SYNOPSIS

Name of Sponsor/Company: Fundación SEIMC-GESIDA	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: RoActemra	**Volume:**	
Name of Active Ingredient: Tocilizumab	**Page:**	

Title of study

A multicentre, open-label clinical trial to evaluate the effectiveness and safety of intravenous tocilizumab for treating patients with COVID-19 pneumonia

Investigators

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Study centres

Hospital Universitario Ramón y Cajal (Madrid), Hospital Universitario Fundación Alcorcón (Madrid), Hospital Universitario Infanta Leonor (Madrid), Hospital General Universitario Gregorio Marañón (Madrid), Hospital Universitario de Fuenlabrada (Madrid), Hospital Universitario HM Sanchinarro (Madrid), Hospital Universitario Infanta Sofía (Madrid), Hospital Rey Juan Carlos (Madrid), Hospital Universitario Fundación Jiménez Díaz (Madrid), Hospital Universitario de Getafe (Madrid), Hospital Universitario 12 de Octubre (Madrid), Hospital de la Santa Creu i Sant Pau (Barcelona), Hospital Universitario Dr. Josep Trueta (Gerona), Hospital Sant Joan de Déu de Manresa (Barcelona), Hospital Universitari de Bellvitge (Barcelona), Hospital Clínic i Provincial Barcelona (Barcelona), Hospital de Mataró (Barcelona), Hospital Nuestra Señora del Prado (Toledo), Hospital Virgen de la Salud (Toledo), Hospital Público General del Tomelloso (Ciudad Real), Complejo Hospitalario Universitario de Albacete (Albacete), Hospital General Universitario de Ciudad Real (Ciudad Real), Hospital Universitario Salamanca (Salamanca), Hospital Universitario de Burgos (Burgos), Hospital Universitario de Galdakao (Vizcaya), Hospital Regional Universitario de Málaga (Málaga), Hospital Universitario Virgen de las Nieves (Granada), Hospital Jerez de la Frontera (Jerez de la Frontera), Hospital Universitario Virgen de la Macarena (Sevilla)*, Hospital Universitario Clínico San Cecilio (Granada)*, Hospital Universitario Virgen del Rocío (Sevilla), Hospital Universitari i Poliectenic La Fe (Valencia), Hospital Clínico Universitario de Valencia (Valencia), Hospital Universitario Dr. Peset (Valencia), Hospital Universitario Miguel Servet (Zaragoza), Hospital Clínico Universitario Lozano Blesa (Zaragoza), Complejo Hospitalario de Navarra (Pamplona), Hospital Universitario de Cabueñes (Gijón), Hospital Universitario Central de Asturias (Oviedo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitari de Son Espases (Palma de Mallorca), Hospital San Pedro Alcántara (Cáceres), Hospital Universitario de Badajoz (Badajoz), Complexo Hospitalario de Ourense (Orense), and Hospital Clínico Universitario de la Arrixaca (Murcia).

*The sites Hospital Universitario Virgen de la Macarena (Sevilla) and Hospital Universitario Clínico San Cecilio (Granada) participated in the study but their data has been excluded from this report as a consequence of the inspections performed in both sites.

Name of Sponsor/Company: Fundación SEIMC-GESIDA	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: RoActemra	**Volume:**	
Name of Active Ingredient: Tocilizumab	**Page:**	

Publication (reference)
The results of this study have not been published.

Study period	**Phase of development:**
First patient first visit– 31 May 2020. Last patient last visit– 23 December 2020.	II

Objectives

Primary objective:

To evaluate the effectiveness of intravenous (IV) tocilizumab in treating patients with COVID-19 pneumonia by describing:

- Improvement of respiratory function based on:
  - Time to intubation (if not previously intubated) and duration of intubation.
  - Time of non-invasive mechanical ventilation (NIMV).
  - Time of oxygen therapy.
- Mortality rate.

Secondary objectives:

1. To describe oxygen saturation (SpO2), PaO2/FiO2 (<300), or the equivalent SaO2/FiO2 (<315) in patients with COVID-19 pneumonia treated with IV tocilizumab.
2. To evaluate radiological evolution in patients with COVID-19 pneumonia treated with IV tocilizumab.
3. To describe the duration of hospitalization and/or intensive care unit (ICU) stay in patients with COVID-19 pneumonia treated with IV tocilizumab.
4. To evaluate the requirement of additional organ support, including kidney dialysis, molecular adsorbent recirculating system (MARS), extracorporeal membrane oxygenation (ECMO), or other in patients with COVID-19 pneumonia treated with IV tocilizumab.
5. To evaluate the effect of IV tocilizumab on the serum levels of inflammatory markers in patients with COVID-19 pneumonia.
6. To describe safety of IV tocilizumab in patients with COVID-19 pneumonia.
7. To identify prognosis factors of IV tocilizumab effectiveness related to inflammatory markers and clinical/radiological features.
8. To assess time to reverse-transcriptase polymerase chain reaction (RT-PCR) virus negativity, as appropriate.
9. To compare the effectiveness and safety outcomes based on the different doses of IV tocilizumab used in the participating centres.
10. To identify patient profile suitable to be benefited with a tocilizumab treatment according to variables related to the treatment (high doses vs. low doses; early-onset vs. late-onset), the disease status at the start of treatment (presence of CSS at the start of treatment vs. absence of CSS) and demographic (sex, age) and clinical factors.

These objectives have been assessed in the entire cohort as well as in the retrospective subcohort.

Methodology

Phase II, one-arm, open-label, and multicentre study. This was a low-interventional clinical trial designed to evaluate the effectiveness of tocilizumab in treating patients with COVID-19 pneumonia. Patients with COVID-19 pneumonia treated with IV tocilizumab before the initiation of the study were also retrospectively included.

The study period was from inclusion until hospital discharge, death, or withdrawal of consent, whichever occurred first. All patients who prematurely withdrew from the study received follow-up medical care provided by the investigator or were referred for appropriate ongoing care.

Number of patients (planned and analysed)

Name of Sponsor/Company: Fundación SEIMC-GESIDA	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: RoActemra	**Volume:**	
Name of Active Ingredient: Tocilizumab	**Page:**	

Planned number of patients: N=500
Patients included: N=462
Patients analysed: N=444
Patients in the retrospective population analysed: N=247
Screening failures: n=18 (noncompliance with inclusion criteria, n=13; noncompliance with exclusion criteria, n=4; unknown/uncompleted screening failure, n=1).
CRFs not completed: n=29.

Diagnosis and main screening criteria

Inclusion criteria:

Patients eligible for inclusion in this study had to provide oral informed consent to participate in this study, be at least 18 years of age, diagnosed with COVID-19 pneumonia by RT-PCR and have received the first dose of tocilizumab from the 1st of April 2020 up to three days the inclusion (retrospective subgroup), or received the first dose of tocilizumab a maximum of two days before the inclusion or be candidates for tocilizumab treatment (prospective subgroup). Patients also had to be hospitalized or admitted to ICU (prospective subgroup) or hospitalised, admitted to ICU, discharged, or not alive (retrospective subgroup).

Exclusion criteria:

The exclusion criteria were any other medical condition or concomitant medication that could, in the opinion of the investigator, compromise the patient's safety or collected data, known severe allergic reactions to tocilizumab or other monoclonal antibodies, active acute and severe infections, including tuberculosis infection and pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination. The investigator could apply no additional exclusions to ensure that the study population was representative of all eligible patients.

Investigational product, dose and mode of administration, batch number

The study treatment was tocilizumab and was administered following the posology indicated in the summary of product characteristics (SmPC) or the recommendations proposed by the Spanish Ministry of Health.

- *SmPC:* 8 mg/kg in patients weighing ≥ 30 kg or 12 mg/kg in patients weighing < 30 kg as a 60-minute IV infusion. If no clinical improvement in the signs and symptoms occurred after the first dose, up to 3 additional doses could be administered. The interval between consecutive doses had to be at least 8 hours. Doses exceeding 800 mg per infusion were not recommended in CSS patients.
- *Spanish Ministry of Health:* first dose 600 mg and second dose 600 mg in patients weighing ≥ 80 kg or first dose 600 mg and second dose 400 mg in patients weighing < 80 kg. The interval between doses was 12 hours. A third dose could be considered 16 to 24 hours after if fever persisted or laboratory parameters (CRP, D-dimer, or IL-6) worsened.

The following batch numbers of the tocilizumab treatment were registered: B2096H02, B3033H04, B3032H03, B2096H01, B2089H02, B2092H01, B3019H03, B2090H02, B2090H01, B2084H15, B3019H05, B2093H01, B4001H02, B3296H01, B3033H02, B2090B02, B2084H09, B3017H39, B4001H25, B3018H02, B2048H09, B3030H01, B3018H05 and B3018H10. However, traceability of all batch numbers was not feasible as the tocilizumab batches used in this study were commercialized, and their numbers were not available in some of the participating sites.

Duration of treatment

All patients included in the clinical trial received tocilizumab according to clinical practice until the patient discharge from the hospital, exitus, or informed consent withdrawal, whichever occurred first.
The investigator provided follow-up medical care for all patients who withdrew prematurely from the study or referred them for appropriate ongoing care.

Name of Sponsor/Company: Fundación SEIMC-GESIDA	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: RoActemra	**Volume:**	
Name of Active Ingredient: Tocilizumab	**Page:**	

Reference therapy, dose and mode of administration, batch number
Not applicable.

Criteria for evaluation
Assessment criterion –Efficacy

The primary study endpoint was the evaluation of the effectiveness of tocilizumab in treating patients with COVID-19 pneumonia measured by respiratory function (start date of intubation in patients not previously initiated, date of extubation, start date of NIMV and date of independence from it and start date of oxygen therapy and date of independence from it) and mortality rate. The secondary efficacy endpoints included levels of oxygen saturation (SpO2), PaO2/FiO2 (<300), or the equivalent SaO2/FiO2 (<315) at 1 day after the first dose and every 3 days during the hospitalization; results from the chest x-ray/CT scan, including extension of lung affection (unilobar or multilobar, unilateral or bilateral, diffuse) and type (opacities, interstitial infiltrates, pneumothorax, pleural effusion), obtained (when available) throughout the study; days of hospitalization in survivors and/or days at ICU throughout the study; need of additional organ support, including kidney dialysis, MARS, ECMO or other throughout the study; levels of IL-6, CRP, procalcitonin (PCT), D-dimer and ferritin (when available) throughout the study; association between the previous mentioned clinical and radiological features and tocilizumab effectiveness; time to RT-PCR virus negativity, as appropriate; respiratory function using different doses of tocilizumab in the participating centres; and categorization of the different parameters of effectiveness and its relation with different factors related to the study treatment, disease status and demographic and clinical factors.

Assessment criterion – Safety

The treatment safety profile was a secondary endpoint, assessed according to adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs).

Statistical methods

Justification of sample size calculation

The sample size was based on calculating the number of patients who had to be included in the study to obtain sufficient data to achieve the primary objective. The secondary objectives were fulfilled according to the sample size determined for the primary objective. To estimate the proportion of deaths and assuming that the population percentage was 15%, it was necessary to obtain a random sample of 500 patients to estimate this percentage, with a confidence of 95% and an accuracy of +/- 3.5 percentage units. The maximum percentage of estimated losses was 20%.

Analysis populations

The following populations were defined for the study analyses:

- *Full analysis set or Intention to treat (ITT):* all the subjects included in the study.
- *Per protocol set:* all patients who received the study treatment, had available measurements of the primary variables, and did not have a major protocol deviation according to the sponsor's criteria.
- *The safety analysis set:* all patients who received at least 1 dose of the trial drug.

The analysis of all the effectiveness variables was performed on the ITT and PP populations. All safety variables were analysed using the safety population.

Statistical methods

A descriptive statistical analysis of the study efficacy variables was performed, including the calculation of central tendency and dispersion for quantitative variables and absolute frequencies and percentages for qualitative variables. The McNemar's or Fisher's exact test was used to compare qualitative variables, while the Paired Wilcoxon test or Mann-Whitney U test was used for quantitative variables. To identify prognosis factors or patients' profiles, multiple linear regressions were used for the continuous and independent variables, and logistic regressions for binary variables. The time-to-event variables were analysed using the Kaplan-

Name of Sponsor/Company: Fundación SEIMC-GESIDA	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: RoActemra	**Volume:**	
Name of Active Ingredient: Tocilizumab	**Page:**	

Meier method. A descriptive statistical analysis of safety data was also performed, including the calculation of absolute frequencies and percentages of AEs, AESIS and SAEs.

Summary - Conclusions

The ITT, PP and SP populations included 444 patients whose mean (±SD) age was 63.6±14.8 years, and 307 (69.1%) were male. All the 444 patients included were positive for COVID-19 by RT-PCR, and 273 (61.5%) exhibited severe or critical disease. Most (98.6%) had a chest x-ray or CT scan with abnormal results (99.3%), mainly interstitial infiltrates (72.9%) and opacities (68.4%). CSS was reported in 364 (82.0%) patients, and the mean (±SD) baseline levels of inflammatory markers were 106.2±194.8 pg/mL for IL-6, 1380.3±1507.6 ng/mL for ferritin, 103.9±91.8 mg/L for CRP, and 1271.5±2002.8 ng/ml for D-dimer. Patients started receiving tocilizumab after a mean (±SD) of 10.3±6.5 days from the onset of symptoms and 1.3±3.0 days after the CSS development.

Nearly all patients from the retrospective subcohort (99.6%) exhibited abnormalities, being the most common interstitial infiltrates and opacities. The mean baseline levels of inflammatory markers were similar to the entire cohort, with 149±219 pg/mL for IL-6, 1559±2159 ng/mL for ferritin, 114±101 mg/L for CRP, and 1263±2148 ng/mL for D-dimer.

Efficacy results

The analysis of the primary study objective about the effectiveness of tocilizumab in terms of respiratory parameters showed mean (±SD) times from the first dose of tocilizumab to intubation of 2.8±4.6 days, NIMV of 2.2±5.0 days, and oxygen therapy initiation of 3.8±8.4 days. They remained for mean (±SD) durations of 17.4±15.2 days, 8.8±8.2 days, and 9.2±10.1 days, respectively. In patients already intubated, on NIMV, or receiving oxygen therapy when starting tocilizumab, their mean (±SD) durations were 18.7±15.7 days, 9.4±9.4 days, and 8.6±10.9 days, respectively. Furthermore, 87 patients died throughout the study, which represents a mortality rate of 19.6%. For patients in the retrospective subcohort, the mean times to the date of intubation, of NIMV and oxygen therapy were 3.1±5.6, 2.8±5.0 and 3.8±8.4 days, respectively. The corresponding mortality rate was 22.7%, with 56 patients who died throughout the study.

The median overall survival was not reached during the study follow-up in the entire cohort as well as the retrospective population, and the median (95% CI) time to COVID-19 negativity was 27 (21.0-36.0) and 21 (16.0-30.0) days, respectively. Approximately 91% of patients were hospitalized and 9% at the ICU at screening, with mean (±SD) durations of hospitalization and ICU stays throughout the study of 20.9±24.8 days and 17.5±16.2 days, respectively. These times were 19.6±16.5 days for hospitalization and 17.7±16.0 days for ICU stay in patients who survived, and 22.1±16.5 days for hospitalization and 21.5±16.0 days for ICU stay in those who finally died. After the start of tocilizumab, the hospitalization lasted for a mean (±SD) of 15.6±15.2 days, and the ICU stay for 17.8±17.0 days, with mean (±SD) durations of 15.8±15.2 and 18.3±16.5 in survivors and 14.9±13.6 and 10.2±15.7 in exitus, respectively. In the retrospective population, the hospitalization after the start of tocilizumab lasted for a mean of 16.5±15.6 days, and the ICU stay for 17.0±17.7 days, respectively.

Although patients in the last available visit less frequently underwent x-ray or CT scan (92.2% vs. 7.8%), the majority still evidenced abnormalities (98%) that most frequently included interstitial infiltrates (74.0%) and opacities (64.0%). Furthermore, 4.5% of patients required at least one additional organ support therapy such as dialysis, ECMO, hyperimmune plasma, vasoactive drug, enteral nutrition, hemofiltration, hemoperfusion, high-flow oxygen system, norepinephrine, orotracheal intubation, or thorax tube. Similar results were observed in the retrospective subcohort, with 97.6% of patients still exhibiting abnormal results and being also the most common interstitial infiltrates and opacities. Regarding additional organ support therapy, 6.1% of retrospective patients required at least one of the therapies indicated above.

When comparing the inflammatory markers between screening and the hospital discharge/end of study visit, the mean (±SD) of IL-6 levels increased from 142.2±353.6 pg/mL to 523.5±1342.6 pg/mL (p<0.001), while

the CRP and ferritin levels decreased from 106.6±92.0 mg/L to 13.8±44.4 mg/L (p<0.001) and 1401.0±1714.0 ng/mL to 1300.0±4292.0 ng/mL (p<0.001), respectively. In the retrospective population, inflammatory markers also significantly changed as described for the entire cohort, with 149.4±219.0 vs. 1359.0±2156.3 pg/mL for IL-6, 114.0±101.0 vs. 18.1±52.2 mg/L for CRP and 1559.0±2159.0 vs. 1073.0±1247.0 ng/mL for ferritin.

The observed oxygenation levels in the entire cohort revealed a mean (±SD) oxygen saturation of 93.1±4.8% and an arterial-to-inspired oxygen ratio (PaFi [SaFi]) that remained under 300 in 254 (72.0%) patients and only reached values under 100 in 106 (30.0%), while the mean oxygen saturation in the retrospective subcohort was 92.7±5.3% and 120 (66.3%) patients had an PaFi (SaFi) under 300. The analysis of prognosis factors showed that PaFi (SaFi) ≥300 was associated with the time to oxygen therapy (ß: -3.9; 95% CI: -8.4- -0.6; p=0.086) and mortality (ß: 0.1; 95% CI: 0.0-0.3; p<0.001), PaFi <200-100 with mortality (ß: 4.7; 95% CI: 1.3-21.9; p=0.027), and PaFi<100-0 with the time to oxygen therapy (ß: 4.6; 95% CI: -0.6-9.9; p=0.083), duration of oxygen therapy in tocilizumab (ß: 4.3; 95% CI: 0.7-8.0; p=0.020) and mortality (ß: 27.5; 95% CI: 9.5-116.8; p<0.001). In the retrospective subcohort, PaFi (SaFi) ranges 0-100, 100-200 and ≥300 were directly associated with the mortality.

The primary outcome analyses conducted according to the use of single or multiple doses of tocilizumab only revealed significant differences in the duration of NIMV, with a mean (SD) length of 7.9±8.1 days in patients with a single dose vs. 11.7±8.1 days in those with multiple doses (p=0.009). However, this variable did not reach statistical significance in the multiple regression analyses performed to identify the patient profile more likely to benefit from tocilizumab in respiratory response variables. These analyses supported that moderate COVID-19 severity significantly increased the duration of intubation in tocilizumab (ß: 21.3; 95% CI: 1.9-40.7; p=0.032), critical COVID-19 severity increased the time to oxygen therapy (ß: 21.3; 95% CI: 8.6-33.9; p<0.001), and the female sex reduced the duration of NIMV in tocilizumab (ß: -5.0; 95% CI: -8.8- -1.2; p=0.010). Regarding mortality, the sub-analyses performed revealed that mortality increased according to age (OR: 1.062; 95% CI: 1.0-1.1; p<0.001) and CRP levels (OR: 1.002; 95% CI: 1.0-1.0; p=0.100), identifying the 65 years old and 19.5 mg/dL as cut-off values maximizing sensitivity-specificity, respectively. Neither other inflammatory markers like IL-6 or ferritin nor the time to tocilizumab resulted statistically significant in terms of mortality.

Additional sub-analyses performed according to the medications administered before starting tocilizumab showed a significantly longer mean (±SD) duration of NIMV in patients with previous corticoids (11.7±10.8 days vs. 7.7±6.8 days, p=0.024) and hydroxychloroquine (12.7±10.1 days vs. 8.0±7.6 days, p=0.035). Furthermore, the concomitant administration of azithromycin showed to reduce the mean (±SD) time to intubation (1.4±2.2 days vs. 3.3±5.1; p=0.041).

In the case of the retrospective cohort, a significant longer duration of NIMV were also observed in patients with a multiple doses (5.6±7.6 vs. 1.9±6.1 days), but it did not result statistically significant in the multiple regression models. Additionally, it was observed that female sex reduced the duration of intubation and NIMV in tocilizumab, moderate COVID-19 severity increased the duration of intubation in tocilizumab, and critical COVID-19 severity increased the time to oxygen therapy. Furthermore, mortality increased according to the age, IL-6 levels and D-dimer levels, with 63 years old, 89 pg/mL and 650 ng/mL as cut-off values, respectively. Additional analyses in this subcohort showed longer time to NIMV in patients with previous lopinavir/ritonavir treatment (10±12.5 days vs. 1.6±4.3 days), and longer mean duration of intubation in tocilizumab in patients with other previous treatments for COVID-19 (38.0±18.5 days vs. 16.5±14.8 days).

Safety results

Patients received a mean (±SD) of 1.3±0.5 doses of tocilizumab throughout the study, with 337 (75.9%) patients receiving a single dose, 102 (23.0%) patients receiving two doses and the remaining 5 (1.1%) patients receiving three or more doses. It was administered at a mean (±SD) dose of 17.5±64.2 mg/Kg, which accounted for a mean (±SD) overall dose of 535.9±103.9 mg. The treatment was permanently discontinued in only 8

(1.8%) patients, including a contraindication in 1 (0.2%) patient (pneumococcal coinfection) and AEs in 7 (1.6%) patients (abdominal wall haemorrhage, ALT increased and hepatic ischaemia, anaemia, anxiety, hepatitis, hepatotoxicity, hyperkalaemia, and metabolic alkalosis). A dose delay was reported in only 1 (0.2%) patient due to a cerebrovascular accident, and dose reductions in 2 (0.5%) patients due to confusional state and ALT-increased.

A total of 533 AEs were reported throughout the study in 240 (54.1%) patients, 125 (28.2%) of whom exhibited 166 AEs that were categorized as severe and mainly included acute respiratory distress syndrome (15.5%) and respiratory failure (5.0%). Twenty-six (5.9%) patients showed at least one of the 30 treatment-related AEs reported, most frequently hypertransaminasaemia (0.7%) and neutropenia (0.7%). They were classified as severe in 6 (1.4%) patients who exhibited pneumonia fungal (0.5%), acute respiratory distress syndrome (0.2%), bacterial infection (0.2%), Escherichia infection (0.2%) and large intestine perforation (0.2%).

One hundred forty-five (32.7%) patients experienced one of the 199 SAEs reported during the study, 12 of which were treatment-related and reported in 11 (2.5%) patients. They included bacterial infection (0.5%), pneumonia fungal (0.5%), acute respiratory distress syndrome (0.2%), Escherichia infection (0.2%), large intestine perforation (0.2%), leucocytosis (0.2%), neutropenia (0.2%), oedematous pancreatitis (0.2%) and thrombocytopenia (0.2%).

Fifty-nine AESIs were reported in 39 (8.8%) patients, including 9 events considered treatment-related in 8 (1.8%) patients. These treatment-related AESIs consisted of herpes zoster (0.5%), pneumonia fungal (0.5%), bacterial infection (0.2%), Escherichia infection (0.2%), large intestine perforation (0.2%) and lung abscess (0.2%). Only did 4 (0.9%) patients show severe treatment-related AESIs: pneumonia fungal (0.5%), Escherichia infection (0.2%) and large intestine perforation (0.2%).

Similar proportions and frequencies were observed in the retrospective population, with 59.9% of patients with at least one AE, 40.9% with at least one SAE, and only 5.7% with treatment-related AEs.

Finally, 85 (19.1%) patients reported at least one AE with a fatal outcome, which mainly were acute respiratory distress syndrome (10.4%), respiratory failure (3.6%), multiorgan dysfunction syndrome (1.1%), and cardio-respiratory arrest (0.9%). However, the reason for death was mostly associated with COVID-19, and the events were considered as treatment-related in only 2 (0.5%) patients who exhibited pneumonia fungal (0.2%) and bacterial infection (0.2%).

Conclusions

This study provides additional information on the effectiveness and safety of tocilizumab in patients with COVID-19 pneumonia in the hospital or ICU setting. It expands the information already available on the disease management and tocilizumab effects in this patient population, including aspects such as respiratory function, oxygenation parameters, radiological evolution, hospitalization/ICU duration, inflammatory parameters, and mortality rate. Nonetheless, further controlled studies are still needed to confirm its findings and clarify the role of potential markers to optimize the treatment of patients with COVID-19.

Report date

Version 1.0 - 06 August 2021.

Version 2.0 – 20 October 2025