1000 (627 to 882) | RR 0.97 (0.81 to 1.15)           | 469 per 1000 (391 to 555) | RR 0.97 (0.81 to 1.15) | 562 (1 RCT) | moderate | Compared to SoC tocilizumab probably reduces the risk of mortality |
| Mortality critical patients [16]     | 483 per 1000 (391 to 555) | RR 1.21 (0.34 to 4.36)           | 45 per 1000 (15 to 198)  | RR 1.21 (0.34 to 4.36) | 179 (1 RCT) | low | Compared to standard treatment could increase the number of patients with ARDS |
| Number of patients with respiratory failure and respiratory distress syndrome [17] | 45 per 1000 (15 to 198) | RR 1.21 (0.34 to 4.36)           | 55 per 1000 (15 to 198) | RR 1.21 (0.34 to 4.36) | 179 (1 RCT) | low | Compared to standard treatment could increase the number of patients with ARDS |

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M

**Abbreviations:** CI=Confidence interval; RR=Risk ratio

### Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab

| Outcome | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|---------|--------------------------------------|--------------------------|----------------------------------|-----------------------|----------|
| Number of patients with any adverse event [19] | 284 per 1000 (156 to 225) | RR 0.71 (0.15 to 3.50) | 400 per 1000 (278 to 342) | RR 0.71 (0.15 to 3.50) | 12 (1 RCT) | very low |
| Number of patients with serious adverse events [19] | No serious adverse event reported | RR 0.71 (0.15 to 3.50) | | No serious adverse event reported | very low |
| Number of patients with significant improvement in lung disease on CT [19] | The study reports that there was a significant difference in favour of favipiravir (P = 0.034), HR 3.16 (95% CI 0.62-16.10) | RR 0.71 (0.15 to 3.50) | | The study reports that there was a significant difference in favour of favipiravir (P = 0.034), HR 3.16 (95% CI 0.62-16.10) | very low |

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M

**Abbreviations:** CI=Confidence interval; RR=Risk ratio
### Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of favipiravir + tocilizumab

| Outcome | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|---------|--------------------------------------|--------------------------|---------------------------------|-----------------------|----------|
|         | Risk with favipiravir | Risk with favipiravir+tocilizumab | RR 2.25 (0.65 to 7.73) | 21 (1 RCT) | very low |
| Number of patients with any adverse event [19] | 286 per 1000 | 643 per 1000 | | | |
| Number of patients with serious adverse events [19] | No serious adverse event reported | | | | very low |
| Number of patients with significant improvement in lung disease on CT [19] | The study reports that the cumulative rate of lung lesion remission on day 14 was significantly higher in the combined group than in the favipiravir group (HR 2.66 95% CI [1.08-6.53], P = 0.019). | | | | very low |

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M  
Abbreviations: CI=Confidence interval; RR=Risk ratio

### Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of favipiravir + tocilizumab

| Outcome | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|---------|--------------------------------------|--------------------------|---------------------------------|-----------------------|----------|
|         | Risk with tocilizumab | Risk with favipiravir+tocilizumab | RR 1.61 (0.51 to 5.04) | 19 (1 RCT) | moderate |
| Number of patients with any adverse event [19] | 400 per 1000 | 644 per 1000 | | | |
| Number of patients with serious adverse events [19] | No serious adverse event reported | | | | very low |
| Number of patients with significant | There was no significant difference in the cumulative remission rate of lung lesions on day 14 between the combination group and the tocilizumab group HR 1.28 [95% CI 0.39-4.23] P = 0.575 | | | | very low |
### Outcome

| | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|---|---|---|---|---|---|
| Risk with tocilizumab | Risk with favipiravir+tocilizumab | |
| | | | | |
| **Improvement in lung disease on CT [19]** | | | | | |

**Source:** Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M  
**Abbreviations:** CI=Confidence interval; RR=Risk ratio

### Table 4-5 Summary of findings (SoF) table for published RCT related to effectiveness and safety of tocilizumab

| Outcome | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
|---|---|---|---|---|---|
| | Risk with sarilumab | Risk with tocilizumab | | | |
| **All-cause mortality [15]** | 208 per 1000 | 277 per 1000 (156 to 494) | RR 1.33 (0.75 to 2.37) | 401 (1 RCT) | moderate |
| | | | | | Compared to sarilumab tocilizumab probably increase the risk of mortality |
| **Number of patients with serious adverse events [15]** | 0 per 1000 (0 to 0) | 0 per 1000 (0 to 0) | RR 2.63 (0.16 to 44.48) | 401 (1 RCT) | low |
| | | | | | Compared to sarilumab tocilizumab probably increase the risk of serious adverse events |

**Source:** Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M  
**Abbreviations:** CI=Confidence interval; RR=Risk ratio
### Certainty assessment

| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | № of patients | Effect | Certainty |
|--------------|--------------|--------------|---------------|--------------|-------------|----------------------|---------------|--------|-----------|
|              |              |              |               |              |             |                      |               |        |           |

#### All-cause mortality

| № of patients | Effect | Certainty |
|---------------|--------|-----------|
| 821/3365 (24.4%) | RR 0.90 (0.80 to 1.0) | MODERATE |
| 908/3138 (28.9%) | | |
| **29 fewer per 1.000** (from 58 fewer to 0 more) | | |

#### Number of patients with any adverse event

| № of patients | Effect | Certainty |
|---------------|--------|-----------|
| 465/806 (57.7%) | RR 1.12 (0.89 to 1.39) | VERY LOW |
| 266/527 (50.5%) | | |
| **61 more per 1.000** (from 56 fewer to 197 more) | | |

#### Number of patients with severe adverse events

| № of patients | Effect | Certainty |
|---------------|--------|-----------|
| 228/1380 (16.5%) | RR 0.92 (0.77 to 1.10) | MODERATE |
| 157/1074 (14.6%) | | |
| **12 fewer per 1.000** (from 34 fewer to 15 more) | | |

#### Length of stay in hospital

| Effect | Certainty |
|--------|-----------|
| Rosas 2020: HR 1.35 [95% CI (1.02; 1.79)] | MODERATE |
| Salama 2020: HR 1.16 [95% CI (0.91; 1.48)] | |
| REMAP study: HR 1.41 [95% CI (1.18; 1.68)] | |
| Cumulatively length of hospitalization differs between the two groups in favour of Tocilizumab (HR: 1.32 (95% CI 1.16, 1.49) p <0.0001) | |
| **18.4 fewer per 1.000** (from 16 fewer to 21 more) | |
| Certainty assessment | Nº of patients | Effect | Certainty |
|----------------------|----------------|--------|-----------|
|                      | Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Monoclonal antibody Tocilizumab | Standard treatment | Relative (95% CI) | Absolute (95% CI) |           |
| Length of stay in hospital (mean days) | 1 7 | randomised trials | serious | not serious | not serious | serious 9 | none | 65 | 64 | SMD 0.42 lower (0.77 lower to 0.07 lower) | LOW |
| Progression of COVID-19 disease | 6 1,2,3,5,8,9 | randomised trials | serious | not serious | not serious | not serious | none | 302/2312 (13.1%) | 351/2189 (16.0%) | RR 0.79 (0.68 to 0.90) | MODERATE |
| Number of patients discharged | 3 2,3,8 | randomised trials | serious | very serious | not serious | not serious | none | 1292/2243 (57.6%) | 1118/2238 (50.0%) | RR 1.06 (0.95 to 1.18) | VERY LOW |
| Duration of hospitalization in intensive care | 1 6 | randomised trials | serious | not serious | not serious | not serious | none | HR 1.42 [IC95% (1.18; 1.71) in favor of tocolizumab] | MODERATE |
| Mortality patients of moderate severity | | | | | | | | | | |

*Certainty assessment: 1 = Low, 2 = Moderate, 3 = High.*

- **Progression of COVID-19 disease**: 34 fewer per 1,000 (from 51 fewer to 16 fewer).
- **Number of patients discharged**: 30 more per 1,000 (from 25 fewer to 90 more).
| Certainty assessment | Nº of patients | Effect | Certainty |
|----------------------|----------------|--------|-----------|
|                       | Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Monoclonal antibody | Tocilizumab | Standard treatment | Relative (95% CI) | Absolute (95% CI) | |
|                       | 1⁸             | randomised trials | serious k | not serious | not serious | not serious | none | 175/935 (18.7%) | 202/933 (21.7%) | RR 0.86 (0.72 to 1.04) | 30 fewer per 1.000 (from 61 fewer to 9 more) |  ⬤⬤⬤◯ MODERATE |
| Mortality severe patients |
|                       | 4¹,²,⁶,⁸       | randomised trials | serious l | not serious | not serious | not serious | none | 454/1530 (29.7%) | 521/1478 (35.3%) | RR 0.88 (0.79 to 0.97) | 42 fewer per 1.000 (from 74 fewer to 11 fewer) |  ⬤⬤⬤◯ MODERATE |
| Mortality critical patients |
|                       | 1⁸             | randomised trials | serious k | not serious | not serious | not serious | none | 125/268 (46.6%) | 142/294 (48.3%) | RR 0.97 (0.81 to 1.15) | 14 fewer per 1.000 (from 92 fewer to 72 more) |  ⬤⬤⬤◯ MODERATE |

Number of patients with respiratory failure and respiratory distress syndrome
### Certainty assessment

| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Monoclonal antibody Tocilizumab | Standard treatment | Relative (95% CI) | Absolute (95% CI) | № of patients | Effect | Certainty |
|---------------|--------------|--------------|---------------|--------------|-------------|---------------------|-----------------------------|--------------------|----------------|----------------|--------------|--------|-----------|
| 1 ⁹           | randomised trials | serious       | not serious   | not serious  | serious ⁹   | none                | 5/91 (5.5%)                 | 4/88 (4.5%)         | RR 1.21 (0.34 to 4.36) | 10 more per 1,000 (from 30 fewer to 153 more) | ⨁⨁◯◯ | LOW      |

### Explanations

- a. Downgraded of one level for performance bias at high risk in 5 studies and at unclear risk in 3 studies, unclear risk of selection bias in 3 studies, unclear risk of detection bias in 3 studies and high risk of attrition bias in one study
- b. Downgraded of one level for performance bias at high risk in 3 studies and at unclear risk in 2 studies, unclear selection bias in 3 studies, unclear detection bias in 3 studies and unclear attrition and reporting bias in one study
- c. Downgraded of two levels for high heterogeneity: $\hat{\rho}^2=69\%$
- d. Downgraded of one level for performance bias at high risk in 5 studies and at unclear risk in 3 studies, unclear selection bias in 4 studies, unclear detection bias in 3 studies and attrition bias at high risk in 1 study and unclear in 1 another study, unclear risk of reporting bias in one study
- e. Downgraded of one level for performance bias at high risk in one study and unclear in another, unclear risk of selection bias in 2 studies, unclear risk of detection bias in one study
- f. Downgraded of one level for performance bias at high risk and at unclear risk of detection bias
- g. Downgraded of one level for small sample size (<200)
- h. Downgraded of one level for performance bias at high risk in 3 studies and unclear in 2 studies, unclear risk of selection bias in 2 studies, unclear risk of detection bias in 2 studies and high risk of attrition bias in one study
- i. Downgraded of one level for performance bias at high risk in 2 studies and unclear in another
- j. Downgraded of two levels for high heterogeneity: $\hat{\rho}^2=77\%$
- k. Downgraded of one level for performance bias at high risk
- l. Downgraded of one level for performance bias at high risk in 3 studies, unclear risk of selection bias in one study and unclear risk of detection bias in one study
- m. Downgraded of one level for high risk of attrition bias and unclear risk of detection bias

### Source
[15]
## Certainty assessment

| # of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Favipiravir | Tocilizumab | Relative (95% CI) | Absolute (95% CI) | Certainty |
|--------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------|-------------|-----------------|-----------------|-----------|
| **Number of patients with any adverse event** | | | | | | | | | | | |
| 1 🔽 | randomised trials | very serious a | not serious | not serious | very serious b | none | 2/7 (28.6%) | 2/5 (40.0%) | RR 0.71 (0.15 to 3.50) | 116 fewer per 1.000 (from 340 fewer to 1.000 more) | ◆ ◆ ◆ ◆ VERY LOW |

| **Number of patients with serious adverse events** | | | | | | | | | | | |
| 1 🔽 | randomised trials | very serious a | not serious | not serious | very serious b | none | No serious adverse event reported | | | | ◆ ◆ ◆ ◆ VERY LOW |

| **Number of patients with significant improvement in lung disease on CT** | | | | | | | | | | | |
| 1 🔽 | randomised trials | very serious a | not serious | not serious | very serious b | none | The study reports that there was a significant difference in favour of favipiravir (P = 0.034), HR 3.16 [95% CI 0.62-16.10] | | | | ◆ ◆ ◆ ◆ VERY LOW |

### Explanations

a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias

b. Downgraded of two levels for very small sample size

**Source:** [17]
### Certainty assessment

| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Favipiravir+Tocilizumab | Tocilizumab | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|--------------|--------------|---------------|---------------|-------------|---------------------|-------------------------|-------------|-----------------|-----------------|-----------|-----------|
| 1 ^ randomised trials | very serious | not serious | not serious | very serious | none | 9/14 (64.3%) | 2/7 (28.6%) | RR 2.25 (0.65 to 7.73) | 357 more per 1.000 (from 100 fewer to 1.000 more) | \(\bigotimes\) \(\bigodot\) \(\bigodot\) \(\bigodot\) VERY LOW |

### Number of patients with any adverse event

- **Number of patients with serious adverse events**
  - 1 ^ randomised trials
  - very serious
  - not serious
  - not serious
  - very serious
  - none
  - No serious adverse event reported
  - \(\bigotimes\) \(\bigodot\) \(\bigodot\) \(\bigodot\) VERY LOW

- **Number of patients with significant improvement in lung disease on CT**
  - 1 ^ randomised trials
  - very serious
  - not serious
  - not serious
  - very serious
  - none
  - The study reports that the cumulative rate of lung lesion remission on day 14 was significantly higher in the combined group than in the favipiravir group (HR 2.66 95% CI [1.08-6.53], P = 0.019).
  - \(\bigotimes\) \(\bigodot\) \(\bigodot\) \(\bigodot\) VERY LOW

### Explanations

- a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias
- b. Downgraded of two levels for very small sample size

### Source

[17]
| Certainty assessment | No of patients | Effect |
|----------------------|----------------|--------|
|favipiravir+tocilizumab | 9/14 (64.3%) | RR 1.61 (0.51 to 5.04) |
|tocilizumab | 2/5 (40.0%) | 244 more per 1,000 (from 196 fewer to 1,000 more) |

Number of patients with serious adverse events

| Certainty assessment | No of patients | Effect |
|----------------------|----------------|--------|
|Tocilizumab | 1 | No serious adverse event reported |

Number of patients with significant improvement in lung disease on CT

| Certainty assessment | No of patients | Effect |
|----------------------|----------------|--------|
|Tocilizumab | 1 | There was no significant difference in the cumulative remission rate of lung lesions on day 14 between the combination group and the tocilizumab group HR 1.28 [95% CI 0.39-4.23] P = 0.575 |

Explanations

a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias
b. Downgraded of two levels for very small sample size
Source [16]

| Certainty assessment | No of patients | Effect |
|----------------------|----------------|--------|
|tocilizumab | 1 | Number of patients with serious adverse events |
|sarilumab | 1 | All-cause mortality |
|RR 1.33 (0.75 to 2.37) | 69 more per 1,000 (from 52 fewer to 285 more) |
### Certainty assessment

| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tocilizumab  | Sarilumab  | Relative (95% CI) | Absolute (95% CI) | Certainty |
|---------------|--------------|--------------|---------------|--------------|-------------|----------------------|--------------|------------|------------------|-------------------|-----------|
| 1             | randomised trials | serious $^a$ | not serious | not serious | serious $^b$ | none | 9/353 (2.5%) | 0/48 (0.0%) | RR **2.63** (0.16 to 44.48) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | LOW |

**Explanations**

a. Downgraded of one level for high risk of performance bias  
b. Downgraded of one level for wide CI

**Source:** [15]
Table 4-6 Study characteristics of included RCTs

| Author, year, reference number/Study name/Study ID | Study design, study phase | Centres (single centre or multicentre), country, setting | Patient population (number of included patients/ Mean age and sex/ Disease severity) |
|-------------------------------------------------|--------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|
| Rosas et al 2020 [9] COVACTA NCT04320615        | randomized, double-blind, placebo-controlled, phase 3 | global, multicenter | 452 patients TCZ: age mean (SD) 60.9 (14.6) 69.7% male placebo: age mean (SD) 60.6 (13.7); 70.1% male; severe |
| Salvarani et al 2020 [10] NCT04346355           | open-label, randomized clinical trial, phase 2          | multicenter, Italy | 126 patients median (range) age of 60.0 (53.0-72.0) years 61.1% male |
| Stone et al 2020 [11] NCT04356937                | randomized, double-blind, placebo-controlled phase 3 trial | multicenter, United States | 243 patients; median age 59.8 years (range, 21.7 to 85.4); 58% male |
| Salama et al 2020 [13] EMPACTA NCT04372186      | randomized, double-blind, placebo-controlled phase 3 trial | global, multicenter | 389 patients TCZ: 60.2% male; mean (± SD) age 56.0 ±14.3 years placebo:57% male; mean (± SD) age 55.6 ±14.9 years |
| Hermine et al 2020 [14] NCT04331808              | cohort-embedded, investigator-initiated, open-label, bayesian randomized phase 2 clinical trial | multicenter, France | 131 patients median (IQR) age was 64 (57.1–74.3) years 68% male moderate, severe |

**Inclusion criteria**

18 years or older with severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test

18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test; acute respiratory distress syndrome

19 to 85 years of age with COVID-19 pneumonia confirmed by positive polymerase chain reaction test; requiring hospital but not mechanical ventilation

18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test

18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test

**Exclusion criteria**

progression to death is imminent and inevitable within the next 24 hours; active tuberculosis or bacterial, fungal, or viral infection

ICU admission, known hypersensitivity to tocilizumab, and any condition preventing future admission to ICU, such as advanced age with multiple comorbidities, as well as the patient’s expressed will to avoid future intubation

Uncontrolled bacterial, fungal, or non-COVID viral infection, active TB

progression to death is imminent and inevitable within the next 24 hours; active tuberculosis or bacterial, fungal, or viral infection

acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, hematological diseases, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected

**Intervention (generic drug name and**

tocilizumab infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose TCZ: 8 mg/kg up to a maximum of 800 mg),

TCZ: 8 mg per kilogram of body weight administered

TCZ 8 mg/kg, maximum 800 mg

TCZ 8 mg/kg, maximum 800 mg +standard care per local practice
| Author, year, reference number/Study name/Study ID | dosage, time frame; number of randomized/enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19 | Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19) | Primary Outcome(s) | Patient-relevant secondary outcome(s) |
|-------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|-------------------|----------------------------------|
| Rosas et al 2020 [9] COVACTA NCT04320615 | 800 mg; up to 1 additional dose may be given if clinical symptoms worsen or show no improvement | placebo | clinical status on a 7-category ordinal scale at day 28 | clinical status at day 14 on the 7-category ordinal scale, mortality at day 28, ventilator-free days to day 28, time to |
| Salvarani et al 2020 [10] NCT04346355 | followed by a second dose after 12 hours | supportive care following the treatment protocols of each center | clinical worsening within 14 days since randomization | evaluation of the efficacy of early vs late administration of tocilizumab in admission to ICU with mechanical |
| Stone et al 2020 [11] NCT04356937 | intravenously, not to exceed 800 mg | placebo | intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo | clinical worsening, discontinuation of supplemental oxygen, time to hospital discharge or ready for discharge; time to a ≥2 category improvement in |
| Salama et al 2020 [13] EMPACTA NCT04372186 | | placebo+standard care per local practice | cumulative proportion of patients requiring mechanical ventilation | clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to |
| Hermine et al 2020 [14] NCT04331808 | | placebo+standard care per local practice | >5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of ventilation at day 14 | |
| Author, year, reference number/Study name/Study ID | Rosas et al 2020 [9] COVACTA NCT04320615 | Salvarani et al 2020 [10] NCT04346355 | Stone et al 2020 [11] NCT04356937 | Salama et al 2020 [13] EMPACTA NCT04372186 | Hermine et al 2020 [14] NCT04331808 |
|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Study characteristics | Improvement from baseline in ≥2 categories on the 7-category ordinal scale, and time to hospital discharge | Ventilation, mortality, and tocilizumab toxic effects | Clinical status; time to clinical failure; mortality rate | Oxygen supply independency, biological factors such as C-reactive protein level, and adverse events. |
| Follow-up (days, months) | 60 days | 30 days | 28 days | 60 days | 90 days |
| Sponsor/ lead institution | Hoffmann-La Roche | Azienda Unità Sanitaria Locale Reggio Emilia | Massachusetts General Hospital | Genentech, Inc. | Assistance Publique - Hôpitaux de Paris |

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19*

**Table 4-7 Study characteristics of included RCTs, continued**

| Author, year, reference number/Study name/Study ID | Gordon et al 2021 [15] REMAP-CAP | Veiga et al. 2021 [12] TOCIBRAS | Horby et al. 2021 [16] RECOVERY | Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India | Wang et al 2020 [18] ChiCTR2000029765 | Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894 |
|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Study design, study phase | Phase IV randomized, open label; multifactorial, adaptive platform trial | Prospective, randomized, superiority, open-label, controlled trial | Phase 2 and 3 randomized, open label; factorial assignment | Open-label, multicentre, randomised, controlled, phase 3 trial | Randomized controlled phase 4 trial | Single-arm, open-label, phase 2 |
| Centres (single centre or multicentre), country, setting | International | Multicenter, Brazil | Multicenter UK | Multicenter India | Multicenter, China | Multicentre China |
| Patient population (number of included patients/ Mean age and) | 353 (toc vs. sarilumab) patients critically ill COVID-19. | 129 patients mean age 57 (SD 14) years; 68% men | 4116 patients mean age 63.6 years (SD 13.7) | 180 patients median age (IQR) 56 (47–63), SoC:54 (43–63) Male 84%; SoC: 86% | 65 patients | 26 patients; median 73.5 years (34–89) 53.8 % (14/26) male Common, severe or critical |

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### Author, year, reference number/Study name/Study ID

| Gordon et al 2021 [15] REMAP-CAP | Veiga et al. 2021 [12] TOCIBRAS | Horby et al. 2021 [16] RECOVERY | Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India | Wang et al 2020 [18] ChiCTR200029765 | Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894 |
|----------------------------------|---------------------------------|---------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|

### sex/ Disease severity (*

| mean age 61.5 (SD: 12.5) years; 73.9% male |

### Inclusion criteria

| Critically ill, >18 years, with Covid-19, admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support |
| severe or critically ill need for oxygen supplementation less than 24 hours before the randomization positive inflammatory tests |
| clinical evidence of progressive COVID-19 |
| moderate to severe COVID-19 |
| 18 to 85 years; diagnosed with the common type of NCP (including severe risk factors) and severe cases of new coronavirus pneumonia |
| Laboratory-confirmed cases according to Chinese guidelines of COVID-19; Male or female more than 18 years old; Increased interleukin-6; Sign the informed consent |

### Exclusion criteria

| presumption that death was imminent with lack of commitment to full support, and prior participation in REMAP-CAP within 90 days. |
| need for mechanical ventilation for 24 hours or more before the randomization active uncontrolled infection liver disease, cirrhosis or elevated AST or ALT above 5 times the upper level limit renal disease with estimate glomerular filtration below 30 mL/min/1.72 m² |
| contra-indication to tocilizumab |
| contra-indication to tocilizumab |
| pregnant or lactating women; 3. ALT / AST> 5 ULN, neutrophils <0.5, platelets less than 50; diagnosis of rheumatic immune-related diseases; active pulmonary tuberculosis, with definite bacterial and fungal infections. |
| Allergic to favipiravir or tocilizumab; Pregnant or lactating woman; ALT or AST > 5 times of upper limit of normal; Patients with active hepatitis, tuberculosis, and definite bacterial or fungal infections; Other conditions judged by the investigators. |

### Intervention (generic drug name and dosage, time frame; number of randomized/enrolled patients in subgroups - Mild, Moderate, Severe)

| tocilizumab single intravenous administration 8mg/Kg |
| TCZ 8 mg/kg, maximum 800 mg +standard care |
| TCZ 8 mg/kg, maximum 800 mg |
| a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg+ additional dose (optional) |
| TCZ 400 mg +standard care per local practice |
| tocilizumab+favipiravir |

Favipiravir: On the 1st day, 1600mg twice a day; from the 2nd to the 7th day, 600mg twice a day. Oral administration, the maximum number of days taken is not more than 7 days. Tocilizumab: The first IV dose is 4 ~ 8mg/kg and the recommended dose.
### Severe, Critical COVID-19)

| Author, year, reference number/Study name/Study ID | Gordon et al 2021 [15] REMAP-CAP | Veiga et al. 2021 [12] TOCIBRAS | Horby et al. 2021 [16] RECOVERY | Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India | Wang et al 2020 [18] ChiCTR2000029765 | Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894 |
|--------------------------------------------------|----------------------------------|---------------------------------|---------------------------------|--------------------------------------------------------------------------------|--------------------------------------|--------------------------------------|
| Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19) | sarilumab single iv administration 400mg | standard care | usual care | standard care | placebo+standard care per local practice | favipiravir (mild n=0; common/moderate n=2; severe n=3; critical n=0) |
| Primary Outcome(s) | an ordinal scale combining in-hospital mortality and days free of organ support to day 21 | clinical status measured at 15 days using a seven level ordinal scale | all-cause mortality | proportion of patients with progression of COVID-19 from moderate to severe or from severe to death up to day 14 | cure rate | cumulative lung lesion remission rate |

is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. (mild n=0; common/moderate n=8; severe n=5; critical n=1) tocilizumab (mild n=0; common/moderate n=2; severe n=5; critical n=0)
| Author, year, reference number/Study name/Study ID | Gordon et al 2021 [15] REMAP-CAP | Veiga et al. 2021 [12] TOCIBRAS | Horby et al. 2021 [16] RECOVERY | Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India | Wang et al 2020 [18] ChiCTR2000029765 | Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894 |
|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|---------------------------------------------------------------------------------|----------------------------------|----------------------------------|
| **Patient-relevant secondary outcome(s)** | all-cause mortality; hospital mortality; Health-related Quality of life assessment, EQ5D-5L and WHODAS 2.0 | all-cause mortality; hospital mortality; improvement of SOFA scale; ventilator free days | duration of hospital stay; composite endpoint of death or need for mechanical ventilation or ECMO | improvement of cytokine release syndrome; ventilator-free days; organ failure-free days; ICU-free days; time to clinical improvement according to COVID-19 grade; time to hospital discharge; mortality | mortality; ventilator utilization; hospitalization day | improvement of clinical symptoms; the changes of blood routine test and IL-6; changes of oxygen therapy |
| **Follow-up (days, months)** | 90 days | 29 days | 28 days and up to 6 months | 28 days | 3 months |
| **Sponsor/lead institution** | MJM Bonten, UMC Utrecht | Beneficência Portuguesa de São Paulo | University of Oxford | Medanta Institute of Education and Research, Roche India, Cipla India, and Action COVID-19 India | The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital) | Peking University First Hospital |

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19*
## Table 4-8 Summary of safety from observational studies (AE and SAE) of tocilizumab

| Author, year       | Country | Sponsor/lead institution                                                                 | Intervention/Product (drug name)                                                                 |
|--------------------|---------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Xu et al 2020 [7]  | China   | Departme nt of Science and Technolo gy of Anhui Province and Health Commissi on of Anhui Province China National Center for Biotechnolog y Developm ent 175 | tocilizumab tocilizumab/ lopinavir/ritonavir; INF-α; ribavirin; tocilizumab/ tocilizumab + methylprednisolone |
| Luo et al 2020 [21]| China   | Zhongfaxin cheng campus of Tongji Hospital                                                  | tocilizumab/ tocilizumab + standard pharmacological protocol                                    |
| Tonia ti et al 2020 [8]| Italy | National Institutes of Health Centers for Disease Control and Prevention American Society for Transplantation and Cellular Therapy New Investigator Award | tocilizumab + standard pharmacological protocol                                                  |
| Sомерs et al 2020 [23]| USA    | Centre Hospitalier Intercommunal Robert Ballanger Groupe Hospitalier Pitie-Salpetriere    | tocilizumab + steroid or vasopressors or hydroxychloroquine and azithromycin                   |
| Rossi et al 2020 [24]| France | n.a.                                                                                     | tocilizumab and/or methylprednisolone + SOC                                                     |
| Petrok et al [25]    | Italy   | n.a.                                                                                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Mikulska et al. [26]| Iran    | n.a.                                                                                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Malekzadeh et al. [27]| Italy | AryoGen Co., Iran                                                                        | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Perrone et al. [28]   | Italy   | National Cancer Institute, Naples                                                         | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Di Niso et al 2020 [29]| Italy | n.a.                                                                                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Sciascia et al 2020 [6]| USA    | ASL Città di Torino                                                                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Price et al 2020 [31]| USA    | The Yale School of Medicine Institutional Review Board (2000027 792)                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Antony et al 2020 [32]| USA    | The Yale School of Medicine Institutional Review Board (2000027 792)                     | tocilizumab + tocilizumab + methylprednisolone + SOC                                             |
| Dosage | 4-8 mg/kg max 800 mg | n.a. | 8 mg/kg max 800 mg | 8 mg/kg max 800 mg | 400 mg | 4 mg/kg max 800 mg | 8 mg/kg max 800 mg, methylprednisolone 1 mg/kg for 5 days intravenously, then 0.5 mg/kg for 5 days | sc 324 mg tocilizumab b <100 kg; ≥100 kg 486 mg + SOC | 2 doses of TCZ 8 mg/kg (up to a maximum of 800 mg per dose), with an interval of 12 hours | sc 324 mg tocilizumab b + SOC | sc 324 mg, iv 8 mg/kg max 800 mg tocilizumab | iv 8 mg/kg tocilizumab | TCZ 4 mg/kg/d ay q12hr |
|--------|----------------------|------|-------------------|-------------------|--------|-------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| Comparator | n.a. | n.a. | n.a. | standard pharmacological protocol | standard pharmacological protocol | n.a. | standard pharmacological protocol | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Study design | observational | observational | observational | observational | observational | observational | observational | observational | observational | observational | observational | observational |
| Setting | hospital | hospital | hospital | hospital | hospital | hospital | hospital | hospital | hospital | hospital | hospital | hospital |
| Number of pts | 21 | 15 | 100 | 154 | 246 | 145 | 196 | 126 | 301 | 70 | 63 | 239 | 80 |
| Inclusion criteria | patients with severe and critical COVID-19 | patients infected with COVID-19 | patients admitted to Michigan Medicine from March 9 - April 20, 2020 for severe COVID-19 pneumonia, required invasive mechanical ventilation | patients hospitalized with COVID-19 | patients hospitalized with COVID-19 | COVID-19 pneumonia | severe or critical COVID-19 | patients hospitalized with COVID-19 | COVID-19 pneumonia | patients infected with COVID-19 | COVID-19 pneumonia | patients infected with COVID-19 | patients infected with COVID-19 | patients infected with COVID-19 oxygen supplement of >3L, pneumonia severity index score ≤130 |
| Exclusion criteria                                                                 | Intubated % (yrs) | Intubated % (IQR) | Intubated % (range) | Intubated % (median) | Intubated % (n.a.) |
|-----------------------------------------------------------------------------------|-------------------|-------------------|---------------------|----------------------|-------------------|
| active pulmonary tuberculosis combined with clear bacterial infection and fungal infection | 56.8±16.5 (25–88) | 62 (IQR 57–71) | 58±14.9 | 67.6 ±15.3 | 58.1 |
| contraindication to TCZ, suspected or confirmed bacterial infection, an active diverticulitis or GIT perforation, neutropenia, thrombocytopenia | <16 years intubated for conditions unrelated to COVID-19, enrolled into a RCT for sarilumab | missing data | n.a. | n.a. | n.a. |
| lack of consent of palliative care patients | intubated treated with remdesivir pregnancy | hyper sensitivity to TCZ, history of infection HBV, HCV, HIV, hepatic disorders, bone marrow suppression, active peptic ulcer, diverticulitis, or any other GI disorders that increase the risk of GI perforation, pregnant, breast-feeding, any concurrent active infection other than COVID-19, and severe renal impairment | contraindicated TCZ, ALT/AST > 5 times the upper limit of the normality, neutrophil count < 500/mmc, platelets < 50,000/mmc, bowel diverticulitis or perforation | suspected or confirmed concomitant bacterial or fungal systemic infection, active diverticulitis or GIT perforation | n.a. | n.a. | mechanic ally ventilated patients, end-stage comorbid conditions, such as cardiomyopathy, cardiac arrhythmia, cancer, septic shock, end-stage renal disease |

**Age of patients (yrs)**

| Age of patients (yrs) | 56.8±16.5 (25–88) | 73 (62-80) | 62 (IQR 57–71) | 58±14.9 | 67.6 ±15.3 | 58.1 |
|-----------------------|-------------------|------------|----------------|---------|-------------|------|
| ≤ 60: 122 (40.5%) | 61-70: 107 (35.5%) | 71+: 72 (23.9%) | median 55 (20–85) years | median 60 (IQR 52, 75) | n.a. | n.a. |
| median 63 (51–72) |
## Disease severity

| Disease severity | severe | moderate/severe | severe | severe | severe | severe | severe | severe | severe | severe | severe | severe |
|------------------|--------|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Follow-up (months) | Hospitalization days (range) 15.1–5.8 (10–31) | 1 week after tocilizumab therapy | 10-day follow-up | Median follow-up 47 days (28–67) | 28-day maximum follow-up | 15.3 days length of hospital stay | median follow-up of 53 days (range 4–70, interquartile range 33–57) | median 8 days (5–12) | up to 30 days | 35 days | 14 days | ≥21 days | 6 days |

### Loss to follow-up, n (%)

|                  | 0 | 0 | 0 | 0 | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |

### RoB

|                  | high | high | high | high | high | high | high | high | high | high | high | high | high |

## Safety – Outcomes*

| Overall AEs, n (%) | n.a. | n.a. | 100% | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
|-------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Serious AE (SAE), n (%) | 0% | n.a. | 3% | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Most frequent AEs n (%) | n.a. | n.a. | 100% | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Most frequent SAEs, n (%) | n.a. | n.a. | 3% | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| AEs of special interest, n (%) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Death as SAE, n (%) | n.a. | n.a. | 2% | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Withdrawals due AEs, n (%) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |

* by arms, if available, (Robins-I):
https://training.cochrane.org/handbook/current/chapter-25

**Abbreviations:** CI=Confidence interval; RR=Risk ratio
### Table 4-9 Ongoing trials of single agent tocilizumab

| Trial Identifier/registry ID(s)/contact | Study design, study phase | Recruitment status | Number of Patients, Disease severity* | Setting (hospital, ambulatory,..) | Intervention drug name and dosage | Comparator (drug name and dosage) |
|---------------------------------------|---------------------------|--------------------|---------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| ChiCTR2000029765 TOCIVID-19          | Phase 4 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). RCT parallel | Recruiting         | 198 severe                            | Hospital                          | tocilizumab, n.a.                  | conventional therapy, n.a.        |
| NCT04317092 TACOS                    | Phase 2 Multicenter single-arm, open-label, phase 2 study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia non randomized | Recruiting         | 301 n.a.                              | Hospital                          | tocilizumab 2 doses of TCZ 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours | n.a.                              |
| NCT04306705 EMPACTA                  | A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19 retrospective | Active, not recruiting | target sample size: 120 n.a.          | Hospital                          | tocilizumab or CRRT (continuous renal replacement therapy) or SoC | n.a.                              |
| NCT04315480                          | Phase 2 Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 (COVID-19) Infection With Severe Multifocal Interstitial Pneumonia non randomized, single arm | Recruiting         | 38 severe                             | Hospital                          | tocilizumab single intravenous administration 8mg/Kg | n.a.                              |
| NCT04372186 REMAP-CAP                 | Phase III A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia RCT parallel | Recruiting         | 379 n.a.                              | Hospital                          | tocilizumab 8 mg/kg IV (max 800 mg) + SOC | placebo+SOC, sarilumab single iv administration 400mg |
| NCT02735707 RECOVERY                  | Phase IV randomized, open label; international, multifactorial, adaptive platform trial | Recruiting         | 353 (toc vs, sarilumab) patients critically ill COVID-19. | Hospital                          | tocilizumab single intravenous administration 8mg/Kg | sarilumab single iv administration 400mg |
| NCT04381936 RECOVERY                  | Phase 2 and 3 randomized, open label; factorial assignment | Recruiting         | 2022 severe participants with progressive COVID-19 | hospital                          | tocilizumab 8 mg/kg IV (max 800 mg). | no additional treatment |
| NCT04871854                           | Phase 2 randomized, open label; factorial assignment | Recruiting         | 60 severe, breast cancer patients and non cancer patients | hospital                          | tocilizumab n.a.                  | n.a.                              |
| Trial Identifier/registry ID(s)/contact | Primary Outcomes                                                                 | Sponsor/ lead institution, country (also country of recruitment if different) |
|--------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| ChiCTR2000029765                      | cure rate mortality; ventilator utilization; hospitalization day                   | The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital) China |
| NCT04317092 TOCIVID-19               | Lethality rate two weeks / one month after registration                           | National Cancer Institute, Naples Italy                                          |
| NCT04306705 TACOS                    | Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14 | Tongji Hospital China                                                             |
| NCT04315480                          | arrest in deterioration of pulmonary function; improving in pulmonary function; need of oro-tracheal intubation; death | Università Politecnica delle Marche Italy                                         |
| NCT04372186 EMPACTA                 | Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28 | Genentech, Inc. USA, Brazil, Kenya, Mexico, Peru, South Africa                   |
| NCT02735707 REMAP-CAP                | respiratory and cardiovascular organ support-free days up to day 21               | MJM Bonten, UMC Utrecht                                                         |
| NCT04381936 RECOVERY                 | all-cause mortality                                                               | University of Oxford                                                             |
| NCT04871854                          | Overall survival (OS) and progression free survival after treatment of tocilizumab | Beni-Suef University                                                             |

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
## Table 4-10 Ongoing trials of combination therapies tocilizumab

| Trial Identifier | Study design, study phase | Recruitment status | Number of Patients, Disease severity | Setting (hospital, ambulatory,..) | Intervention drug name and dosage | Comparator (drug name and dosage) |
|------------------|---------------------------|--------------------|-------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| NCT04332094      | Phase 2, Pilot, Randomized, Multicenter, Open-label RCT parallel, open label | Recruiting         | 276 patients Severity 3-4 according to the WHO 7-point ordinal scale | hospital                       | tocilizumab, hydroxychloroquine, azithromycin | hydroxychloroquine, azithromycin |
| NCT04424056      | Phase 3 open label randomized therapeutic trial RCT parallel, open label | Not yet recruiting | 216 patients COVID19 infection pneumonia at stage 2b or advanced stage 3 | hospital                       | anakinra +/- ruxolitinib, tocilizumab +/- ruxolitinib | standard of care |
| NCT04310228      | Not Applicable Phase, Multicenter, RCT parallel, open label | Recruiting         | 150 patients n.a. severe COVID-19 infection | hospital                       | favipiravir + tocilizumab 8mg/kg/dose + Therapeutic dosage heparin | favipiravir, tocilizumab |
| NCT04600141      | Phase III, Parallel Assignment RCT parallel, open label | Not yet recruiting | 342, critical ill | hospital                       | tocilizumab (iv 8mg/kg/dose) tocilizumab+anakinra (100 mg for 28 days) anakinra anakinra+siltuximab (iv 11 mg/kg) siltuximab | tocilizumab |
| NCT04330638 COV-AID | Phase III; randomized, open label | Recruiting         | 150 patients severe COVID-19. | hospital                       | Heparin - Therapeutic dosage (Group 1) and Heparin - Prophylactic | Heparin |
| NCT04678739      | Phase III; randomized, open label | Active, not recruiting | 150 patients severe COVID-19. | hospital                       | usual care | Treatment as given without Remdesivir and Tocilizumab |
| NCT04779047      | Phase 4 randomized, open label | Recruiting         | 150 patients n.a. | hospital                       | remdesivir iv 200 mg at day 1 then 100 mg once daily for 5 days and tocilizumab 800 mg once | hydroxychloroquine 400 mg twice daily at day 1 then 200 mg twice daily for 5 days and tocilizumab 800 mg once |
### Trial Identifier

| Identifier | NCT04332094 | NCT04424056 | NCT04310228 | NCT04600141 | NCT04330638 COV-AID | NCT04678739 | NCT04779047 |
|------------|-------------|-------------|-------------|-------------|---------------------|-------------|-------------|
| **Primary Outcomes** | | | | | | | |
| in-hospital mortality | ventilation free days at D28 | Clinical cure rate | Proportion of patients with clinical improvement in 30 days | Time to clinical improvement | Time to clinical improvement | Duration of ICU Stay; Mortality Rate; Time to Recovery, Hospital stay | percentage of clinical cure |

**Sponsor/lead institution, country (also country of recruitment if different)**

| Sponsor/lead institution, country (also country of recruitment if different) | Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Spain | Assistance Publique Hopitaux De Marseille, France | Peking University First Hospital, China | University of Sao Paulo, Brazil | University Hospital, Ghent, Belgium | M Abdur Rahim Medical College and Hospital | October 6 University |

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19*
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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were searched in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).
### Table 6-1 Search strategy to identify randomised controlled studies

| Database | URL                      | Search line / Search terms                                                                                                                                                                                                 | Date of search |
|----------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Pubmed   | pubmed.ncbi.nlm.nih.gov  | 1. ((((("Coronavirus"[Mesh]) OR coronavirus*[Title/Abstract]) OR Coronavirus*[Title/Abstract]) OR Coronavirus*[Title/Abstract]) OR Coronavirus*[Title/Abstract]) OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan*[Title/Abstract] OR "2019-nCoV*[Title/Abstract] OR 2019nCoV*[Title/Abstract] OR nCoV2019*[Title/Abstract] OR "nCoV-2019*[Title/Abstract] OR "COVID-19*[Title/Abstract] OR COVID19*[Title/Abstract] OR "CORVID-19*[Title/Abstract] OR CORVID19*[Title/Abstract] OR "WN-CoV*[Title/Abstract] OR WNCov*[Title/Abstract] OR "HCoV-19*[Title/Abstract] OR HCoV19*[Title/Abstract] OR CoV*[Title/Abstract] OR 2019 novel*[Title/Abstract] OR Ncov*[Title/Abstract] OR "n-cov*[Title/Abstract] OR "SARS-CoV-2*[Title/Abstract] OR "SARSCoV-2*[Title/Abstract] OR "SARSCoV2*[Title/Abstract] OR "SARS-CoV-2*[Title/Abstract] OR "SARS-Cov19*[Title/Abstract] OR "SARSCov-19*[Title/Abstract] OR "SARS-Cov-19*[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorno*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract]) OR (((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*)) [Title/Abstract] OR "seafood market*[Title/Abstract] OR "food market*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR "severe acute respiratory syndrome*[Title/Abstract]) OR ((corona*[Title/Abstract] OR corono*[Title/Abstract] AND (virus*[Title/Abstract]) OR viral*[Title/Abstract] OR virinae*[Title/Abstract])) AND (((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab]) OR (placebo [tiab]) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab]) OR (trial [ti])) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp]) | 03/05/2021      |
| Database | URL | Search line/ Search terms | Date of search |
|----------|-----|----------------------------|----------------|
| Ovid MEDLINE(R) (ALL) | ovidsp.dc2.ovid.com | 1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or viirinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirusae* or Coronavirus* or Coronavirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or COVID-19 or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov*" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-CoV-19" or "SARS-CoV-19" or Ncovor or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current" | 03/05/2021 |
| OVID EMBASE | ovidsp.dc2.ovid.com | 1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or ("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or (Corona virinae19 or "Corona virinae2019" or "corona virus2019" or "corona virus2019" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2") | 03/05/2021 |
| | | or/1-3 | 4. | 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribute$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current" |
6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [33],[34]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in table 6.2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated along with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

Table 6.2 Search strategy to identify observational studies

| Database | URL | Search terms / Search modality | Date of search | Hits retrieved |
|----------|-----|--------------------------------|----------------|---------------|
| Embase  | Ovid | 1
1974 to 2021 | MEDLINE(R) ALL 1946 to 2021 | Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase | From 06/04/2021 until 03/05/2021 | 1032 |
|          | MEDLINE(R) ALL 1946 to 2021 | 2
|          | MEDLINE(R) ALL 1946 to 2021 | (((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncv19-19 or 2019-novel CoV or sars-cov2 or sars-cov2 or sarccov2 or sarccov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 19 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] | | |
or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh.dj.) use oemedz [COVID-19 in Embase]

3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacasedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use oemedz [MeSH-terms for drugs in MEDLINE]

4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamostat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use oemedz [Emtree-terms for drugs in Embase]

5 (((convalescent adj (plasma or sera or serum)) or serothep* or (((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or rituximab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamostat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or (interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kinera) or (alunacasedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favip/avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novafenon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or llars) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?- vitamin?) adj4 (high-dose* or highdose or supplement*)) or (ivermect* or MK-933 or MK933)).mp,bt,ot,du,dy,t,n.nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase]

6 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041 OR 2021042 OR 2021043 OR 202105).dt. use oemedz [time limits in MEDLINE]

7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041 OR 2021042 OR 2021043 OR 202105).dt. use oemedz [time limits in MEDLINE]
6.3 Search strategy to identify ongoing studies

NIPN is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and tocilizumab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

| Database               | URL                              | Search line / search terms                                                                 | Date of search | Hits retrieved |
|------------------------|----------------------------------|-------------------------------------------------------------------------------------------|----------------|----------------|
| ClinicalTrials.gov     | https://clinicaltrials.gov/      | “Basic search mode”** Terms used at “condition or disease”: covid19 Terms used at “other terms”: tocilizumab Actemra | 07/05/2021     | 56 2 new      |
| ISRCTN                 | https://www.isrctn.com/          | Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra | 07/05/2021     | 3 0 new       |
| European Clinical Trials Registry | https://www.clinicaltrialsregister.eu/ | Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra | 07/05/2021     | 35 0 new      |

* In Basic Search mode, one term was added to the field “condition or disease” and one term in the field “other terms”.
6.4 Flow diagrams

![Flow diagram depicting the selection process of RCTs]

12.206 records
PubMed (3596); Ovid MEDLINE(R) (3666), Ovid Embase(4526), LOVE Platform (416)

80 records identified through other sources, including Cochrane Covid-19 study register, international trial registries, medRxiv, bioRxiv, arXiv, EuropePMC preprint server, and industry websites

12,055 excluded
3151 because of title and abstract
8904 because study duplicate

151 full-text articles assessed for eligibility

55 excluded
5 comparison not fulfilling eligibility criteria
15 population not fulfilling eligibility criteria
17 outcomes not fulfilling eligibility criteria
4 no useful data
7 study design
6 type of intervention not included

96 published studies selected for inclusion
49 preprint selected for inclusion

145 randomised controlled trials included in quantitative synthesis*
- 10 RCTs comparing tocilizumab with standard of care
- 1 RCTs comparing tocilizumab with favipiravir
- 1 RCTs comparing tocilizumab with sarilumab
- 133 RCTs comparing other active substances not relevant to this report with control*

31 excluded
16 study design not fulfilling eligibility criteria
5 intervention not fulfilling eligibility criteria
1 comparison not fulfilling eligibility criteria
9 outcomes not fulfilling eligibility criteria

Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs
RCT = randomised controlled trial;
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
**studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews