**Research Paper** 

# Association between tocilizumab treatment and clinical outcomes of COVID-19 patients: a systematic review and meta-analysis

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# ABSTRACT

To explore and summarize the association between treatment with tocilizumab and clinical outcomes in COVID-19 patients. We performed a systematic review and meta-analysis (10 RCTs including 3378 patients in the tocilizumab group and 3142 patients in the control group). We systematically searched PubMed and MedRxiv for all RCTs as of June 1, 2021, to assess the benefits and harms of tocilizumab to treat patients with COVID-19. All analyses were carried out using RevMan version 5.4.1. There were nine RCTs published in peer-reviewed journals and one RCTs published as a preprint. The summary RR for all-cause mortality with tocilizumab was 0.89 (95% CI= 0.82-0.96, P= 0.003). There was no significant between-trial heterogeneity ( $l^2=$  28%, P= 0.19). However, all peerreviewed RCTs showed no significant associations between treatment with tocilizumab and reductions in all-cause mortality. We notably found that tocilizumab significantly reduced the rate of intubation or death in patients with COVID-19 with 3 RCTs. Across the 8 RCTs, the summary RR for discharge with tocilizumab was 1.10 (95% CI= 1.03-1.16, P< 0.00001). There was no significant association of tocilizumab with harm on other patient-relevant clinical outcomes, including increasing secondary infection risk, patients of adverse events, or patients of serious adverse events. Tocilizumab significantly increased the rate of hospital discharges in COVID-19 patients. Still, it did not decrease all-cause mortality or increase the risk of secondary infections, patients of adverse events, or patients for serious adverse events. Evidence that tocilizumab affects clinical outcomes in patients with COVID-19 requires further proof.

# **INTRODUCTION**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human pathogen, is one of the most considerable global challenges facing public health and humanity [1–3]. With the development of the coronavirus disease 2019 (COVID-19) pandemic, there has been unwarranted enthusiasm for using tocilizumab [4–12], but the clinical evidence of its benefits or harm is limited.

COVID-19 is associated with dysregulated immune responses and hyper inflammation, including releasing of proinflammatory cytokines and chemokines. It can cause or worsen acute respiratory distress syndrome and multiple organ failure [13–15]. Several scholars have recently suggested that tocilizumab may be positively associated with a lower risk of intubation or death in patients with severe and critically ill COVID-19 pneumonia [11, 13–20]. Inhibitors of Interleukin 6 (IL-6) or its receptor have successfully treated different cytokine storm syndromes or powerful chimerical antigen receptor T cell -mediated cytokine release syndrome [2, 13]. The randomized evaluation of the COVID-19 therapy platform (RECOVERY) trial is by far the largest randomized clinical trial (RCT) on COVID-19 treatments [21]. It has provided essential evidence for several promising therapies, including hydroxychloroquine, dexamethasone, lopinavirritonavir, convalescent plasma, and azithromycin.

Given the previously reported RCTs, we conducted the systematic review and meta-analysis (10 RCTs including 3378 patients in the tocilizumab group and 3142 in the control group) to explore and summarize the association between tocilizumab treatment and clinical outcomes in COVID-19 patients.

# **RESULTS**

We noted 39 records in the related databases, registries, and other sources. We included 9 RCTs published in peer-reviewed journals and 1 RCTs published as preprints. Of the ten included RCTs, three were in the USA, two were in India, and one each in France, Italy, Brazil, International, and the UK. Only 1 RCT was prematurely interrupted after an interim analysis for futility (NCT04346355). There were three double-blind RCTs (NCT04356937, NCT04372186, and NCT04320615), whereas the other 7 were open-label RCTs (CTRI/2020/05/024959, NCT04331808, NCT04346355, NCT04403685, CTRI/2020/05/025369, NCT02735707, and NCT04381936).

From 9 RCTs published in peer-reviewed journals, there were 2404 patients (1048 to placebo together with the standard of care or only standard of care and 1356 randomized to tocilizumab) in our meta-analysis. There were 4116 patients (2094 to the only standard of care and 2022 randomized tocilizumab) in the RECOVERY trial (NCT04381936). Comorbidities at randomization were universal when reported in most studies. Detailed information on patient characteristics was accessible to all RCTs (Table 1 and Supplementary Table 1).

# Association of tocilizumab with clinical outcomes

For all RCTs, the all-cause mortality in patients receiving tocilizumab was 23.98% (810/3378) and 28.74% (903/3142) in control patients. We found the summary RR for all-cause mortality with tocilizumab was 0.89 (95% CI= 0.82-0.96, P= 0.003). There was no significant between-trial heterogeneity ( $I^2$ = 28%, P= 0.19). However, 9 peer-reviewed RCTs showed that no significant association between tocilizumab treatment and all-cause mortality reduction (RR= 0.87, 95% CI= 0.73-1.04, P = 0.13).

Three double-blind RCTs received placebo, no significant association between tocilizumab treatment and all-cause mortality reduction (RR= 1.10, 95% CI= 0.79-1.54, P=0.57). We notably found that tocilizumab significantly reduced the rate of intubation or death in patients with COVID-19 with 3 RCTs (RR= 0.85, 95% CI= 0.78-0.92, P= 0.0002) (Figure 1A, 1D, and Supplementary Figure 1).

We conducted a Begg/Egger test and used a funnel plot to assess the publication bias of our meta-analysis (*P*-value of publication bias was 0.596). We also performed a sensitivity analysis by omitting one study when calculating the summary results. After eliminating the RECOVERY trial (NCT04381936), the combined OR value and 95%CI changed from positive to adverse. As the amount of the RECOVERY trial data accounts for 76% of the total data and the risk of bias in the RECOVERY trial was considered high, which may cause the combined results of the RECOVERY trial to be not very reliable (Supplementary Figure 2).

Across the 8 RCTs, the summary RR for discharge with tocilizumab was 1.10 (95% CI=1.03-1.16, P<0.0001). Similar results were also observed for the preprint, peerreviewed RCTs, double-blind (placebo plus standard care) and open label RCTs (standard care) for discharge (RR= 1.08, 95% CI= 1.00-1.18, P=0.06; RR= 1.14, 95% CI= 1.07-1.21, P<0.0001; RR= 1.10, 95% CI= 0.93-1.29, P=0.27; RR= 1.10, 95% CI= 1.03-1.18, P=0.008) (Figure 1B and Supplementary Figure 3).

We unobserved a significant association between tocilizumab and a decreased risk of secondary infections in the overall analysis (RR= 1.05, 95% CI= 0.89-1.24). However, there was a slight between-trial heterogeneity ( $I^2$ = 48%; P= 0.08). We did not discover significant associations between tocilizumab treatment and secondary infection risk in peer-reviewed, preprint RCTs, double-blind (placebo plus standard care), and open-label RCTs (standard care) subgroups. We also failed to find significant associations between tocilizumab and patients of adverse events as well as patients of serious adverse events (Figure 1C and Supplementary Figures 4, 5).

# **Risk of bias**

The risk of bias for all-cause mortality, in-patient discharge rate, number of patients experiencing serious adverse events and adverse events, number of patients' intubation or death, and number of secondary infections were thought low for 8 of the 10 RCTs. The other two RCTs have some concerns (NCT04346355), and 1 RCT was considered high (NCT04381936) (Figure 2).

Author		Olivier Hermine	Carlo Salvarani	J.H. Stone	Carlos Salama	I.O. Rosas	Viviane C Veiga	Suresh Kumar	Arvinder S Soin	Anthony C. Gordon	Peter W Horby
Trial registration		NCT 04331808	NCT 04346355	NCT 04356937	NCT 04372186	NCT 04320615	NCT 04403685	CTRI/2020/05/ 024959	CTRI/ 2020/05/0 25369	NCT 02735707	NCT 04381936
Time		20201020	20201020	20201021	20201217	20210225	20210120	20201201	20210504	20210422	20210211
Country		France	Italy	USA	USA	USA	Brazil	India	India	International	UK
Race		Caucasian	Caucasian	Mix	Mix	Mix	Mix	Asian	Caucasian	Mix	Mix
Disease severity		Moderate or severe	NA	Severe	NA	Severe	Severe or critical	Moderate or severe 1.6mg/kg	Moderate or severe	Critical	Severe
Dose description		8mg/kg maximum 800 mg	8mg/kg maximum 800 mg	8mg/kg maximum 800 mg	8mg/kg maximum 800 mg	8mg/kg maximum 800 mg	8mg/kg maximum 800 mg	and continued with 0.8 mg/kg dose weekly regimen	6mg/kg maximum 800 mg	8mg/kg maximum 800 mg	400mg- 800mg
Type of control		Usual care	Standard care	Placebo plus standard care	Placebo plus standard care	Placebo plus standard care	Standard care	Best supportive care	Standard care	Standard care	Standard care
Study type		Open-label RCT	Open-label RCT	Double- blind RCT	Double- blind RCT	Double- blind RCT	Open-label RCT	Open-label RCT	Open- label RCT	Open-label RCT	Open-label RCT
Peer-reviewed		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Publication format		Publish	Publish	Publish	Publish	Publish	Publish	Publish	Publish	Publish	Preprint
No. planned of inclusion		131	126	1560	445	479	129	36	183	2046	21550
No. included		130	123	243	377	438	129	30	180	865	4116
Tocilizumab		63	60	161	249	294	65	20	91	353	2022
Control		67	63	82	128	144	64	10	88	402	2094
Mortality	Tocilizumab	28d:7	30d:2	28d: 9	28d:26	28d:58	28d:14	30d:0	28d:11	30d:87	28d:596
Monunty	Control	28d:8	30d:1	28d:3	28d:11	28d:28	28d:6	30d:3	28d:15	30d:134	28d:694
Discharge	Tocilizumab	28d:52	30d:54	28d:147		28d:180	28d:35	30d:16		30d:190	28d:1093
C	Control	28d:49	30d:58	28d:72		28d:74	28d:31	30d:6		30d:184	28d:999
Patients of	Tocilizumab	28d:28			60d:127	28d:228	28d:29	30d:18	28d:30		
adverse events	Control	28d:36			60d:67	28d:116	28d:21	30d:4	28d:22		
Patients of serious adverse events	Tocilizumab Control	28d:20 28d:29		28d:28 28d:12		28d:103 28d:55	28d:11 28d:7		28d:15 28d:15	30d:9 30d:11	
Secondary	Tocilizumab	28d:2	30d:1	28d:13	60d:25	28d:113	28d:10	30d:1	28d:5	30d:1	
infection	Control	28d:14	30d:4	28d:14	60d:16	28d:58	28d:10	30d:3	28d:5	30d:0	
Incubation or death	Tocilizumab	15 24		17 10	00410	200100	200.10	20012	2000	20010	571(1754) 687(1800)

#### Table 1. Characteristics of the 8 RCTs in the meta-analysis.

The mix of Severity, Symptoms of the disease include moderate, severe, and critical; Mix of Race, including Asian, Caucasian, African, and so on; RCT, Randomized controlled trial; NA, no appearance.

# **DISCUSSION**

9 RCTs were published in peer-reviewed journals in the meta-analysis. We revealed that tocilizumab treatment was not significantly associated with reducing all-cause mortality among COVID-19 patients compared with placebo plus standard of care or standard of care alone. However, combined with additional 1 RCTs published in preprint journals, we observed that tocilizumab treatment significantly reduced all-cause mortality in COVID-19 patients. The risk of bias in the

RECOVERY trial (NCT04381936) is very high, and the combined results of the RECOVERY trial are not very reliable. Evidence that tocilizumab reduces all-cause mortality in COVID-19 patients requires further proof.

In the overall analysis, we discovered a significant increase in hospital discharge rates after patients with COVID-19 pneumonia received tocilizumab. We observed similar results for the peer-reviewed, preprint RCTs, double-blind (placebo plus standard care), and open-label RCTs (standard care) for discharge. We



Figure 1. Association of tocilizumab with all-cause mortality, discharge, patients of adverse events, and date of incubation or death in the published study and preprint study (A) all-cause mortality (B) discharge (C) patients of adverse events (D) date of incubation or death.

notably also found that tocilizumab significantly reduced the rate of intubation or death in COVID-19 patients in 3 RCTs.

Tocilizumab was not significantly associated with harm on other patient-relevant clinical outcomes, including increasing secondary infection risk, patients of adverse events, or patients of serious adverse events. The possible reason is tocilizumab treatment significantly increased COVID-19 discharge rates in patients with mild disease compared to standard care alone or placebo. In severe or critically ill patients, because mortality is a multifactorial outcome. In critically ill patients, medical personnel use all available medical means to save patients' lives; we did not find that tocilizumab significantly reduced all-cause mortality.

We found our evidence was dominated mainly by the RECOVERY trial (NCT04381936), which amounted to 76% of the meta-analysis weight [21]. After eliminating the RECOVERY trial, we failed to find a significant association between tocilizumab and all-cause mortality, intubation, or mortality in patients with COVID-19 [21]. However, excluding the RECOVERY trial, we found that tocilizumab effectively increased patients' discharge rate with COVID-19.

Carlo Salvarani et al. [7] was prematurely interrupted the trial after an interim analysis for futility. Three randomized, double-blind, placebo-controlled trials reported tocilizumab treatment did not significantly result in better clinical status or lower mortality than placebo at point time [5, 6, 8]. Three open-label published RCTs also said tocilizumab treatment plus standard care was not slightly superior to usual care alone in improving clinical outcomes [4, 7, 9].

Viviane C Veiga et al. [9] reported that two patients in the standard care group received tocilizumab treatment. Peter W Horby et al. [21] also said that forty-four participants (3%) assigned to usual care received at least one dose of tocilizumab in the RECOVERY trial. Timotius Ivan Hariyanto et al. [22] also observed that tocilizumab is effective in reducing the biomarkers of the COVID-19 infection. Overall, we believe that tocilizumab significantly increased the discharge rate of patients with COVID-19 but did not decrease all-cause mortality and increase the risk of secondary infection, patients with adverse events, or patients with serious adverse events in the meta-analysis. Therefore, we recommend that clinicians be cautious in using tocilizumab in patients with COVID-19pneumonia.

We have to consider several limitations in our study. Firstly, in the absence of every patient's clinical test data, patients with high clinical indicators (such as IL-6, C-reactive protein, and so on) will benefit most when tocilizumab treatment. Secondly, two of the 10 RCTs



Figure 2. Risk of bias assessments for the outcomes of all RCTs.

had some concerns, and one RCT have an increased risk of bias. The RECOVERY trial (NCT04381936) accounted for 76% of the weight in our meta-analysis. Thirdly, two RCTs reported that some patients in the standard care group also received tocilizumab, which may affect the efficacy evaluation [1, 23–25].

#### **CONCLUSIONS**

Tocilizumab significantly increased the discharge rate of patients with COVID-19. Still, it did not decrease allcause mortality and increased the risk of secondary infection, patients of adverse events, or patients of serious adverse events.

# **MATERIALS AND METHODS**

We conducted the systematic review and meta-analysis of 10 RCTs examining the association between tocilizumab treatment and clinical outcomes in COVID-19 patients (Figure 3). We recorded the metaanalysis under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

#### PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 3. Flow diagram of the study selection process.

#### Search strategy

Three review authors (Jingwen Peng, Weida Liu, and Huan Mei) systematically searched PubMed and MedRxiv for all RCTs as of June 1, 2021, to assess the benefits or harms of tocilizumab to treat patients with COVID-19 pneumonia (Figure 3). We additionally reviewed the references for included articles and previous systematic reviews. We compared included items and resolved disagreements.

# **RCTs selection**

The selected RCTs included participants with suspected or confirmed SARS-CoV-2 infection randomly assigned to receive tocilizumab, only standard of care or best supportive care, or a placebo together with the standard of care. We included all RCTs regardless of the tocilizumab dose (i.e., 400 mg-800 mg, 1.6 mg/kg and weekly continued with 0.8 mg/kg dose regimen or 8 mg/kg maximum 800 mg) or health care setting. We excluded retrospective studies, case reports, and the RCTs designed to prevent the occurrence of COVID-19.

# **Data extraction**

We carefully extracted the relevant information for all RCTs: baseline characteristics of the patients, trial design characteristics (Trial registration, blinding, and randomization procedure), description of the experimental and control groups, tocilizumab dose, and trial location. Data on outcomes (Jingwen Peng and Huan Mei) and features (Jingwen Peng and Weida Liu) were extracted independently by two reviewers.

# Outcomes

The outcomes were:

- 1. All-cause mortality 28 days or 30 days.
- 2. In-patient discharge rate.
- 3. The number of patients experiencing serious adverse events and adverse events.
- 4. The number of secondary infections.
- 5. The number of patients' intubation or death.

#### **Risk of bias assessment**

Two investigators (Jingwen Peng and Weida Liu) independently assessed the risk of bias for clinical outcomes in all trials using the internationally recognized tool (Revised Cochrane risk of bias tool for randomized trials, RoB 2.0). All authors accounted for any discrepancies in the investigator's quality assessment and discussed until everyone reached a consensus.

#### Statistical analyses

We performed the meta-analysis to assess the treatment effects using risk ratio (RR) and corresponding 95% confidence intervals (CI). We analyzed outcomes with available data (all-cause mortality, in-patient discharge rate, number of patients experiencing serious adverse events and adverse events, number of secondary infections, and patient intubation or death). We use DerSimonian and Laird methods to pool data from the meta-analysis with the random-effects model and the fixed-effects model of the Mantel-Haenszel method. We used Begg/Egger test and visually on a funnel plot to assess the metaanalysis and examine publication bias. We have not summarized treatment effects for clinical improvement or deterioration, length of hospital stay, and the number of mechanical ventilation due to inconsistent definitions of these outcomes and insufficient reporting of pertinent details. All analyses were carried out using RevMan version 5.4.1.

# Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

# **AUTHOR CONTRIBUTIONS**

JWP, XDS, and WDL conceived and designed the experiments. JWP, WDL, and HM performed publication searches and selection. JWP, QW, and HLZ analyzed the data. JWP, GZL, and XDS prepared the figures. JWP and MHF contributed materials/analysis tools. JWP and WDL wrote and revised the paper. All authors reviewed and considered the manuscript.

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# **CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

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# REFERENCES

- Jiang W, Li W, Xiong L, Wu Q, Wu J, He B, Shen J, Pang R, Luo T, Guo Y, Yang Y, Han Y, Dai W, et al. Clinical efficacy of convalescent plasma therapy on treating COVID-19 patients: Evidence from matched study and a meta-analysis. Clin Transl Med. 2020; 10:e259. <u>https://doi.org/10.1002/ctm2.259</u> PMID:<u>33377664</u>
- Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, Walzer T, François B, Sève P. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020; 19:102567. <u>https://doi.org/10.1016/j.autrev.2020.102567</u> PMID:32376392
- Peng J, Wang Q, Mei H, Zheng H, Liang G, She X, Liu W. Fungal co-infection in COVID-19 patients: evidence from a systematic review and meta-analysis. Aging (Albany NY). 2021; 13:7745–57. <u>https://doi.org/10.18632/aging.202742</u> PMID:33744863
- Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, Bureau S, Dougados M, Tibi A, Azoulay E, Cadranel J, Emmerich J, Fartoukh M, and CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021; 181:32–40.

https://doi.org/10.1001/jamainternmed.2020.6820 PMID:<u>33080017</u>

- Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, Skiest D, Aziz MS, Cooper N, Douglas IS, Savic S, Youngstein T, Del Sorbo L, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021; 384:1503–16. <u>https://doi.org/10.1056/NEJMoa2028700</u> PMID:<u>33631066</u>
- Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021; 384:20–30. <u>https://doi.org/10.1056/NEJMoa2030340</u> PMID:<u>33332779</u>
- Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, et al, and RCT-TCZ-COVID-

19 Study Group. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021; 181:24–31. https://doi.org/10.1001/jamainternmed.2020.6615 PMID:33080005

- Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, et al, and BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020; 383:2333–44. <u>https://doi.org/10.1056/NEJMoa2028836</u> PMID:33085857
- Veiga VC, Prats JA, Farias DL, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LC, Avezum Á, Lisboa TC, Rojas SS, et al, and Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021; 372:n84. <u>https://doi.org/10.1136/bmj.n84</u> PMID:<u>33472855</u>
- Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A, Di Gaetano M, Puzzolante C, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020; 2:e474–84.

https://doi.org/10.1016/S2665-9913(20)30173-9 PMID:<u>32835257</u>

- Kewan T, Covut F, Al-Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study. EClinicalMedicine. 2020; 24:100418. <u>https://doi.org/10.1016/j.eclinm.2020.100418</u> PMID:<u>32766537</u>
- Schett G, Manger B, Simon D, Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020; 16:465–70. <u>https://doi.org/10.1038/s41584-020-0451-z</u> PMID:32561873
- Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, Husain AN, Mutlu EA, Mutlu GM. IL-6 Inhibition in Critically III COVID-19 Patients Is Associated With Increased Secondary Infections. Front Med (Lausanne). 2020; 7:583897. <u>https://doi.org/10.3389/fmed.2020.583897</u>

https://doi.org/10.3389/fmed.2020.58389 PMID:<u>33195334</u>

 Tian J, Zhang M, Jin M, Zhang F, Chu Q, Wang X, Chen C, Yue H, Zhang L, Du R, Zhao D, Zeng Z, Zhao Y, et al. Repurposed Tocilizumab in Patients with Severe COVID-19. J Immunol. 2021; 206:599–606. https://doi.org/10.4049/jimmunol.2000981 PMID:<u>33298617</u>

- Potere N, Di Nisio M, Cibelli D, Scurti R, Frattari A, Porreca E, Abbate A, Parruti G. Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyperinflammation: a casecontrol study. Ann Rheum Dis. 2021; 80:1–2. <u>https://doi.org/10.1136/annrheumdis-2020-218243</u> PMID:<u>32647027</u>
- 16. Rodríguez-Baño J, Pachón J, Carratalà J, Ryan P, Jarrín I, Yllescas M, Arribas JR, Berenguer J, Aznar Muñoz E, Gil Divasson P, González Muñiz P, Muñoz Aguirre C, Díaz Menéndez M, et al, and SAM-COVID Study Group, and Fundación SEIMC-GESIDA, and Hospital Universitario La Paz, and Hospital Universitario Gregorio Marañón, and Hospital Infanta Leonor, and Complejo Hospitalario Virgen de la Salud, and Hospital Universitario Rafael Méndez, and Hospital Universitario de Cruces, and Hospital de Melilla, and Hospital San Eloy de Barakaldo, and Hospital Universitario Central de Asturias, and Hospital Universitario Puerto Real, and Hospital do Salnés, and Hospital del Mar, and Hospital Virgen de la Arrixaca, and Hospital Clínico San Cecilio, and Parc Sanitari Sant Joan de Déu, and Hospital Josep Trueta, and Hospital Dos De Maig - Consorci Sanitari Integral, and Hospital Clínico Universitario de Valencia, and Complejo Asistencial de Ávila, and Hospital Universitario Marqués de Valdecilla, and Hospital de Barcelona SCIAS, and Hospital Álvaro Cunqueiro, and Hospital Universitario Severo Ochoa, and Hospital CIMA-Sanitas, and Hospital La Inmaculada, and Hospital de Guadalajara, and Hospital Universitario Infanta Sofia, and Hospital Comarcal de Blanes, and Hospital Universitario de Gran Canaria Dr Negrín, and Hospital Son Espases, and Complejo Hospitalario Universitario A Coruña, and Hospital Costa del Sol, and Hospital Clínico Universitario Lozano Blesa, and Hospital Mutua de Terrassa, and Hospital Universitario Virgen Macarena, and Hospital Universitari de Bellvitge, and Hospital Universitario y Politécnico La Fe, and Hospital de Sabadell (Parc Tauli), and Hospital Fundación Jiménez Díaz, and Hospital Clínico Universitario de Valladolid, and Hospital Son Llatzer, and Hospital Universitario de Álava, and Complejo Hospitalario Universitario Santa Lucía, and Hospital General Universitario Reina Sofía, and Complejo Hospitalario Universitario de Ferrol, and Hospital Universitario los Arcos del Mar Menor, and Hospital Universitario de Jerez, and Hospital de Donostia, and Hospital Juan Ramón Jiménez, and Hospital Vega Baja, and Hospital Puerta de Hierro, and Hospital Universitario de Getafe, and Hospital General de la Palma, and Fundación Hospital de Calahorra, and Hospital Alto Deba, and Hospital Universitario de

Jaén, and Hospital de Palamós, and Hospital Universitario de Valme, and Hospital Universitario Virgen del Rocío, and Hospital Universitario Ramón y Cajal, and Hospital Universitario San Pedro, and Hospital Regional de Málaga. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). Clin Microbiol Infect. 2021; 27:244–52.

https://doi.org/10.1016/j.cmi.2020.08.010 PMID:<u>32860964</u>

 Ruiz-Antorán B, Sancho-López A, Torres F, Moreno-Torres V, de Pablo-López I, García-López P, Abad-Santos F, Rosso-Fernández CM, Aldea-Perona A, Montané E, Aparicio-Hernández RM, Llop-Rius R, Pedrós C, et al, and TOCICOV-study group. Combination of Tocilizumab and Steroids to Improve Mortality in Patients with Severe COVID-19 Infection: A Spanish, Multicenter, Cohort Study. Infect Dis Ther. 2021; 10:347–62.

https://doi.org/10.1007/s40121-020-00373-8 PMID:<u>33280066</u>

- Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, Zhou N, Petty LA, Baang JH, Dillman NO, Frame D, Gregg KS, Kaul DR, et al. Tocilizumab for Treatment of Mechanically Ventilated Patients With COVID-19. Clin Infect Dis. 2021; 73:e445–54. <u>https://doi.org/10.1093/cid/ciaa954</u> PMID:<u>32651997</u>
- Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, Govil D, Deswal V, Chaudhry D, Singh PK, Gupta A, Agarwal V, Kumar S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021; 9:511–21. https://doi.org/10.1016/S2213-2600(21)00081-3 PMID:33676589
- 20. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJ, Bradbury CA, et al, and REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically III Patients with Covid-19. N Engl J Med. 2021; 384:1491–502. <u>https://doi.org/10.1056/NEJMoa2100433</u> PMID:<u>33631065</u>
- 21. Recovery Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397:1637–45. <u>https://doi.org/10.1016/S0140-6736(21)00676-0</u> PMID:<u>33933206</u>

- 22. Ivan Hariyanto T, Kurniawan A. Tocilizumab administration is associated with the reduction in biomarkers of coronavirus disease 2019 infection. J Med Virol. 2021; 93:1832–6. <u>https://doi.org/10.1002/jmv.26698</u> PMID:<u>33241872</u>
- Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, Smith ER, Haber NA, Khanna N, Moher D, Goodman SN, Ioannidis JP, Hemkens LG. Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA. 2021; 325:1185–95. <u>https://doi.org/10.1001/jama.2021.2747</u> PMID:<u>33635310</u>
- 24. Kouzy R, Abi Jaoude J, Garcia Garcia CJ, El Alam MB, Taniguchi CM, Ludmir EB. Characteristics of the Multiplicity of Randomized Clinical Trials for Coronavirus Disease 2019 Launched During the Pandemic. JAMA Netw Open. 2020; 3:e2015100. https://doi.org/10.1001/jamanetworkopen.2020.15100 PMID:<u>32658285</u>
- 25. Lan SH, Lai CC, Huang HT, Chang SP, Lu LC, Hsueh PR. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents. 2020; 56:106103. https://doi.org/10.1016/j.ijantimicag.2020.106103

PMID:<u>32712333</u>

# SUPPLEMENTARY MATERIALS

# **Supplementary Figures**

Study or Subgroup	Events	mab Total	Contr Events	ol Total	Weinbt	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl	
CTRI/2020/05/024959	Cvents	20	2 Series	10	0.5%	0.07 [0.00, 1.32]	4	
CTRV2020/05/025369	11	91	15	88	1.7%	0.71 [0.34, 1.46]		
NCT02735707	87	353	134	402	14.0%	0.74 [0.59, 0.93]		
		294		144				
NCT04320615	58 7		28		4.2%	1.01 [0.68, 1.52]		
NCT04331808		63	8	67	0.9%	0.93 [0.36, 2.42]		_
NCT04346355	2	60	1	63	0.1%	2.10 [0.20, 22.56]		
NCT04356937	9	161	3	82	0.4%	1.53 [0.43, 5.49]		
NCT04372186	26	249	11	128	1.6%	1.22 [0.62, 2.38]		
NCT04381936	596	2022	694	2094	75.9%	0.89 [0.81, 0.97]		
NCT04403685	14	65	6	64	0.7%	2.30 [0.94, 5.61]		
Total (95% CI)		3378		3142	100.0%	0.89 [0.82, 0.96]	•	
Total events	810		903					
Heterogeneity: Chi <sup>2</sup> = 12	.50, df = 9	(P = 0.1)	9); l <sup>2</sup> = 2	8%			0.02 0.1 1 10	
Test for overall effect: Z =	= 2.95 (P =	0.003)						5Ò
3							Favours Tocilizumab Favours Control	
-	Tocilizu		Contr			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
1.5.1 Placebo (Yes)								
NCT04320615	58	294	28	144	4.2%	1.01 [0.68, 1.52]		
NCT04356937	9	161	3	82	0.4%	1.53 [0.43, 5.49]		
NCT04372186	26	249	11	128	1.6%	1.22 [0.62, 2.38]		
Subtotal (95% CI)		704		354	6.2%	1.10 [0.79, 1.54]	+	
Total events	93		42				-	
		0 - 0 70						
Heterogeneity: Chi <sup>2</sup> = 0.4			0,109	>				
Test for overall effect: Z =	= 0.57 (P =	0.57)						
1.5.2 Placebo (No)								
CTRI/2020/05/024959	0	20	3	10	0.5%	0.07 [0.00, 1.32]	• • • • • • • • • • • • • • • • • • •	
CTRI/2020/05/025369	11	91	15	88	1.7%	0.71 [0.34, 1.46]	+-	
NCT02735707	87	353	134	402	14.0%	0.74 [0.59, 0.93]	-	
NCT04331808	7	63	8	67	0.9%	0.93 [0.36, 2.42]		
NCT04346355	2	60	1	63	0.1%	2.10 [0.20, 22.56]		
NCT04381936	596	2022	694	2094	75.9%	0.89 [0.81, 0.97]		
NCT04403685	14	65	6	64	0.7%	2.30 [0.94, 5.61]		
Subtotal (95% CI)		2674		2788	93.8%	0.87 [0.80, 0.95]	•	
Total events	717		861					
Heterogeneity: Chi <sup>2</sup> = 10.	.38, df = 6	(P = 0.1)	1); $ ^2 = 4$	2%				
Test for overall effect: Z =	= 3.26 (P =	0.001)						
		,						
Total (95% CI)		3378		3142	100.0%	0.89 [0.82, 0.96]	•	
Total events	810	0010	903	0112	1001070	and Interiored		
		~ ~ ~		0.07				
Heterogeneity: Chi <sup>2</sup> = 12			9); P = 2	8%			0.05 0.2 1 5	20
Test for overall effect: Z =	= 2.95 (P =							
							Favours Tocilizumab Favours Control	
Test for subaroup differe	ences: Chi <sup>a</sup>		. df = 1 (F	P = 0.18	i). <b>I</b> ² = 44.	2%	Favours Tocilizumab Favours Control	
Test for subaroup differe	ences: Chi <sup>a</sup> Tocilizui	= 1.79	. df = 1 (F Contr		i). <b>I</b> ² = 44.	2% Risk Ratio	Favours Tocilizumab Favours Control <b>Risk Ratio</b>	
		² = 1.79 mab	Contr	ol				
2	Tocilizu	² = 1.79 mab	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup 1.6.1 Open label RCT	Tocilizu	<sup>2</sup> = 1.79 mab <u>Total</u>	Contr Events	ol Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio	
Study or Subgroup 1.6.1 Open label RCT CTRI/2020/05/024959	Tocilizu Events	<sup>2</sup> = 1.79 mab <u>Total</u> 20	Contr <u>Events</u> 3	rol <u>Total</u> 10	Weight 0.5%	Risk Ratio M-H, Fixed, 95% Cl 0.07 [0.00, 1.32]	Risk Ratio	
Study or Subgroup 1.6.1 Open label RCT CTRI/2020/05/024959 CTRI/2020/05/025369	Tocilizu Events 0 11	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91	Contr Events 3 15	rol <u>Total</u> 10 88	Weight 0.5% 1.7%	Risk Ratio M-H, Fixed, 95% Cl 0.07 (0.00, 1.32) 0.71 (0.34, 1.46)	Risk Ratio	
Study or Subgroup 1.6.1 Open label RCT CTRI/2020/05/024959 CTRI/2020/05/025369 NCT02735707	Tocilizur Events 0 11 87	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353	Contr Events 3 15 134	rol Total 10 88 402	Weight 0.5% 1.7% 14.0%	Risk Ratio M-H, Fixed, 95% Cl 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93)	Risk Ratio	
Study or Subgroup 1.6.1 Open label RCT CTRI/2020/05/024959 CTRI/2020/05/025369 NCT02735707 NCT04331808	Tocilizur Events 0 11 87 7	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63	Contr Events 3 15 134 8	rol Total 10 88 402 67	Weight 0.5% 1.7% 14.0% 0.9%	Risk Ratio M-H, Fixed, 95% CI 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTRV/2020/05/024959           CTRV/2020/05/025369           NCT02735707           NCT04731808           NCT04346355	Tocilizur Events 0 11 87 7 2	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63 63	Contr Events 3 15 134 8 1	rol Total 10 88 402 67 63	Weight 0.5% 1.7% 14.0% 0.9% 0.1%	Risk Ratio M-H, Fixed, 95% Cl 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTRV2020/05/024959           CTRV2020/05/025369           NCT02735707           NCT04231808           NCT04331808           NCT04381936	Tocilizur Events 0 11 87 7	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63	Contr Events 3 15 134 8	rol Total 10 88 402 67 63 2094	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9%	Risk Ratio M-H, Fixed, 95% CI 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTRV/2020/05/024959           CTRV/2020/05/025369           NCT02735707           NCT04731808           NCT04346355	Tocilizur Events 0 11 87 7 2	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63 63	Contr Events 3 15 134 8 1	rol Total 10 88 402 67 63	Weight 0.5% 1.7% 14.0% 0.9% 0.1%	Risk Ratio M-H, Fixed, 95% Cl 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTRV2020/05/024959           CTRV2020/05/025369           NCT02735707           NCT04231808           NCT04331808           NCT04381936	Tocilizur Events 0 11 87 7 2 596	* = 1.79 mab Total 20 91 353 63 60 2022	Contr Events 3 15 134 8 1 694	rol Total 10 88 402 67 63 2094	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9%	Risk Ratio M-H, Fixed, 95% CI 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTRV2020/05/024959           CTRV2020/05/025369           NCT02735707           NCT04731808           NCT04331805           NCT04381936           NCT04381936           NCT043885           NCT043885	Tocilizur Events 0 11 87 7 2 596	* = 1.79 mab Total 20 91 353 63 60 2022 65	Contr Events 3 15 134 8 1 694	rol Total 10 88 402 67 63 2094 64	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7%	Risk Ratio M-H, Fixed, 95% Cl 0.77 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97) 2.30 (0.94, 5.61)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTRV2020/05/024959           CTRV2020/05/025369           NCT02735707           NCT04231808           NCT04331808           NCT04331936           NCT04381936           NCT04381936           NCT04381936           NCT04381936           NCT044381936           NCT044381936           Subtotal (95% CI)	Tocilizur Events 0 11 87 7 2 596 14 717	* = 1.79 mab Total 20 91 353 63 60 2022 65 2074	Contr Events 3 15 134 8 1 694 6 861	10 10 88 402 67 63 2094 64 2788	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7%	Risk Ratio M-H, Fixed, 95% Cl 0.77 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97) 2.30 (0.94, 5.61)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT02735707           NCT04331808           NCT04348255           NCT043481936           Subtotal (95% CI)           Total events           Heterogeneity. ChIP = 10	Tocilizun Events 0 11 87 7 2 596 14 717 1.38, df = 6	<sup>2</sup> = 1.79 mab 20 91 353 63 60 2022 65 2674 (P = 0.1	Contr Events 3 15 134 8 1 694 6 861	10 10 88 402 67 63 2094 64 2788	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7%	Risk Ratio M-H, Fixed, 95% Cl 0.77 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97) 2.30 (0.94, 5.61)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTRV202005/024959           CTRV2020005/024959           CTRV2020005/024959           NCT0273570           NCT04331808           NCT04430855           NCT04403885           Subtotal (95% C))           Total events	Tocilizun Events 0 11 87 7 2 596 14 717 1.38, df = 6	<sup>2</sup> = 1.79 mab 20 91 353 63 60 2022 65 2674 (P = 0.1	Contr Events 3 15 134 8 1 694 6 861	10 10 88 402 67 63 2094 64 2788	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7%	Risk Ratio M-H, Fixed, 95% Cl 0.77 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97) 2.30 (0.94, 5.61)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4569           NCT02/35707           NCT04/36355           NCT04/381936           NCT04/381936           Subtotal (95% CI)           Total events           Heterogeneity. ChI <sup>#</sup> = 10           Test for overall effect Z =	Tocilizun Events 0 11 87 7 2 596 14 717 1.38, df = 6	<sup>2</sup> = 1.79 mab 20 91 353 63 60 2022 65 2674 (P = 0.1	Contr Events 3 15 134 8 1 694 6 861	10 10 88 402 67 63 2094 64 2788	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7%	Risk Ratio M-H, Fixed, 95% Cl 0.77 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 22.56) 0.89 (0.81, 0.97) 2.30 (0.94, 5.61)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTR/202005/024559           CTR/202005/02569           NCT02735707           NCT04348355           NCT04348355           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity: Chi# = 10           Test for overall effect Z =           1.6.2 Double-blind RCT	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P =	* = 1.79 mab 20 91 353 63 60 2022 65 2674 (P = 0.1 0.001)	Contr Events 3 15 134 8 1 694 6 861 1);   <sup>2</sup> = 4	10 88 402 67 63 2094 64 2788 2%	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8%	Risk Ratio M.H. Fixed, 95% C1 0.07 (0.0.0, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.83) 0.93 (0.36, 2.42) 2.10 (0.20, 2.2.56) 0.89 (0.81, 0.87) 2.30 (0.94, 5.81) 0.87 (0.80, 0.95)	Risk Ratio	
Study or Subgroup           16.1 Open tabel RCT           CTR/2020/05/024959           CTR/2020/05/024959           CTR/2020/05/024959           NCT02/35707           NCT02/35707           NCT04/31808           NCT04/31808           NCT04/31936           NCT04/30585           Subtotal (95% CI)           Total events           Heterogeneity, ChIP = 10           Test for overall effect Z =           16.2 Double-bind RCT           NCT04/30515	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58	*= 1.79 mab Total 20 91 353 63 60 2022 65 2674 (P = 0.1 0.001) 294	Contr Events 3 15 134 8 1 694 6 861 1);  ² = 4 28	10 10 88 402 67 63 2094 64 2788 2%	Weight 0.5% 1.7% 14.0% 0.1% 0.1% 75.9% 0.7% 93.8%	Risk Ratio M.H. Fixed, 95% C1 0.07 (10.00, 1.32) 0.71 (10.34, 1.46) 0.74 (10.59, 0.93) 0.39 (10.36, 2.42) 2.10 (10.20, 22.56) 0.89 (10.81, 0.97) 2.30 (10.94, 5.61) 0.87 [0.80, 0.95] 1.01 [0.68, 1.52]	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT042331008           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneily Chi <sup>#</sup> = 10           Test for overall effect Z =           16.2 Double-blind RCT           NCT0420613           NCT04230813	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9	* = 1.79 mab Total 20 91 353 60 2022 65 2674 (P = 0.1 0.001) 294 161	Contr Events 3 15 134 8 94 6 861 1);  ² = 4 28 3	Total 10 88 402 67 63 2094 64 2788 2% 144 82	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4%	Risk Ratio M.H. Fixed, <b>5</b> 5% C1 0.07 (10.01, 132) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.25) 0.98 (0.81, 0.95) 2.30 (0.94, 9.67) 2.30 (0.94, 0.95) <b>1.01</b> (0.68, 1.52) 1.53 (0.43, 5.49)	Risk Ratio	
Study or Subgroup           16.1 Open tabel RCT           CTR/202005/024650           CTR/202005/02569           NCT02735707           NCT04348255           NCT0438255           NCT0438255           Subtotal (95% Cf)           Total events           Heterogeneily: ChiP = 10           Test for overail effect Z =           16.2 Double-blind RCT           NCT04365937           NCT04320615           NCT04320615           NCT0432186	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58	*= 1.79 mab 20 91 353 63 60 2022 65 <b>2674</b> (P = 0.1 0.001) 294 161 249	Contr Events 3 15 134 8 1 694 6 861 1);  ² = 4 28	Total 10 88 402 67 63 2094 64 2788 2% 144 82 128	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4559           NCT042/35707           NCT042/3550           NCT043/31508           NCT043/31508           Subtotal (95% CI)           Test for overall effect 2 =           1.6.2 Double-blind RCT           NCT043/256937           NCT043/272/86           Subtotal (95% CI)	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26	* = 1.79 mab Total 20 91 353 60 2022 65 2674 (P = 0.1 0.001) 294 161	Contr <u>Events</u> 3 15 134 8 1 6 861 1);   <sup>2</sup> = 4 28 3 11	Total 10 88 402 67 63 2094 64 2788 2% 144 82	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4%	Risk Ratio M.H. Fixed, <b>5</b> 5% C1 0.07 (10.0, 1.32) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.25) 0.98 (0.81, 0.95) 2.30 (0.94, 9.67) 2.30 (0.94, 0.95) <b>1.01</b> (0.68, 1.52) 1.53 (0.43, 5.49)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTR/202005/024559           CTR/202005/025589           NCT02735707           NCT043403685           Subtotal (95% CI)           Total events           Heterogeneily: Chi# = 10           Test for overall effect Z =           16.2 Double-blind RCT           NCT04340585           Subtotal (95% CI)           Total events           Heterogeneily: Chi# = 10           Test for overall effect Z =           16.2 Double-blind RCT           NCT04372186           Subtotal (95% CI)           Total events	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93	* = 1.79 mab 20 91 353 63 60 2022 65 <b>2674</b> (P = 0.1 0.001) 294 161 249 <b>704</b>	Contr Events 3 155 134 8 1 694 6 861 1);   <sup>2</sup> = 4 28 3 11 42	10 88 402 67 63 2094 64 2788 2% 144 82 128 354	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTR/202005/024559           CTR/202005/02569           NCT02735707           NCT04340365           NCT04340365           Subtotal (95% CI)           Total events           Heterogeneity: Chi# = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04320615           Subtotal (95% CI)           Total events	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93	* = 1.79 mab 20 91 353 63 60 2022 65 <b>2674</b> (P = 0.1 0.001) 294 161 249 <b>704</b>	Contr Events 3 155 134 8 1 694 6 861 1);   <sup>2</sup> = 4 28 3 11 42	10 88 402 67 63 2094 64 2788 2% 144 82 128 354	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           16.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT042331008           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneily Chi <sup>#</sup> = 10           Test for overall effect Z =           16.2 Double-blind RCT           NCT0420613           NCT04230813	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63 63 60 2022 265 <b>2674</b> (P = 0.1 (P = 0.1 249 <b>704</b> P = 0.78	Contr Events 3 155 134 8 1 694 6 861 1);   <sup>2</sup> = 4 28 3 11 42	10 88 402 67 63 2094 64 2788 2% 144 82 128 354	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4559           NCT02/35707           NCT04/381938           NCT04/381938           NCT04/381938           Subtoal (95% CI)           Total events           Heterogeneity: ChF = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04/356937           NCT04/356937           NCT04/326951           NCT04/326951           NCT04/32186           Subtoal (95% CI)           Total events           Heterogeneity: ChF = 0.4	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63 63 60 2022 265 <b>2674</b> (P = 0.1 (P = 0.1 249 <b>704</b> P = 0.78	Contr Events 3 155 134 8 1 694 6 861 1);   <sup>2</sup> = 4 28 3 11 42	10 88 402 67 63 2094 64 2788 2% 144 82 128 354	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           1.6.1 Open tabel RCT           CTR/202005/024650           CTR/202005/02569           NCT02735707           NCT04348255           NCT04348255           NCT04348255           Subtotal (95% CI)           Total events           Heterogeneilty: Chi <sup>2</sup> = 10           Test for overail effect Z =           1.6.2 Double-blind RCT           NCT04320615           NCT04326937           NCT04320615           NCT0432186           Subtotal (95% CI)           Total events           Heterogeneily: Chi <sup>2</sup> = 0,4           Total events           Heterogeneily: Chi <sup>2</sup> = 0,4	Tocilizuu Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l	<sup>2</sup> = 1.79 mab <u>Total</u> 20 91 353 63 63 60 2022 265 <b>2674</b> (P = 0.1 (P = 0.101) 294 161 249 <b>704</b> P = 0.78	Contr Events 3 155 134 8 1 694 6 861 1);   <sup>2</sup> = 4 28 3 11 42	100 88 402 67 63 2094 84 <b>2788</b> 2%	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6% 6.2%	Risk Ratio M.H. Fixed, 55% C1 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.83) 0.93 (0.36, 2.42) 0.99 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4559           NCT042/35707           NCT042/3550           NCT042/3550           NCT042/3555           NCT042/3556           Subtotal (95% CI)           Total events           Heierogeneity, Chi <sup>#</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT042/356937           NCT042/356937           NCT042/356937           NCT042/356937           Total events           Heterogeneity; Chi <sup>#</sup> = 0.4           Test for overall effect Z =           Total staff of S% CI)           Total events           Heterogeneity; Chi <sup>#</sup> = 0.4           Test for overall effect Z =           Total (95% CI)	Tocilizum Events 0 11 7 2 596 14 717 1.38, df = 6 = 3.26 (P = 58 9 26 933 49, df = 2 (I = 0.57 (P =	= 1.79 mab Total 20 91 353 60 2022 65 2674 (P = 0.1 (P = 0.101) 294 161 249 704 P = 0.757	Contr <u>Events</u> 3 15 134 8 1 694 6 861 1);  ≠ = 4 28 3 11 42 1);  ≠ = 0%	100 88 402 67 63 2094 84 <b>2788</b> 2%	Weight 0.5% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6%	Risk Ratio M.H. Fixed, 95% C1 0 07 (0.00, 1.32) 0 71 (0.34, 1.46) 0 74 (0.59, 0.83) 0 93 (0.36, 2.42) 0 89 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1 01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38)	Risk Ratio	
Study or Subgroup           1.6.1 Open label RCT           CTR/202005/024559           CTR/202005/024559           NCT02735707           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04349365           Subtotal (95% CI)           Total events           Heterogeneity Chi <sup>#</sup> = 10           NCT04320615           Subtotal (95% CI)           Total events           Heterogeneity Chi <sup>#</sup> = 0.4           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04356937           NCT0436937           Total events           Heterogeneity Chi <sup>#</sup> = 0.4           Test for overall effect Z =           Total (95% CI)           Total events	Tocilizum <u>Events</u> 0 11 87 7 2 586 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (f = 0.57 (P = 810	= 1.79 mab Total 20 91 353 63 60 2022 5 2674 (P = 0.1 0.001) 294 161 249 704 P = 0.76 0.57) 3378	Contr <u>Events</u> 3 15 134 8 1 6 94 6 861 1);  P = 4 28 3 11 42 28 3 11 42 28 3 11 42 28 3 11 42 28 3 11 43 43 43 43 43 43 43 43 43 43	10 10 88 402 67 32094 44 2788 2% 144 82 128 354 3142	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6% 6.2%	Risk Ratio M.H. Fixed, 55% C1 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.83) 0.93 (0.36, 2.42) 0.99 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54)	Risk Ratio	,
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4559           NCT042/35/07           NCT043/355           NCT043/355           NCT043/3625           Subtotal (95% CI)           Total events           Heterogeneilty: Chi <sup>P</sup> = 10           Total events           Heterogeneilty: Chi <sup>P</sup> = 0.4           Total events           Heterogeneilty: Chi <sup>P</sup> = 10           Total events           Heterogeneilty: Chi <sup>P</sup> = 0.4           Total events           Heterogeneilty: Chi <sup>P</sup> = 10           Total events           Heterogeneilty: Chi <sup>P</sup> = 10	Tocilizum Events 0 11 87 7 2 596 14 77 2 596 14 138, df = 6 9 26 9 9 26 9 93 49, df = 2 (f = 0.57 (P = 0.57) 810 810 810 810 810 810 810 810	<sup>≠</sup> = 1.79 mab 20 91 353 63 63 60 2022 65 2674 (P = 0.1 0.001) 294 161 249 704 P = 0.78 0.57) 3378 (P = 0.1	Contr <u>Events</u> 3 15 134 8 1 6 94 6 861 1);  P = 4 28 3 11 42 28 3 11 42 28 3 11 42 28 3 11 42 28 3 11 43 43 43 43 43 43 43 43 43 43	10 10 88 402 67 32094 44 2788 2% 144 82 128 354 3142	Weight 0.5% 1.7% 14.0% 0.9% 0.1% 75.9% 0.7% 93.8% 4.2% 0.4% 1.6% 6.2%	Risk Ratio M.H. Fixed, 55% C1 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.59, 0.83) 0.93 (0.36, 2.42) 0.99 (0.81, 0.97) 2.30 (0.94, 5.61) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           1.6.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT04233100           NCT0433100           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity Chi <sup>2</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04372186           Subtotal (95% CI)           Total events           Heterogeneity, Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity, Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Test for overall effect Z =           Test for overall effect Z =	Tocilizu <u>Events</u> 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810) 810 810 810 810 810 810 810 810	*= 1.79 mab Total 20 91 363 63 60 2022 2674 (P = 0.11 (P = 0.11 294 161 249 704 P = 0.76 0.57) 3378 (P = 0.103)	Contr Events 3 15 134 8 1 15 94 6 8 6 8 6 1 1 1); I <sup>a</sup> = 4 28 8 6 11 1); I <sup>a</sup> = 4 28 11 1 1; I <sup>a</sup> = 4 9(); I <sup>a</sup> = 9() 9(); I <sup>a</sup> = 9(); I <sup>a</sup>	100 100 88 402 67 73 2094 64 2788 2% 144 82 128 354 5 3142 8%	Weight 0.5% 1.7% 14.0% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0	Risk Ratio M.H. Fixed, 95% C1 0.07 (10.0, 1.32) 0.74 (0.34, 1.46) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.42) 2.30 (0.94, 0.97) 2.30 (0.94, 0.97) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54) 0.89 (0.82, 0.96)	Risk Ratio M-H, Fixed, 95% Cl	100
Study or Subgroup           1.6.1 Open label RCT           CTR/202005/024559           CTR/202005/025589           NCT02735707           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT043403865           Subtotal (95% CI)           Total events           Heterogeneity ChF = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT0434037           NCT04320615           NCT0436937           NCT0437186           Subtotal (95% CI)           Total events           Heterogeneity ChF = 0.4           Test for overall effect Z =           Total events           Heterogeneity ChF = 1.7           Test for overall effect Z =           Test for overall effect Z =           Test for overall offect Z           Test for overall offect Z =	Tocilizu <u>Events</u> 0 11 87 7 2 596 14 77 2 596 14 77 3.38, df = 6 3.26 (P = 9 26 93 49, df = 2 (f = 0.57 (P = 810 .50, df = 9 2.2.55 (P = 810 .50, df = 9 2.2.55 (P = 810 .50, df = 9 2.2.55 (P = 810 .50, df = 9 .50, df = 9	= 1.79 mab Total 20 91 363 63 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 2*1.79	Contr Events 3 15 134 8 1 15 4 8 8 1 1 5 94 4 8 8 11 1 2 8 3 11 42 2 8 3 11 42 903 9);   <sup>≠</sup> = 0 90 903 9);   <sup>≠</sup> = 0 91 11 11 11 11 11 11 11 11 11 11 11 11	nol <u>Total</u> 10 88 402 67 32094 64 2788 2% 144 82 128 354 5 3142 8%	Weight 0.5% 1.7% 14.0% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0	Risk Ratio M.H. Fixed, 95% C1 0.07 (10.0, 1.32) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.42) 2.10 (0.20, 2.42) 2.30 (0.94, 0.97) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54) 0.89 (0.82, 0.96)	Risk Ratio M-H, Fixed, 95% Cl	100
Study or Subgroup           1.6.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT04233100           NCT0433100           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity Chi <sup>2</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04372186           Subtotal (95% CI)           Total events           Heterogeneity, Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity, Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Total events           Heterogeneity, Chi <sup>2</sup> = 12           Test for overall effect Z =           Test for overall effect Z =	Tocilizum <u>Events</u> 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810) 810 810 810 810 810 810 810 810	= 1.79 mab Total 20 91 363 63 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 2*1.79	Contr Events 3 15 134 8 1 15 94 6 8 6 8 6 1 1 1); I <sup>a</sup> = 4 28 8 6 11 1); I <sup>a</sup> = 4 28 11 1 1; I <sup>a</sup> = 4 9(); I <sup>a</sup> = 9() 9(); I <sup>a</sup> = 9(); I <sup>a</sup>	nol <u>Total</u> 10 88 402 67 32094 64 2788 2% 144 82 128 354 5 3142 8%	Weight 0.5% 1.7% 14.0% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0.9% 0	Risk Ratio M.H. Fixed, 95% C1 0.07 (10.0, 1.32) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.42) 2.10 (0.20, 2.42) 2.30 (0.94, 0.97) 0.87 (0.80, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54) 0.89 (0.82, 0.96)	Risk Ratio M-H, Fixed, 95% Cl	100
Study or Subgroup           1.6.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT0423350           NCT0423350           NCT04348355           NCT04348355           Subtotal (95% C)           Total events           Heterogeneity, Chi <sup>P</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04356937           NCT04356937           NCT04356937           NCT04356937           NCT04356937           NCT04356937           NCT04356937           Total events           Heterogeneity, Chi <sup>P</sup> = 0.4           Test for overall effect Z =           Total (95% CI)	Tocilizu Events 0 11 87 7 2 586 14 717 .38, df = 6 8 9 26 93 49, df = 2 (P = 810 .50, df = 9 810 .50, df = 9 exercise Children (P = 810 .50, df = 9 .50, df = 9 .50	$\begin{array}{c} = 1.79 \\ \hline \text{mab} \\ \hline \text{Total} \\ 200 \\ 911 \\ 353 \\ 63 \\ 853 \\ 60 \\ 2022 \\ 65 \\ 2674 \\ (P=0.1 \\ 0.001) \\ 294 \\ 161 \\ 249 \\ 704 \\ P=0.75 \\ 0.57) \\ \hline 3378 \\ (P=0.1 \\ 0.003) \\ e^2 = 1.79 \\ \hline mab \end{array}$	Contr Events 3 15 134 8 1 1 594 8 6 1 1 594 8 6 1 1); P = 4 28 3 11 1); P = 4 28 3 11 28 3 11; 5 9); P = 20 90 3 9); P = 0 90 4 9); P = 0 90 90; P = 0 90 90; P = 0 90; P = 0 90	144 144 144 10 88 402 67 7 83 2094 64 2788 2% 144 82 128 354 5 3142 8% P = 0.116 rol (1)	Weight 0.5% 1.7% 1.4% 0.9% 0.9% 0.7% 93.8% 4.2% 0.4% 6.2% 100.0%	Hisk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.04, 132)           0.07 (10.04, 132)           1.01 (0.59, 0.93)           0.31 (0.36, 2.42)           2.10 (0.20, 2.25)           2.30 (0.94, 0.97)           2.30 (0.94, 0.97)           2.30 (0.94, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.52, 2.38)           1.10 (0.79, 1.54)           0.89 (0.82, 0.96)           2%           Risk Ratio	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           1.6.1 Open label RCT           CTR/202005/024558           CTR/202005/024558           VCT02735707           NCT04348355           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           NCT04320615           NCT04320615           NCT04320615           NCT04320615           NCT04320615           NCT04320615           NCT04320615           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Testfor overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Testfor overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Testfor overall effect Z =           Networks           Nortal events           Heterogeneity: Chi <sup>2</sup> = 12           Testfor overall effect Z =	Tocilizu <u>Events</u> 0 11 87 7 2 596 14 717 .38, df = 6 3.26 (P = 58 9 26 93 49, df = 2 (I e.57 (P = 810 .50 (df = 9 e.295 (P = 2.95 (P = 2.95 (C = 2.95 (P = 1.95 (C = 2.95 (P	= 1.79 mab 200 91 353 63 60 2022 65 2674 (P = 0.1 0.001) 294 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) mab Total	Contr Events 3 15 134 8 1 14 6 8 6 1 1 1 1 1; i <sup>p</sup> = 4 28 3 11 1; i <sup>p</sup> = 4 28 3 11 1; i <sup>p</sup> = 4 9; i <sup>p</sup> = 0% 9; i <sup>p</sup> = 0%	100 Total 100 88 4022 67 63 2094 4 2788 2% 144 82 128 354 5 3142 8% P = 0.118 P = 0.118 Total	Weight 0.5% 1.7% 0.9% 0.9% 0.7% 93.8% 4.2% 0.4% 6.2% 100.0% Weight	Risk Ratio <u>M.H. Fixed, 95% C1</u> 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.34, 1.46) 0.74 (0.59, 0.33) 0.33 (0.36, 2.42) 2.30 (0.36, 2.42) 0.89 (0.81, 0.87) 2.30 (0.84, 5.61) 1.51 (0.43, 5.49) 1.52 (0.43, 5.49) 1.52 (0.43, 5.49) 1.52 (0.42, 2.38) 1.10 (0.79, 1.54) 0.89 (0.82, 0.96] 0.89 (0.82, 0.96] 2% Risk Ratio <u>M.H. Fixed, 95% C1</u>	Risk Ratio M-H, Fixed, 95% Cl	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/024959           CTR/2020/05/024959           NCT042365/025369           NCT0423650           NCT04331808           NCT04381938           NCT04381938           NCT04381938           NCT043865           Subtotal (95% CI)           Total events           Heterogenelly: ChIP = 0.4           Total 5% CI)           Total 5% CI)           Total 495% CI)           Total 5% CI)           Total 6%% CI)           Total 700% CIP           Total 700% CIP           Total 700% CIP           Subtotal 6%% CIP	Tocilizu Events 0 11 87 7 2566 14 717 138, df = 6 3.26 (P = 58 9 26 9 26 9 349, df = 2(1) 50, df = 9 2.95 (P = 810 50, df = 9 2.50, df = 9 3.50, df = 9 3.50, df = 9 3.50, df	= 1.79 mab Total           200         91           353         63           63         63           00         2022           65         2674           (P = 0.1         0.001)           294         161           249         161           294         0.001)           294         161           299         704           90         0.003           2*= 1.79         mab           Total         20	Contr <u>Events</u> 3 15 134 8 1 694 6 861 1); P=4 28 3 11 28 3 11 42 903 9); P=2 df=1 (F Contr <u>Events</u> 3 3 3 3 3 3 3 3 3 3 3 5 5 3 4 4 5 3 3 5 5 5 5 5 5 5 5 5 5 5 5 5	nol <u>Total</u> 10 88 4022 67 63 2094 <b>2788</b> 2% 144 82 128 354 354 354 368% ≥ = 0.18 01 <u>Total</u> 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 1.7% 1.7% 0.1% 0.9% 0.7% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% 100.0%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.01 (0.50, 0.63)           0.08 (0.81, 0.63)           0.087 (0.80, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.62, 2.38)           1.01 (0.79, 1.54)           0.89 (0.82, 0.96)           2%           Risk Ratio           M.H. Fixed, 95% CI	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/022005/024559           CTR/022005/024559           NCT042355           NCT04331608           NCT04331809           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity. Chi <sup>P</sup> = 10           Testfor overall effect Z =           1.6.2 Double-blind RCT           NCT04320615           NCT04320615           NCT04320615           NCT04320615           NCT04320615           Subtotal (95% CI)           Total events           Heterogeneity. Chi <sup>P</sup> = 0.4           Test for overall effect Z =           Total (95% CI)           Total (95% CI)           Total events           Heterogeneity. Chi <sup>P</sup> = 12           Test for overall effect Z =           CTR/202005/022045/02           CTR/202005/02568	Tocilizum <u>Events</u> 0 11 87 7 2 596 14 717 1.38, df = 6 8 9 26 93 49, df = 2 (f = 0.57 (f) = 2 810 .50, df = 2(5) (f) = 810 .50, df = 2(1) (f) (f) (f) (f) (f) (f) (f) (f) (f) (f	Zer 1.79 mab Total 200 91 353 60 2022 26 6 2674 (P = 0.1 0.001) 2024 704 (P = 0.1000) 704 P = 0.75 704 P = 0.75 704 P = 0.75 704 249 704 704 249 704 704 249 704 249 704 704 249 704 704 704 704 704 704 704 704 704 704	Contr Events 3 15 134 8 134 8 6 8 11 1 5 94 6 8 11 1 28 3 11 1 28 3 11 1 42 9 90 3 9); P= 4 4 20 42 90 3 9); P= 4 4 20 3 11 14 14 8 15 15 14 14 8 15 134 16 11 12 12 13 12 12 12 13 12 12 12 12 12 12 12 12 12 12 12 12 12	100 Total 100 88 4022 67 63 2094 4 2788 22% 144 82 23% 354 354 5 3142 8% P = 0.18 10 10 88 P = 0.718 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.7% 93.8% 4.2% 100.0% 100.0% 100.0% 100.0%	101         0.07         0.03         1.03         0.04         1.04         0.05         0.03	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/202005/024559           CTR/202005/024559           NCT02735/07           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04349365           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           NCT0434020615           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 12           Total events           Heterogeneith; Chi <sup>2</sup> = 12           Test for overall effect Z =           Test for overall effect Z =     <	Tocilizu Events 0 11 87 7 2 596 14 77 2 596 14 77 3.38, df = 6 3.26 (P = 9 9 26 9 26 9 26 9 26 9 9 26 9 20 50, df = 2 (C) 50, df = 9 2.25 (C) 7 9 7 7 7 7 7 7 7 7 7 7 7 7 7	<sup>2</sup> = 1.79 mab Total 200 91 353 63 63 60 2022 2022 2024 (P = 0.1 200 2024 (P = 0.1 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) <sup>2</sup> = 1.79 mab Total 20 0 3338	Contr <u>Events</u> 3 3 1 3 4 8 8 1 1 6 9 4 2 28 3 3 11 4 2 28 3 3 11 4 2 8 3 3 1 4 4 8 8 1 1 4 8 8 1 1 4 8 8 1 1 4 8 1 1 4 8 8 1 1 8 1 4 8 8 1 1 8 1 4 8 1 1 8 1 4 8 8 1 1 1 8 1 1 1 8 1 1 1 1 1 1 1 1 1 1 1 1 1	Total Total 10 88 402 67 63 2094 4 2788 2% 144 82 128 354 5 3142 8% P = 0.16 10 10 14 8% 209 144 82 128 354 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.7% 93.8% 4.2% 0.4% 6.2% 100.0% 100.0% 100.0%	Risk Ratio <u>M.H. Fixed, 95% CI</u> 0.07 (10.0, 1.32) 0.71 (10.34, 1.46) 0.74 (10.59, 0.93) 0.93 (10.36, 2.42) 2.10 (10.20, 2.256) 0.89 (0.81, 0.97) 2.30 (0.94, 5.81) 0.87 (0.80, 0.95] 1.01 (0.68, 1.52) 1.52 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54) 0.89 [0.82, 0.96] 2% Risk Ratio <u>M.H. Fixed, 95% CI</u> 0.07 (10.34, 1.46) 0.74 (10.35, 0.83)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/224559           CTR/2020/05/2359           NCT042331608           NCT04331808           NCT04331808           NCT04331808           Subtotal (95% C)           Total events           Heterogeneity, Chi <sup>®</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04356937           NCT04326938           Subtotal (95% C)           Total events           Heterogeneity, Chi <sup>®</sup> = 10           Test for overall effect Z =           Total (95% C)           Total events           Heterogeneity, Chi <sup>®</sup> = 12           Test for overall effect Z =           Total (95% CI)           Total events           Heterogeneity, Chi <sup>®</sup> = 12           Test for overall effect Z =           Test for overall effect Z =           Test for subaroup diffect           CTR/202005/024595           NCT04232015	Tocilizu Events 0 11 87 7 2 598 14 717 1.38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (P = 810 .50, df = 9 = 2.95 (P = 810 .50, df = 9 2.057 (P = 810 .50, df = 9 1.38, df = 6 .50, df = 9 .50, df = 10 .50, df = 9 .50, df = 9	= 1.79 mab Total 200 91 353 63 63 65 2674 (P = 0.1 0.001) 2944 161 249 704 P = 0.70 3378 (P = 0.1 0.057) 3378 Total Total Total 204 91 353 294	Contr Events 3 15 134 8 8 8 11 15 9 9 9 9 9 9 1 1 9 0 3 11 42 2 8 3 11 1 42 9 9 9 9 9 9 9 9 0 3 9 9 7 8 2 8 15 134 134 8 134 134 8 134 134 8 134 134 8 134 134 8 134 134 8 134 134 8 134 134 134 134 134 134 134 134 134 134	Total Total 10 88 402 67 63 2094 64 2788 22% 144 22% 3142 8% 2=0.18 6 3142 8% 2=0.18 10 88 10 10 88 10 10 88 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 0.1% 75.9% 0.4% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 7.1%	Hisk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.03 (10.30, 242)           0.03 (10.30, 242)           0.03 (10.30, 242)           0.04 (10.59, 0.93)           0.33 (10.30, 242)           0.05 (10.80, 0.95]           1.01 (10.68, 1.52]           1.53 (10.43, 549)           1.22 (10.52, 3.38)           1.01 (0.79, 1.54)           0.89 (0.82, 0.96)           2%           Risk Ratio           0.07 (10.00, 1.32)           0.77 (10.34, 1.46)           0.74 (10.59, 0.55)           0.77 (10.34, 1.46)           0.74 (10.58, 1.52)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/202005/024559           CTR/202005/024559           NCT02735/07           NCT04348355           NCT04348355           NCT04348355           NCT04348355           NCT04349365           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           NCT0434020615           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity: Chi <sup>2</sup> = 12           Total events           Heterogeneith; Chi <sup>2</sup> = 12           Test for overall effect Z =           Test for overall effect Z =     <	Tocilizu Events 0 11 87 7 2 596 14 77 2 596 14 77 3.38, df = 6 3.26 (P = 9 9 26 9 26 9 26 9 26 9 9 26 9 20 50, df = 2 (C) 50, df = 9 2.25 (C) 7 9 7 7 7 7 7 7 7 7 7 7 7 7 7	<sup>2</sup> = 1.79 mab Total 200 91 353 63 63 60 2022 2022 2024 (P = 0.1 200 2024 (P = 0.1 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) <sup>2</sup> = 1.79 mab Total 20 0 3338	Contr <u>Events</u> 3 3 1 3 4 8 8 1 1 6 9 4 2 28 3 3 11 4 2 28 3 3 11 4 2 8 3 3 1 4 4 8 8 1 1 4 8 8 1 1 4 8 8 1 1 4 8 1 1 4 8 8 1 1 8 1 4 8 8 1 1 8 1 4 8 1 1 8 1 4 8 8 1 1 1 8 1 1 1 8 1 1 1 1 1 1 1 1 1 1 1 1 1	Total Total 10 88 402 67 63 2094 4 2788 2% 144 82 128 354 5 3142 8% P = 0.16 10 10 14 8% 209 144 82 128 354 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.7% 93.8% 4.2% 0.4% 6.2% 100.0% 100.0% 100.0%	Risk Ratio <u>M.H. Fixed, 95% CI</u> 0.07 (10.0, 1.32) 0.71 (10.34, 1.46) 0.74 (10.59, 0.93) 0.93 (10.36, 2.42) 2.10 (10.20, 2.256) 0.89 (0.81, 0.97) 2.30 (0.94, 5.81) 0.87 (0.80, 0.95] 1.01 (0.68, 1.52) 1.52 (0.43, 5.49) 1.22 (0.62, 2.38) 1.10 (0.79, 1.54) 0.89 [0.82, 0.96] 2% Risk Ratio <u>M.H. Fixed, 95% CI</u> 0.07 (10.34, 1.46) 0.74 (10.35, 0.83)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/02/4559           CTR/2020/05/02/4559           CTR/2020/05/02/4559           NCT04735707           NCT04733100           NCT04331808           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04320615           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 0.2           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04372185           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 0.2           Test for overall effect Z =           Test for overall effect Z =           Test for subgroup           CTR/202005/02.4559           NCT0232559           NCT0235267           NCT04331808	Tocilizu Events 0 11 87 7 2 596 14 71 .38, df = 6 3.26 (P = 58 9 26 93 26 93 26 93 26 93 49, df = 2 (I e 0.57 (P = 810 50.67 (P = 93 810 50.67 (P = 810 50.67 (P = 810 50.67 (P = 810 50.67 (P = 93 810 50.67 (P = 810 50.67 (P = 810) 50.67 (P = 810) 50.67 (P = 810) 50.67 (P = 810) 50.67 (P = 810) 50.67 (P = 810) 50.67 (P = 810)	= 1.79 mab Total 200 91 363 65 2674 (P = 0.1 0.001) 294 161 294 161 249 704 P = 0.762 0.003) a378 (P = 0.1 0.003) atotal Total 200 <td>Contr Events 3 3 1 3 1 3 4 8 8 1 1 5 9 4 2 8 8 3 1 1 4 2 2 8 8 3 1 1 4 2 2 8 3 3 1 1 4 4 8 8 1 4 8 1 5 9 4 8 8 1 1 5 9 4 8 1 1 5 9 4 8 1 1 5 9 4 8 3 3 1 1 4 8 8 1 1 5 9 4 8 3 3 1 1 1 1 1 4 8 8 1 1 5 9 4 8 3 3 1 1 1 1 1 1 1 1 1 1 1 1 1</td> <td>Total Total 10 88 402 67 63 2094 42 278 22% 144 82 23% 3142 8% 2 = 0.186 rotal 10 8% 2 = 0.186 rotal 10 8% 2 = 0.186 rotal 10 8 8 40 2 7 8 8 8 4 2 8 8 8 8 10 10 10 10 10 10 10 10 10 10</td> <td>Weight 0.5% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 0.9% 14.0% 0.9% 0.9% 14.0% 0.9% 0.9% 0.1% 0.1% 0.7% 0.9% 0.1% 0.1% 0.7% 0.7% 0.7% 0.1% 0.7%</td> <td>Risk Ratio M.H. Fixed, 95% CI 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.36, 0.33) 0.33 (0.36, 2.42) 2.30 (0.36, 2.42) 2.30 (0.36, 0.87) 0.87 (0.80, 0.87) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.00 (0.79, 1.54) 0.89 (0.82, 0.96] 28 Risk Ratio M.H. Fixed, 95% CI 0.07 (0.00, 1.32) 0.71 (0.34, 3.49) 1.20 (0.01, 1.32) 0.71 (0.34, 3.49) 1.20 (0.01, 1.32) 0.71 (0.34, 3.49) 0.71 (0.36, 3.42) 0.71 (0.36, 3.42) 0.</td> <td>Risk Ratio M.H. Fixed, 95% CI</td> <td>100</td>	Contr Events 3 3 1 3 1 3 4 8 8 1 1 5 9 4 2 8 8 3 1 1 4 2 2 8 8 3 1 1 4 2 2 8 3 3 1 1 4 4 8 8 1 4 8 1 5 9 4 8 8 1 1 5 9 4 8 1 1 5 9 4 8 1 1 5 9 4 8 3 3 1 1 4 8 8 1 1 5 9 4 8 3 3 1 1 1 1 1 4 8 8 1 1 5 9 4 8 3 3 1 1 1 1 1 1 1 1 1 1 1 1 1	Total Total 10 88 402 67 63 2094 42 278 22% 144 82 23% 3142 8% 2 = 0.186 rotal 10 8% 2 = 0.186 rotal 10 8% 2 = 0.186 rotal 10 8 8 40 2 7 8 8 8 4 2 8 8 8 8 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 0.9% 14.0% 0.9% 0.9% 14.0% 0.9% 0.9% 0.1% 0.1% 0.7% 0.9% 0.1% 0.1% 0.7% 0.7% 0.7% 0.1% 0.7%	Risk Ratio M.H. Fixed, 95% CI 0.07 (0.00, 1.32) 0.71 (0.34, 1.46) 0.74 (0.36, 0.33) 0.33 (0.36, 2.42) 2.30 (0.36, 2.42) 2.30 (0.36, 0.87) 0.87 (0.80, 0.87) 1.01 (0.68, 1.52) 1.53 (0.43, 5.49) 1.22 (0.62, 2.38) 1.00 (0.79, 1.54) 0.89 (0.82, 0.96] 28 Risk Ratio M.H. Fixed, 95% CI 0.07 (0.00, 1.32) 0.71 (0.34, 3.49) 1.20 (0.01, 1.32) 0.71 (0.34, 3.49) 1.20 (0.01, 1.32) 0.71 (0.34, 3.49) 0.71 (0.36, 3.42) 0.71 (0.36, 3.42) 0.	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/204559           CTR/2020/05/2589           NCT02735707           NCT04331808           NCT04348355           NCT0430865           Subtoal (95% C)           Total events           Heierogeneily, Chi <sup>®</sup> = 10           Test for overall effect 2 =           16.2 Double-blind RCT           NCT04356937           NCT04356937           NCT043266937           NCT04356937           NCT04356037           NCT04356037           NCT04356037           NCT04356037           Subtotal (95% C)           Total events           Heierogeneily, Chi <sup>®</sup> = 12           Test for overall effect Z =           Test for subgroup           CTRU220205/024595           NCT02435024595           NCT04331808           NCT04331805           NCT0433555	Tocilizum Events 0 11 87 7 2 596 14 77 1.38, df = 6 8.326 (P = 58 9 26 9 20 67 7 7 7 7 7 7 7 7 7 7 7 7 7	■ = 1.79 mab Total 20 91 363 63 60 2022 65 2674 (P = 0.1 0.001) 294 161 249 704 P = 0.757) 3378 (P = 0.1 704 P = 0.757) 3378 (P = 0.1 29 3378 (P = 0.1 29 3378 (P = 0.1 20 20 91 353 294 65 20 91 10 20 20 20 20 20 20 20 20 20 20 20 20 20	Contr Events 3 3 5 134 8 1 134 8 1 1 594 6 861 1); P=4 28 3 11 42 28 3 11 42 28 3 11 42 593 4 6 11 12 12 13 13 13 13 13 13 13 13 13 13	Total Total 10 88 402 67 67 67 67 82 2094 64 2788 22% 144 82 128 354 5 3142 8% 2 = 0.18 8% 2 = 0.18 10 8% 2 = 0.18 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.4% 0.4% 0.4% 0.4% 0.4% 0.5% 0.5%	Risk Ratio M.H. Fixed, 95% CI 0.07 (10.01, 132) 0.74 (0.34, 1.46) 0.74 (0.59, 0.63) 0.93 (10.32, 242) 0.93 (10.32, 242) 0.98 (0.81, 0.95) 1.01 (0.68, 1.52) 1.53 (0.43, 549) 1.22 (0.62, 2.38) 1.01 (0.62, 1.54) 0.89 (0.82, 0.96) 2% Risk Ratio M.H. Fixed, 95% CI 0.07 (10.00, 1.32) 0.74 (0.59, 0.83) 1.01 (0.68, 1.52) 0.74 (0.59, 0.83) 1.01 (0.68, 1.52) 0.74 (0.59, 0.83) 1.01 (0.68, 1.52) 0.74 (0.59, 0.83) 1.01 (0.68, 1.52) 0.33 (0.32, 2.42) 0.33 (0.32, 2.42) 0.33 (0.32, 2.42)	Risk Ratio M.H. Fixed, 95% CI	- 100
Study or Subgroup           1.6.1 Open label RCT           CTR/0202005/024559           CTR/022005/024559           NCT04235707           NCT04331808           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>P</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04372186           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>P</sup> = 0.4           Test for overall effect Z =           Total events           Heterogeneity: Chi <sup>P</sup> = 12           Total events           Heterogeneity: Chi <sup>P</sup> = 12           Test for overall effect Z =           Total (95% CI)           Total events           Heterogeneity: Chi <sup>P</sup> = 12           Test for overall effect Z =           Test for overall effect Z =           CTR/02020/5024595           NCT0432005/024595           NCT0432005/024595           NCT04331808           NCT04330808           NCT04330803           NCT043685           NCT04368637	Tocilizu <u>Events</u> 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810 50, df = 2 (l = 0.57 (P = 10)) 50, df =	= 1.79 mab Total 200 91 363 65 2674 (P = 0.1 2022 265 2674 264 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) = 1.79 2003 2014 1003 2015 2016 2017 202 204 161 3378 3294 63 63 63 60 161	Contr Events 3 3 5 134 8 1 1 694 6 881 1 1); IP=4 28 3 3 11 1 (); IP=4 903 3 9); IP=2 903 3 9); IP=2 903 3 11 1 1 1 2 8 8 1 3 5 11 4 2 8 8 1 3 1 5 134 8 1 8 1 8 1 8 1 8 1 8 1 8 1 1 8 1 8 1	Total Total 10 88 402 67 63 2094 64 2788 2% 144 82 354 5 3142 8% P = 0.18 8% P = 0.18 10 88 402 128 354 5 10 88 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 9.3.8% 4.2% 0.7% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% 100.0% 100.0% 100.0% 17.7% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.7% 1.6% 1.8% 1.8% 1.8%	Risk Ratio M.H. Fixed, 95% CI 0.07 (10.01, 132) 0.74 (0.34, 1.46) 0.74 (0.59, 0.93) 0.93 (0.36, 2.42) 2.10 (0.20, 2.42) 2.10 (0.20, 2.42) 2.30 (0.94, 0.95) 0.87 (0.80, 0.95] 1.01 (0.68, 1.52) 1.52 (0.43, 5.49) 1.22 (0.62, 2.38) 1.00 (0.79, 1.54) 0.89 (0.82, 0.96] 2% Risk Ratio M.H. Fixed, 95% CI 0.07 (0.00, 1.32) 0.77 (0.34, 1.46) 0.74 (0.59, 0.93) 1.01 (0.68, 1.52) 0.77 (0.34, 1.46) 0.74 (0.59, 0.93) 1.01 (0.68, 1.52) 0.71 (0.34, 1.46) 0.74 (0.59, 0.93) 1.01 (0.68, 1.52) 0.93 (0.36, 2.42) 2.10 (0.20, 2.56)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/224559           CTR/2020/05/23589           NCT042365/07           NCT04331908           NCT04331938           NCT043381938           NCT043885           Subtotal (95% CI)           Total events           Heterogeneily: ChIP = 0.1           Total events           Heterogeneily: ChIP = 10           Total events           Heterogeneily: ChIP = 1.2           Total events           NCT0432005025369           NCT043200502525707           NCT043320615           NCT04331008           NCT04332085           NCT043321808           NCT04321865           NCT043232685           NCT043232	Tocilizu Events 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 9 349, df = 2 (l = 0.57 (P = 810 150, df = 9 2.95 (P = 810 150, df = 9 2.95 (P = 810 11 87 7 2 810 150, df = 9 2.95 (P = 810 11 87 7 2 9 2 8 14 14 15 8 14 15 8 16 16 16 16 16 16 16 16 16 16	= 1.79 mab Total 200 91 353 63 60 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2024 40 0.001) 294 161 201 201 204 704 P = 0.76 207 3378 (P = 0.1 0.003) 3378 (P = 0.704) 204 704 P = 0.76 207 3378 (P = 0.1 0.003) 101 3378 60 101 353 204 63 60 161 124 249 249 249 249	Contr Events 3 3 15 134 8 1 134 8 1 14 8 1 14 8 1 15 14 8 1 14 8 1 14 8 1 14 8 1 14 15 134 8 1 14 15 134 8 1 14 15 134 8 1 14 15 134 15 14 15 14 15 14 15 14 15 15 15 15 15 15 15 15 15 15	Total Total 10 88 402 67 67 67 67 82 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 1288 354 2095 1288 2095 1295	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 1.7% 0.9% 0.	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.05, 0.03)           0.087 (0.84, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           1.52 (0.43, 549)           1.22 (0.62, 2.38)           1.00 (0.78, 1.52)           0.89 (0.82, 0.96)           2%           Risk Ratio           M.H. Fixed, 95% CI           0.74 (0.59, 0.93)           1.01 (0.68, 1.52)           0.74 (0.59, 0.93)           1.01 (0.68, 1.52)           1.00 (0.72, 1.54)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/022005/024599           CTR/022005/024599           NCT04331608           NCT04331608           NCT04331808           NCT04331808           Subtotal (95% C)           Total events           Helerogeneily, ChP = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04332188           Subtotal (95% C)           Total events           Helerogeneily, ChP = 0.4           Fest for overall effect Z =           Total (95% C)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Total (95% C)           Total 95% CI)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Study or Suboroup differe           VCTU432005/025369           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331936           NCT04331936           NC	Tocilizu Events 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 93 49, df = 2 (C 50, df = 9 50, df = 9 10 50, df = 9 810 50, df = 9 11 87 7 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 11 810 11 810 11 810 11 11 11 11 11 11 11 11 11	≈ 1.79 mab Total 20 91 353 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) ≈ 1.79 mab Total 20 91 3573 294 46 249 20 91 3533 294 65 20 20 20 20 20 20 20 20 20 20 20 20 20	Contr Events 3 3 1 3 1 3 4 1 4 4 2 8 3 1 1 4 2 2 8 3 1 1 4 2 2 8 3 1 1 4 4 2 8 3 1 1 4 4 5 4 4 5 5 5 4 4 5 5 5 5 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	rol Total 10 10 10 10 10 10 84 402 67 10 14 27% 3142 8% 2% 2% 3142 8% 2° 0 10 8% 2% 144 27% 3142 10 8% 40 2% 144 10 10 8% 142 12% 144 12% 144 12% 144 144 148 148 148 148 148 148	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 0.1% 75.9% 0.4% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 0.5% 0.5% 0.5%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.03 (10.30, 242)           2.10 (10.01, 20, 22)           2.10 (10.01, 20, 20)           0.08 (10.81, 0.93)           0.03 (10.30, 242)           2.30 (10.94, 0.967)           2.30 (10.94, 0.967)           1.53 (10.43, 649)           1.22 (10.62, 2.38)           1.10 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)	Risk Ratio M.H. Fixed, 95% CI	
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/224559           CTR/2020/05/23589           NCT042365/07           NCT04331908           NCT04331938           NCT043381938           NCT043885           Subtotal (95% CI)           Total events           Heterogeneily: ChIP = 0.1           Total events           Heterogeneily: ChIP = 10           Total events           Heterogeneily: ChIP = 1.2           Total events           NCT0432005025369           NCT043200502525707           NCT043320615           NCT04331008           NCT04332085           NCT043321808           NCT04321865           NCT043232685           NCT043232	Tocilizu Events 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 9 349, df = 2 (l = 0.57 (P = 810 150, df = 9 2.95 (P = 810 150, df = 9 2.95 (P = 810 11 87 7 2 810 150, df = 9 2.95 (P = 810 11 87 7 2 9 2 8 14 14 15 8 14 15 8 16 16 16 16 16 16 16 16 16 16	= 1.79 mab Total 200 91 353 63 60 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2022 2024 40 0.001) 294 161 201 201 204 704 P = 0.76 207 3378 (P = 0.1 0.003) 3378 (P = 0.704) 204 704 P = 0.76 207 3378 (P = 0.1 0.003) 101 3378 60 101 353 204 63 60 161 124 249 249 249 249	Contr Events 3 3 15 134 8 1 134 8 1 14 8 1 14 8 1 15 14 8 1 14 8 1 14 8 1 14 8 1 14 15 134 8 1 14 15 134 8 1 14 15 134 15 14 15 14 16 14 15 16 16 16 16 16 17 17 17 17 17 17 17 17 17 17	Total Total 10 88 402 67 67 67 67 82 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 64 2788 2094 1288 354 2095 1288 2095 1295	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 1.7% 0.9% 0.	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.05, 0.03)           0.087 (0.84, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           2.30 (0.94, 561)           1.52 (0.43, 549)           1.22 (0.62, 2.38)           1.00 (0.78, 1.52)           0.89 (0.82, 0.96)           2%           Risk Ratio           M.H. Fixed, 95% CI           0.74 (0.59, 0.93)           1.01 (0.68, 1.52)           0.74 (0.59, 0.93)           1.01 (0.68, 1.52)           1.00 (0.72, 1.54)	Risk Ratio M.H. Fixed, 95% CI	100
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/022005/024599           CTR/022005/024599           NCT04331608           NCT04331608           NCT04331808           NCT04331808           Subtotal (95% C)           Total events           Helerogeneily, ChP = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04332188           Subtotal (95% C)           Total events           Helerogeneily, ChP = 0.4           Fest for overall effect Z =           Total (95% C)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Total (95% C)           Total 95% CI)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Study or Suboroup differe           VCTU432005/025369           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331936           NCT04331936           NC	Tocilizu Events 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 93 49, df = 2 (C 50, df = 9 50, df = 9 10 50, df = 9 810 50, df = 9 11 87 7 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 11 810 11 810 11 810 11 11 11 11 11 11 11 11 11	≈ 1.79 mab Total 20 91 353 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) ≈ 1.79 mab Total 20 91 3573 294 46 249 20 91 3533 294 65 20 20 20 20 20 20 20 20 20 20 20 20 20	Contr Events 3 3 5 134 8 1 1 694 6 6 6 6 1 1 1,    = 4 2 8 3 11 1 ,    = 4 2 8 3 11 1 ,    = 4 2 8 3 11 1 ,    = 4 90;    = 2 90;	rol Total 10 10 10 10 10 10 84 402 67 10 14 27% 3142 8% 2% 2% 3142 8% 2° 0 10 8% 2% 144 27% 3142 10 8% 40 2% 144 10 10 8% 142 12% 144 12% 144 12% 144 144 148 148 148 148 148 148	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 0.1% 75.9% 0.4% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 0.5% 0.5% 0.5%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.03 (10.30, 242)           2.10 (10.01, 20, 22)           2.10 (10.01, 20, 20)           0.08 (10.81, 0.93)           0.03 (10.30, 242)           2.30 (10.94, 0.967)           2.30 (10.94, 0.967)           1.53 (10.43, 649)           1.22 (10.62, 2.38)           1.10 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)	Risk Ratio M.H. Fixed, 95% CI	
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/022005/024599           CTR/022005/024599           NCT04331608           NCT04331608           NCT04331808           NCT04331808           Subtotal (95% C)           Total events           Helerogeneily, ChP = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04332188           Subtotal (95% C)           Total events           Helerogeneily, ChP = 0.4           Fest for overall effect Z =           Total (95% C)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Total (95% C)           Total 95% CI)           Total events           Helerogeneily, ChP = 12           Test for overall effect Z =           Study or Suboroup differe           VCTU432005/025369           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331808           NCT04331936           NCT04331936           NC	Tocilizu Events 0 11 87 7 2 596 14 717 138, df = 6 3.26 (P = 58 9 26 93 49, df = 2 (C 50, df = 9 50, df = 9 10 50, df = 9 810 50, df = 9 11 87 7 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 2 810 50, df = 9 11 810 50, df = 9 11 810 11 810 11 810 11 11 11 11 11 11 11 11 11	≈ 1.79 mab Total 20 91 353 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) ≈ 1.79 mab Total 20 91 3573 294 46 249 20 91 3533 294 65 20 20 20 20 20 20 20 20 20 20 20 20 20	Contr Events 3 3 5 134 8 1 1 694 6 6 6 6 1 1 1,    = 4 2 8 3 11 1 ,    = 4 2 8 3 11 1 ,    = 4 2 8 3 11 1 ,    = 4 90;    = 2 90;	rol Total 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 0.1% 75.9% 0.4% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 0.5% 0.5% 0.5%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           0.03 (10.30, 242)           2.10 (10.01, 20, 22)           2.10 (10.01, 20, 20)           0.08 (10.81, 0.93)           0.03 (10.30, 242)           2.30 (10.94, 0.967)           2.30 (10.94, 0.967)           1.53 (10.43, 649)           1.22 (10.62, 2.38)           1.10 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)	Risk Ratio M.H. Fixed, 95% CI	
Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/024559           DCTR/2020/05/024559           NCT042355           NCT042355           NCT04331808           NCT04331808           Subtotal (95% C)           Total events           Heierogeneity, Chi <sup>®</sup> = 10           Test for overall effect 2 =           1.6.2 Double-blind RCT           NCT04356937           NCT04356937           NCT0432658           Subtotal (95% C)           Total events           Heterogeneity, Chi <sup>®</sup> = 10           Test for overall effect 2 =           Total (95% C)           Total events           Heterogeneity, Chi <sup>®</sup> = 12           Test for overall effect 2 =           Total (95% C)           Total (95% C) <td>Tocilizum Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 2.65 (P = 810 50, df = 9 2.95 (P = 810 50, df = 9 11 11 87 57 2 9 2.65 11 11 11 11 11 11 11 11 11 1</td> <td>≥ = 1.79 mab Total 20 91 353 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 3378 (P = 0.1 0.003) 249 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 3378 249 202 294 65</td> <td>Contr Events 3 3 5 134 8 1 1 694 6 861 1 1); I<sup>P</sup> = 4 28 3 11 1 1; I<sup>P</sup> = 4 28 3 9); I<sup>P</sup> = 2 9); I<sup>P</sup> = 2 9); I<sup>P</sup> = 2 9); I<sup>P</sup> = 2 9); I<sup>P</sup> = 2 1 9); I<sup>P</sup> = 2 1 1 1 4 2 8 8 1 1 1 1 1 2 8 8 1 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 1 2 8 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 1</td> <td>rol Total 10 10 10 10 10 10 10 10 10 10</td> <td>Weight 0.5% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 2.5% 0.5% 2.8% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1%</td> <td>Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.59, 0.93)           0.33 (1.36, 2.42)           2.10 (12.02, 2.26)           0.88 (0.81, 0.97)           2.30 (0.94, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.52, 3.38)           1.01 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)           0.71 (0.34, 1.46)           0.74 (10.54, 5.52)           1.01 (0.58, 5.52)           2.10 (10.20, 2.256)           1.10 (0.59, 0.31)           2.21 (0.20, 2.256)           1.10 (0.51, 5.21)           0.71 (0.34, 1.46)           0.74 (10.58, 1.52)           0.71 (0.34, 1.46)           0.74 (10.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.52 (0.43, 5.49)           0.21 (0.22, 2.26)           1.52 (0.42, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.52 (0.42, 2.38)&lt;</td> <td>Risk Ratio M.H. Fixed, 95% CI</td> <td></td>	Tocilizum Events 0 11 87 7 2 596 14 717 .38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 = 2.95 (P = 810 50, df = 9 2.65 (P = 810 50, df = 9 2.95 (P = 810 50, df = 9 11 11 87 57 2 9 2.65 11 11 11 11 11 11 11 11 11 1	≥ = 1.79 mab Total 20 91 353 60 2022 265 2674 (P = 0.1 0.001) 294 161 161 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 3378 (P = 0.1 0.003) 249 249 704 P = 0.76 0.57) 3378 (P = 0.1 0.003) 3378 249 202 294 65	Contr Events 3 3 5 134 8 1 1 694 6 861 1 1); I <sup>P</sup> = 4 28 3 11 1 1; I <sup>P</sup> = 4 28 3 9); I <sup>P</sup> = 2 9); I <sup>P</sup> = 2 9); I <sup>P</sup> = 2 9); I <sup>P</sup> = 2 9); I <sup>P</sup> = 2 1 9); I <sup>P</sup> = 2 1 1 1 4 2 8 8 1 1 1 1 1 2 8 8 1 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 2 8 1 1 1 2 8 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 2 8 1 1 1 1	rol Total 10 10 10 10 10 10 10 10 10 10	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 2.5% 0.5% 2.8% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.59, 0.93)           0.33 (1.36, 2.42)           2.10 (12.02, 2.26)           0.88 (0.81, 0.97)           2.30 (0.94, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.52, 3.38)           1.01 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)           0.71 (0.34, 1.46)           0.74 (10.54, 5.52)           1.01 (0.58, 5.52)           2.10 (10.20, 2.256)           1.10 (0.59, 0.31)           2.21 (0.20, 2.256)           1.10 (0.51, 5.21)           0.71 (0.34, 1.46)           0.74 (10.58, 1.52)           0.71 (0.34, 1.46)           0.74 (10.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.52 (0.43, 5.49)           0.21 (0.22, 2.26)           1.52 (0.42, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.52 (0.42, 2.38)<	Risk Ratio M.H. Fixed, 95% CI	
Study or Subgroup           Study or Subgroup           1.6.1 Open label RCT           CTR/2020/05/224559           NCT02/235707           NCT042/3550           NCT043/31008           NCT043/3108           NCT043/3108           NCT043/3108           NCT043/3108           Subtotal (95% CI)           Total events           Heterogeneity: ChP = 10           Test for overall effect Z =           1.5.2 Double-blind RCT           NCT043/32015           NCT043/32015           NCT043/32015           NCT043/32166           Subtotal (95% CI)           Total events           Heterogeneity: ChP = 12           Test for overall effect Z =           Total (95% CI)           Total events           Heterogeneity: ChP = 12           Test for overall effect Z =           CTRU/2020/05/02/3589           NCT02/3570           NCT043/3080           NCT043/3108           NCT043/31808           NCT043/31936           NCT043/31936           NCT043/31936           NCT043/31936           NCT043/31936           NCT043/31936	Tocilizu Events 0 11 87 7 2596 14 77 138, df = 6 3.26 (P = 58 9 26 9 349, df = 2 (l 0.57 (P = 810 50, df = 9 2.95 (P = 810 11 11 11 11 11 12 12 12 12 12	= 1.79 mab Total 200 91 353 63 60 2022 2674 (P = 0.1 0.070 294 161 249 704 P = 0.72 202 202 3378 (P = 0.1 0.070 3378 (P = 0.1 201 202 205 336	Contr Events 3 3 5 134 8 1 134 8 1 134 8 1 5 94 6 6 6 11); P=4 28 3 11 42 28 30 11 42 9 9 03 9 9; F=2 9 03 15 14 4 11 42 8 11 11 11 11 11 11 11 11 11	Total 100 88 402 67 763 2094 42 788 22% 144 82 1288 354 354 354 354 354 2094 402 108 8% 2094 402 128 2094 64 108 84 2094 64 108 84 2094 64 108 108 108 108 108 108 108 108	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 2.5% 0.5% 2.8% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1% 2.1% 2.1% 2.1% 2.5% 2.1%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.59, 0.93)           0.33 (1.36, 2.42)           2.10 (12.02, 2.26)           0.88 (0.81, 0.97)           2.30 (0.94, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.52, 3.38)           1.01 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)           0.71 (0.34, 1.46)           0.74 (10.54, 5.52)           1.01 (0.58, 5.52)           2.10 (10.20, 2.256)           1.10 (0.59, 0.31)           2.21 (0.20, 2.256)           1.10 (0.51, 5.21)           0.71 (0.34, 1.46)           0.74 (10.58, 1.52)           0.71 (0.34, 1.46)           0.74 (10.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.52 (0.43, 5.49)           0.21 (0.22, 2.26)           1.52 (0.42, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.52 (0.42, 2.38)<	Risk Ratio M.H, Fixed, 95% CI	-
Study or Subgroup           1.6.1 Open label RCT           CTR/022005/024559           CTR/022005/024559           NCT04235707           NCT04331808           NCT04348355           NCT04348355           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           Test for overall effect Z =           1.6.2 Double-blind RCT           NCT04372186           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 10           Total events           Heterogeneity: Chi <sup>2</sup> = 1           Total events           Heterogeneity: Chi <sup>2</sup> = 10           Total events           Heterogeneity: Chi <sup>2</sup> = 12           Test for overall effect Z =           Subtotal (95% CI)           Total events           NCT043202005/0245950           NCT043202005/0245950	Tocilizum Events 0 11 87 7 2 596 14 717 1.38, df = 6 = 3.26 (P = 58 9 26 93 49, df = 2 (l = 0.57 (P = 810 50, df = 9 20, df = 10 20, df = 9 20, df = 9	= 1.79 mab Total 200 91 353 60 60 2022 65 2674 (P = 0.1 2022 65 2674 161 249 704 P = 0.75 3378 (P = 0.1 20 704 P = 0.1 20 20 704 P = 0.1 20 20 20 20 704 P = 0.1 20 20 20 20 20 20 20 20 20 20 20 20 20	Contr Events 3 3 5 134 8 1 134 8 1 134 8 1 5 94 6 6 6 11); P=4 28 3 11 42 28 30 11 42 9 9 03 9 9; F=2 9 03 15 14 4 11 42 8 11 11 11 11 11 11 11 11 11	Total 100 88 402 67 763 2094 42 788 22% 144 82 1288 354 354 354 354 354 2094 402 108 8% 2094 402 128 2094 64 108 84 2094 64 108 84 2094 64 108 108 108 108 108 108 108 108	Weight 0.5% 14.0% 0.9% 14.0% 0.9% 93.8% 4.2% 0.4% 1.6% 6.2% 100.0% Weight 2.1% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 7.1% 58.0% 0.5%	Risk Ratio           M.H. Fixed, 95% CI           0.07 (10.01, 132)           0.07 (10.01, 132)           0.07 (10.01, 132)           1.01 (0.59, 0.93)           0.33 (1.36, 2.42)           2.10 (12.02, 2.26)           0.88 (0.81, 0.97)           2.30 (0.94, 0.95)           1.01 (0.68, 1.52)           1.53 (0.43, 5.49)           1.22 (0.52, 3.38)           1.01 (0.79, 1.54)           Risk Ratio           0.07 (10.00, 1.32)           0.71 (0.34, 1.46)           0.74 (10.54, 5.52)           1.01 (0.58, 5.52)           2.10 (10.20, 2.256)           1.10 (0.59, 0.31)           2.21 (0.20, 2.256)           1.10 (0.51, 5.21)           0.71 (0.34, 1.46)           0.74 (10.58, 1.52)           0.71 (0.34, 1.46)           0.74 (10.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.51 (0.42, 2.38)           0.71 (0.22, 2.66)           1.52 (0.43, 5.49)           0.21 (0.22, 2.26)           1.52 (0.42, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.51 (2.22, 2.38)           0.52 (0.42, 2.38)<	Risk Ratio M.H. Fixed, 95% CI	

Supplementary Figure 1. Association of tocilizumab with all-cause mortality (A) all RCTs (B) study type (C) type of control (D) Forest plot without the RECOVERY trial.



**Supplementary Figure 2.** Association of tocilizumab with all-cause mortality (A) funnel plot to assess the publication bias of the metaanalysis (B) sensitivity analysis.

Α	Tocilizu	mab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CTRI/2020/05/024959	16	20	6	10	0.5%	1.33 [0.77, 2.31]	
NCT02735707	190	353	184	402	11.5%	1.18 [1.02, 1.36]	
NCT04320615	180	294	74	144	6.7%	1.19 [0.99, 1.43]	
NCT04331808	52	63	49	67	3.2%	1.13 [0.94, 1.36]	+
NCT04346355	54	60	58	63	3.8%	0.98 [0.87, 1.09]	
NCT04356937	147	161	72	82	6.4%	1.04 [0.95, 1.14]	-+• <u>-</u> _
NCT04381936	1093	2022	999	2094	65.8%	1.13 [1.07, 1.20]	<b>+</b>
NCT04403685	35	65	31	64	2.1%	1.11 [0.79, 1.56]	
Total (95% CI)		3038		2926	100.0%	1.13 [1.08, 1.18]	<b>•</b>
Total events	1767		1473				
Heterogeneity: Chi <sup>2</sup> = 10	.58, df = 7	(P = 0.1	l 6); l² = 3	4%		_	0.5 0.7 1 1.5 2
Test for overall effect: Z =	: 5.18 (P <	0.0000	11)				Favours Tocilizumab Favours Control
3	Tocilizumab Ibgroup Events Total		ab Contro			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Events Total		M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.8.1 Open label RCT							
CTRI/2020/05/024959	16	20	6	10	1.1%	1.33 [0.77, 2.31]	
NCT02735707	190	353	184	402	12.2%	1.18 [1.02, 1.36]	
NCT04331808	52	63	49	67	8.4%	1.13 [0.94, 1.36]	
NCT04346355	54	60	58	63	17.0%	0.98 [0.87, 1.09]	
NCT04381936	1093	2022	999	2094	29.3%	1.13 [1.07, 1.20]	
NCT04403685	35	65	31	64	2.9%	1.11 [0.79, 1.56]	
Subtotal (95% CI)		2583		2700	71.0%	1.10 [1.03, 1.18]	◆
Total events	1440		1327				
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> =	7.33, df	= 5 (P =	0.20); P	²= 32%		
Test for overall effect: Z =	2.64 (P =	0.008)	Ì	21			
1.8.2 Double-blind RCT							
NCT04320615	180	294	74	144	8.5%	1.19 [0.99, 1.43]	
NCT04356937	147	161	72	82	20.6%	1.04 [0.95, 1.14]	
Subtotal (95% CI)		455		226	<b>29.0</b> %	1.10 [0.93, 1.29]	
Total events	327		146				
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =			'= 1 (P =	0.10); P	²= 63%		
Total (95% Cl)		3038		2926	100.0%	1.10 [1.03, 1.16]	◆
Total events	1767		1473				
	0.01.2		w	0.4 65	17 - 0400		
Heterogeneity: Tau <sup>2</sup> = 0.0	JU; Chr=	10.58.0	at=7 (P=	= 0.10).	F = 34%		0.7 0.85 1 1.2 1.5

#### Supplementary Figure 3. Association of tocilizumab with discharge (A) all RCTs (B) study type.

Test for subaroup differences:  $Chi^2 = 0.00$ . df = 1 (P = 0.96).  $I^2 = 0\%$ 

	Tocilizu	Tocilizumab Control				Risk Ratio	Risk Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CTRI/2020/05/025369	15	91	15	88	10.1%	0.97 (0.50, 1.86)	
NCT02735707	9	353	11	402	6.8%	0.93 [0.39, 2.22]	
NCT04320615	103	294	55	144	49.1%	0.92 [0.71, 1.19]	
NCT04331808	20	63	29	67	18.7%	0.73 [0.47, 1.16]	
NCT04356937	28	161	12	82	10.6%	1.19 [0.64, 2.21]	
NCT04403685	11	65	7	64	4.7%	1.55 [0.64, 3.74]	
Total (95% CI)		1027		847	100.0%	0.95 [0.78, 1.15]	-
Total events	186		129				
Heterogeneity: Chi <sup>2</sup> = 2.9	98, df = 5 (	P = 0.70	); I <b>²</b> = 0%	5		-	
Test for overall effect: $Z = 0.55$ (P = 0.58)							0.5 0.7 1 1.5 2 Favours Tocilizumab Favours Control

#### Supplementary Figure 4. Association of tocilizumab with patients of serious adverse events.



Supplementary Figure 5. Association of tocilizumab with secondary infections risk (A) all RCTs (B) peer-reviewed (C) type of control.

# **Supplementary Table**

Supplementar	y Table 1. Patient baseline characteristics of 8 RCTs in the meta-analysis.
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Author		Olivier Hermine	Carlo Salvarani	J.H. Stone	Carlos Salama	I.O. Rosas	Viviane C Veiga	Suresh Kumar	Arvinder S Soin	Anthony C. Gordon	Peter W Horby
Trial registration		NCT 04331808	NCT 04346355	NCT 04356937	NCT 04372186	NCT 04320615	NCT 04403685	CTRI/2020/0 5/024959	CTRI/202 0/05/0253 69	NCT 02735707	NCT 04381936
Treatment since	Tocilizumab	10 (7-13) (n=62)	7.0 (4.0-11.0)	9.0 (6.0–13.0)		12.1±6.6 (n=291)	10.0±3.1				9 (7-13)
symptom onset d	Control	10 (8-13) (n=66)	8.0 (6.0-11.0)	10.0 (7.0–13.0)		11.4±6.9 (n=143)	9.5±3.0				10 (7-14)
4.99	Tocilizumab	64.0 (57.1-74.3)	61.5 (51.5-73.5)	61.6 (46.4–69.7)	56.0±14.3	60.9±14.6	57.4±15.7	49.55±12.49	56 (47–63)	61.5±12.5	63.3 ±13.7
Age	Control	63.3 (57.1-72.3)	60.0 (54.0-69.0)	56.5 (44.7–67.8)	55.6±14.9	60.6±13.7	57.5±13.5	48.30±14.62	54 (43–63)	61.1±12.8	$63.9 \pm \! 13.6$
Gender	Tocilizumab	44/19	40/20	96/65	150/99	205/89	44/21	19/1	76/15	261/92	1335/687
(Male/Female)	Control	44/23	37/29	45/37	73/55	101/43	44/20	7/3	76/12	283/119	1437/657
Hypertension	Tocilizumab		27	80		178	30		36		
Hypertension	Control		29	38		94	34		34		
Diabetes	Tocilizumab	20(n=61)	10	45		105	22		31		569
Diabetes	Control	23(n=67)	9	30		62	20		43		600
Cardiac disease	Tocilizumab	20(n=61)		17		88	4		15		435
Calulae disease	Control	20(n=67)		7		35	3		12		497
Pulmonary	Tocilizumab	3(n=61)	2	15		49	2		1		473
disease	Control	3(n=67)	2	7		22	2		2		484
Chronic kidney	Tocilizumab	5(n=61)		29			5		4		118
disease	Control	13(n=67)		13			1		4		99
Cancer	Tocilizumab	4(n=61)		22			5				
Calicel	Control	5(n=67)		8			5				
Asthma	Tocilizumab	5(n=61)		15			4				
Astillia	Control	3(n=67)		7			1				
Liver disease	Tocilizumab					6					14
Liver disease	Control					2					10
Body mass	Tocilizumab	27.9 (23.3-30.8) (n=46)		29.9 (26.0–34.2)	32.0±7.9						
index(BMI)	Control	27.4 (24.5-31.3) (n=46)		30.2 (25.7–33.8)	33.1±7.2						
Obesity	Tocilizumab		16	80		63	15				
(BMI≥30)	Control		22	42		27	16				