

Actemra Use in Coronavirus Disease 2019 (COVID-19)

This document responds to your request for information on the use of Actemra® (tocilizumab) in patients with coronavirus disease 2019 (COVID-19).

This response was developed according to principles of evidence-based medicine and includes data from published prospective and retrospective studies ($N \geq 40$). Preprints of studies with $N \geq 60$ describing adverse events of special interest related to Actemra during treatment for COVID-19 are included.

In Brief

- Elevated levels of cytokines, including IL-6, have been observed in severely- or critically-ill COVID-19 patients. Actemra has been suggested to play a potential role in COVID-19 through its inhibition of IL-6, though the role of IL-6 in mediating cytokine storm associated with COVID-19 remains unclear.
- Actemra is not indicated for the treatment of COVID-19 pneumonia. At present, there are no well-controlled studies and very limited published evidence exists on the safety or efficacy of Actemra in the treatment of patients with COVID-19 pneumonia. The risks and benefits of treatment should be considered prior to initiating Actemra in patients with COVID-19.
- Actemra has a safety warning for risk of serious infections. Please refer to the product label for important safety information, including Warnings, Precautions, and Contraindications.
 - Several preprinted studies have reported increased incidence of bacterial infections in patients with COVID-19 receiving Actemra.
- Independent clinical trials have begun globally to explore the efficacy and safety of Actemra for the treatment of patients with COVID-19 pneumonia.
- In a prospective study of 100 patients with severe COVID-19 infection and acute respiratory distress syndrome, at 24-72 hours after administration of Actemra, 58 patients demonstrated clinical and respiratory improvement, 37 were stable, and 5 deteriorated. By 10 days, 15 patients were discharged and 23 patients worsened. A total of 20 patients died.
- In another single-arm, prospective study evaluating Actemra in 63 hospitalized patients with severe COVID-19, improvements in inflammatory markers and respiratory status were observed. No difference in mortality was observed between those who received intravenous (12.9%) vs subcutaneous (10.3%) administration. The use of Actemra within 6 days of hospital admission was associated with an increased chance of survival ($p < 0.05$). No moderate to severe adverse events related to Actemra were reported.
- A prospective, single arm study evaluating Actemra in 51 patients with severe COVID-19 and elevated inflammatory markers reported a 30-day mortality rate of 27%. The multivariate Cox proportional hazard model showed mechanical ventilation at time of treatment was associated with an increased risk of death (hazard ratio=7.18; 95% CI, $p=0.002$). Fourteen patients experienced bacteremia.
- Additional data are limited to small retrospective, observational studies.
- REMDACTA is an ongoing randomized, double-blind, placebo-controlled Phase 3 trial that is evaluating the efficacy and safety of Actemra plus remdesivir in hospitalized patients with severe COVID-19 pneumonia.

- COVACTA is a randomized, double-blind, placebo-controlled Phase 3 trial assessing the efficacy and safety of Actemra in hospitalized adult patients with severe COVID-19 pneumonia.
- EMPACTA is a randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy and safety of Actemra in hospitalized patients with COVID-19 pneumonia. It will focus on recruiting patients at trial sites known to provide critical care to underserved and minority populations that often do not have access to clinical trials. Patients requiring continuous positive airway pressure, bi-level airway pressure, or invasive mechanical ventilation are excluded.
- MARIPOSA is an ongoing randomized, open-label Phase 2 clinical trial investigating the pharmacodynamics, pharmacokinetics, safety and efficacy of Actemra in hospitalized patients with moderate to severe COVID-19 pneumonia.
- Actemra is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and chimeric antigen receptor T cell-induced cytokine release syndrome.
- We fully respect the clinical decision and independent choice of healthcare providers and medical institutions.

Abbreviations

AE=adverse event	HR=hazard ratio
ALT=alanine aminotransferase	HTN=hypertension
ARDS=acute respiratory distress syndrome	ICU=intensive care unit
AST=aspartate aminotransferase	IL=interleukin
BMI=body mass index	IQR=interquartile range
CAR=chimeric antigen receptor	PaO ₂ =partial pressure of oxygen
CDC=Centers for Disease Control and Prevention	PICU=pediatric intensive care unit
CKD=chronic kidney disease	pJIA=polyarticular juvenile idiopathic arthritis
COVID-19=Coronavirus Disease 2019	RA=rheumatoid arthritis
CRP=C-reactive protein	RCC=renal cell carcinoma
CRS=cytokine release syndrome	SC=subcutaneous
ESRD=end-stage renal disease	SOC=standard of care
FiO ₂ =percentage of inspired oxygen	sJIA=systemic juvenile idiopathic arthritis
GCA-giant cell arteritis	WHO=World Health Organization

Background

High concentrations of cytokines have been reported in severely- or critically-ill patients infected with COVID-19, though the role of IL-6 in mediating cytokine storm associated with COVID-19 remains unclear.^{1,2}

In a Lancet publication, a retrospective, multicenter, cohort study of 191 hospitalized patients with COVID-19 from Wuhan observed that age, lymphopenia, leukocytosis, and elevated levels of ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6 prothrombin time, creatinine, and procalcitonin were associated with death (univariable analysis).¹ In a temporal analysis, elevated levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6 were observed in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration. Due to the retrospective study design, not all laboratory tests, including IL-6, were done in all patients. Several factors that may have contributed to the poor clinical outcomes in some patients, such as delayed transfer to hospitals, lack of effective antivirals, inadequate adherence to standard support therapy and use of high-dose corticosteroids.

In a letter to the editors in Intensive Care Medicine, investigators informed a retrospective study of 68 death cases and 82 discharged cases with laboratory-confirmed COVID-19 from 2 hospitals in Wuhan, China.³ Patients who died were statistically significantly older in age and had a greater proportion of underlying disease and secondary infections compared with those in the discharged group. There was

no statistical difference in the time from onset of symptoms to laboratory testing between the 2 groups. Significant differences in the white blood cell counts, absolute values of lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, blood creatinine, myoglobin, cardiac troponin, CRP and IL-6 (mean 11.4 vs 6.8 ng/mL, $p < 0.001$) were observed between those who died vs those who were discharged.

In another Lancet publication describing 41 patients in Wuhan hospitalized for COVID-19, there was no evidence of marked IL-6 elevation between patients requiring ICU admission (n=13) and those who did not (n=28) ($p=0.13$).² Due to the small sample size, there was difficulty assessing host risk factors for disease severity and mortality with multivariable-adjusted methods

Actemra, an IL-6 inhibitor, is approved for the treatment of RA, pJIA, sJIA, GCA, and CAR T cell-induced CRS. Actemra has a safety warning for risk of serious infections. Serious infections leading to hospitalization or death including tuberculosis, bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving Actemra. The risks and benefits of treatment should be considered prior to initiating Actemra in patients with COVID-19. Please refer to the locally approved product label for important safety information of Actemra, including Warnings, Precautions, and Contraindications.

Use in Coronavirus Disease 2019 (COVID-19)

Actemra is not indicated for the treatment of COVID-19 pneumonia. At present, there are no well-controlled studies and limited published evidence exists on the safety or efficacy of Actemra in the treatment of patients with COVID-19 pneumonia. The risks and benefits of treatment should be considered prior to initiating Actemra in patients with COVID-19. We fully respect the clinical decision and independent choice of healthcare providers and medical institutions.

Health Authorities

Information from several health authorities for the treatment of COVID-19 infection is summarized below. It is for informational purposes and should not be interpreted as recommendations from Genentech/Roche on management of COVID-19.

[The World Health Organization](#)

An expert panel was convened to discuss the potential role of IL-6 inhibition in the clinical management of COVID-19 infection.⁴ In an update, the panel discussed several anecdotal reports from single-center observational studies, concluding that “[Further] clinical trials are needed to determine the role of IL-6 blockers in COVID-19, especially the dose and timing of administration (early or late in disease course).”

[The Centers for Disease Control and Prevention](#)

In the current *Interim Clinical Guidance for Management of Patients with Confirmed COVID-19* by the CDC, the following is stated⁵ (last updated May 20, 2020)⁴: “No specific treatment for COVID-19 is currently FDA-approved...Inpatient management revolves around the supportive management of the most common complications of severe COVID-19...”

[The National Health Commission of the People’s Republic of China](#)

Actemra was included in the 7th update *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)* released by the National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020 (Chinese only).⁶ In a translation organized by the WHO China Office, Actemra was mentioned as a treatment option for severe and critical cases.

Clinical Experience

Prospective Studies

Toniati et al. conducted a prospective study evaluating the use of Actemra in 100 patients with confirmed COVID-19 pneumonia and ARDS requiring ventilatory support.⁷ Actemra was given at 8 mg/kg IV q12h x 2 followed by a third dose 24 hours after the second infusion, based on clinical response. The primary outcome was improvement in ARDS based on the Brescia COVID Respiratory Severity Score at 24-72 hours and 10 days after Actemra. The median age was 62 years (IQR, 57-71 years), 88% were male, and comorbidities included HTN (46%), obesity (31%), diabetes (17%), and cardiovascular disease (16%). Majority of patients received 2 doses of Actemra (87%) with the remaining receiving 3 doses (13%). All patients had elevated inflammatory markers (CRP, fibrinogen, ferritin and IL-6). At 24-72 hours, 58 patients demonstrated clinical and respiratory improvement, 37 were stable, and 5 deteriorated, of whom 4 died. By 10 days, 15 patients were discharged and 23 patients worsened. A total of 20 patients died. C-reactive protein, fibrinogen, and ferritin decreased in patients who had improved clinical status, while IL-6 and D-dimer increased in both improved and worsened patients. Serious adverse events included septic shock (n=2; both died) and GI perforation (n=1).

In another single-arm, prospective study, Sciascia et al. reported the use of Actemra in 63 hospitalized patients with confirmed COVID-19 infection.⁸ All patients were required to have marked elevation of at least 3 of the following inflammatory markers: CRP, ferritin, D-dimer, or LDH. IL-6 levels were also measured. The primary endpoint was safety, and secondary endpoints were improvement in respiratory and laboratory status (data collected at baseline and on Days 1, 2, 7, and 14). Actemra was administered at 8 mg/kg IV (n=34) or 324 mg SC (n=29). Among 31 patients who received IV for their first dose, 91% received a second dose (IV, n=25; SC at 162 mg, n=6). Twenty-one patients in the SC group received a second dose of Actemra 162 mg SC. An improvement in CRP, ferritin, D-dimer and lymphocyte counts were observed and respiratory parameters as measured by PaO₂/FiO₂, were also improved. At Day 14, a total of 7 (11.5%) patients died. No difference in mortality was observed between those who received IV (12.9%) vs SC (10.3%) administration. Five patients required mechanical ventilation on admission, and by Day 14, 2 patients remained on mechanical ventilation and 1 patient died. All patients who died received 2 doses of Actemra and death occurred within the first week of receiving Actemra (mean 5±1.5 days). Baseline D-dimer levels were predictive of death (HR=5.01; 95% CI, 1.04-29.17). The use of Actemra within 6 days of hospital admission was associated with an increased chance of survival (HR=2.2; 95% CI, 1.3-6.7; p<0.05). No moderate to severe AEs related to Actemra were reported.

In an open-label prospective study, Morena et al. reported the clinical characteristics and outcomes of 51 patients with confirmed, severe COVID-19 pneumonia treated with Actemra.⁹ All patients were required to have an IL-6 level of >40 pg/mL. The primary endpoints were death or hospital discharge. Secondary endpoints included change in disease severity and change in oxygen requirements at different timepoints after Actemra administration. Actemra 400 mg IV q12h x2 or 8 mg/kg IV q12h x2 (for patients ≥60 kg) was administered. A total of 18 (35%) patients received the fixed dose of Actemra and 33 (65%) received the 8 mg/kg doses. Two patients did not receive a second dose of Actemra (due to death and rash, respectively). Select baseline characteristics include (median values): 60 years (IQR, 50-70); majority male (78.4%); history of cardiovascular disease (49%), HTN (29.4%) and diabetes (11.8%); CRP of 189 mg/L (IQR, 138-268 mg/L); d-dimer of 1706 pg/L (IQR, 860-5261 pg/mL); and IL-6 of 116 pg/mL (IQR, 65-180). Concomitant medications included hydroxychloroquine (98%), lopinavir/ritonavir (84%), remdesivir (45%), and antibiotics (76%). At baseline, 84% of patients were classified as severe and 12% as critically severe. After a median follow-up of 34 days (IQR, 32-37 days) after the first dose of Actemra, 31 (61%) patients were discharged, 14 (27%) died, and 2 (12%) remain hospitalized. The mortality rate was 27% (14/51), of which 83% (5/6) were receiving mechanical ventilation and 20% (9/45) were receiving non-invasive oxygen support (p=0.0001). The multivariate Cox proportional hazard model showed mechanical ventilation at time of treatment was associated with an increased risk of death (HR=7.18; 95% CI, 2-25; p=0.002). The most common cause of death was ARDS; 4 patients had concomitant septic shock and multi-organ failure. Thirty-four (67%) patients experienced an improvement in their clinical severity, while 16 (33%) patients had no change in status, and no patients on mechanical ventilation were extubated. Laboratory parameters showed a decrease in CRP and a significant increase in

transaminases within 7 days of Actemra administration. C-reactive protein levels returned to normal in 36 (71%) patients. The most common AEs were increased hepatic enzymes $\geq 3 \times \text{ULN}$ (29%), thrombocytopenia (14%), neutropenia (6%), and cutaneous rash (2%). Fourteen (27%) patients experienced bacteremia (median time to onset from Actemra administration, 11 days, IQR, 9-13 days).

Retrospective Studies (N \geq 40)

In a retrospective analysis of confirmed COVID-19 cases from the SMAteo COvid19 REgistry (SMACORE), Colaneri et al. compared the outcomes of 112 patients treated with Actemra and SOC (n=21) or SOC only (n=91).¹⁰ The primary outcome was ICU admission and 7-day mortality rate, analyzed in the propensity-score matched population (21 patients who received Actemra plus SOC matched to 21 patients who received SOC). Eligibility for Actemra included CRP $> 5 \text{ mg/dL}$, procalcitonin $< 0.5 \text{ ng/mL}$, $\text{PaO}_2/\text{FiO}_2 < 300$ and ALT $< 500 \text{ U/L}$. Data were collected on the day of Actemra administration and 7 days later. Actemra was administered at 8 mg/kg IV (max 800 mg per dose), repeated 12 hours later if no side effects were observed. The SOC group included hospitalized adult patients treated with a combination of hydroxychloroquine, azithromycin (once), prophylactic low-molecular-weight heparin, and methylprednisolone for 10 days. The median age in the Actemra group was 62.3 years (SOC group, 63.7 years) and 90% were male (SOC group, 69%). In logistic regression analyses, Actemra did not significantly affect mortality (OR 0.78; 95% CI 0.06-9.34; $p=0.84$) or ICU admission (OR 0.11; 95% CI 0.00-3.38; $p=0.22$) compared with the SOC only group. Elevated CRP and INR significantly decreased after treatment with Actemra. Although AST was elevated in the Actemra group, no severe hepatic injuries were observed.

Quartuccio et al. conducted a single-center retrospective study evaluating anti-cytokine treatments for severe COVID-19 pneumonia with hyperinflammatory features.¹¹ Out of 111 hospitalized patients, 42 patients (TOCI group) with elevated CRP and IL-6 levels received Actemra 8mg/kg IV once and 69 patients received SOC. Two patients who failed Actemra received anakinra 200 mg/day SC for 3 days. The mean age was 62.4 ± 11.8 years in the TOCI group vs 56.2 ± 14.2 years in the SOC group ($p=0.02$). C-reactive protein levels ($p<0.0001$), LDH ($p=0.001$), and IL-6 ($p<0.0001$) were significantly higher in the TOCI group at baseline compared to the SOC group. Additional key baseline characteristics in the TOCI and SOC groups include: male (78.6% vs 63.8%) and HTN (47.6% vs 30.4%). In the TOCI group, all patients received antiviral treatments and 40% received glucocorticoids compared to 80% and 0% in the SOC group, respectively. The mean time from disease onset to administration of Actemra was 8.4 ± 3.7 days. Twenty-seven (64%) patients in the TOCI group were treated in the ICU, of which 26 (96.3%) were intubated. Eight (7.2%) of these patients received tracheostomies. In the TOCI group, 9/42 (21.4%) patients completely recovered and 21/42 (50%) rapidly improved following treatment with Actemra. Among the 21 patients who showed improvement, complicating infections occurred in 11 (52.4%). Overall, bacterial superinfections occurred in 18/111 (16.2%) patients, mostly in the TOCI group. A total of 4 (9.5%) in the TOCI group died and no deaths occurred in the SOC group.

In a retrospective study conducted by Capra et al., 85 consecutive patients with confirmed COVID-19 pneumonia and acute respiratory syndrome were observed following treatment with Actemra and/or SOC.¹² Patients requiring mechanical ventilation at admission were not included. The primary endpoint was survival rate. The aim was to treat patients with Actemra early in the hospital admission, therefore, patients who received Actemra within 4 days from hospital admission were included. Control patients included those who were admitted 4 days before Actemra was available. Out of 85 patients, 23 patients received SOC, which included hydroxychloroquine, and lopinavir/ritonavir, and 62 patients received Actemra plus SOC. Among those who received Actemra, 3.22% (2/62) received Actemra 800 mg IV once, 53% (33/62) received Actemra 400 mg IV once and 43.5% (27/62) received 324 mg SC once. All patients received non-invasive or invasive oxygen supplementation based on their needs. Select baseline characteristics of patients in the Actemra plus SOC vs SOC alone were as follows: median age (63 years vs 70 years), male (73% vs 83%), HTN (46% vs 48%), diabetes (14% vs 22%), and heart disease (14% vs 26%). At the end of the observation period (March 13-April 2, 2020), 3.22% (2/62) of patients in the Actemra group and 47.8% (11/23) patients in the SOC group died. After adjusting for age, comorbidities, and PCR baseline levels, patients receiving Actemra demonstrated a significantly improved survival rate compared to SOC alone (HR=0.035; 95% CI, 0.004-0.347; $p=0.004$). After a mean of 12.5

days, 92% (23/62) of patients in the Actemra group and 42.1% (8/23) of patients in the SOC group completely recovered (8% [2/62] and 57.9% [11/23] died, respectively). Among 37 patients in the Actemra group who were still hospitalized, 64.8% were improving, and 27% worsened. In the SOC group, the remaining 4 patients had worsened and were put on mechanical ventilation. Overall, no infections related to Actemra were observed and serum procalcitonin levels did not increase.

A retrospective study conducted by Marfella et al. evaluated the effect of Actemra in hyperglycemic patients with moderate to severe COVID-19.¹³ Patients were included if they had a blood glucose of ≥ 140 mg/dL at admission and during their hospital stay. A total of 31 (39.7%) hyperglycemic and 47 (60.3%) normoglycemic patients were included, of whom 20 (64%) and 11 (23.4%) had a diagnosis of diabetes ($p < 0.01$), respectively. Oral anti-diabetic drugs were held on admission and all patients received insulin to control hyperglycemia during hospitalization. Glucose levels at admission were higher in the hyperglycemic patients compared to the normoglycemic patients (187 ± 48 mg/dL vs 103 ± 23 mg/dL [$p < 0.01$], respectively). Mean glucose levels during hospitalization were 157 ± 15 mg/dL in hyperglycemic patients vs 122 ± 12 mg/dL in normoglycemic patients ($p < 0.01$). Actemra was administered at 8 mg/kg (max 800 mg) IV in all patients. Seven hyperglycemic and 2 normoglycemic patients received a second dose of Actemra within 8-12 hours of the first dose. On admission, hyperglycemic patients had higher IL-6 levels compared to normoglycemic patients. Following Actemra administration, IL-6 levels decreased in both groups, but remained higher in the hyperglycemic group. A risk-adjusted Cox regression analysis showed that despite treatment with Actemra, hyperglycemia was associated with more severe outcomes (HR=0.168; 95% CI, 0.044-0.640; $p = 0.009$). Additionally, Kaplan-Meier analysis showed that hyperglycemic patients with no prior history of diabetes had poorer outcomes compared to both hyperglycemic and normoglycemic patients with a history of diabetes, including those who were normoglycemic with no history of diabetes.

Campochiari et al. conducted a retrospective study on non-ICU, confirmed severe COVID-19 patients with hyperinflammatory features (elevated CRP ≥ 100 mg/L or ferritin ≥ 900 ng/mL, with increased LDH > 220 U/L).¹⁴ All patients received SOC which included hydroxychloroquine, lopinavir/ritonavir, ceftriaxone, azithromycin, and anticoagulation prophylaxis with enoxaparin. Concomitant glucocorticoids were not permitted. Actemra was administered at a dose of 400 mg IV with an additional 400 mg IV given 24 hours later for worsening respiratory status ($n = 32$). Patients who would otherwise fulfill eligibility for Actemra but were unable to receive it due to a shortage served as the comparison group (SOC alone group, $n = 33$). Outcomes were clinical status using a 6-category ordinal scale, overall survival and proportion of patients with clinical improvement (defined as live discharge from hospital or decrease of ≥ 2 points from baseline on the 6-category ordinal scale) at 28 days. Select baseline characteristics in the Actemra and SOC alone group include: median age (65 years vs 60 years), male (91% vs 82%), CRP (156 vs 169 mg/mL), ferritin 1400 ng/mL vs 1448 ng/mL and non-invasive ventilation (78% vs 61%). A total of 9/32 (28%) patients received 2 doses of Actemra, of whom 7 were on non-invasive ventilation at baseline. Four out of 32 (13%) patients in the Actemra group and 2/33 (6%) patients in the SOC required mechanical ventilation. By Day 28, deaths occurred in 5/32 (16%) patients in the Actemra group and 11/33 (33%) patients in the SOC group. Twenty (63%) patients in the Actemra group were discharged home by Day 28 compared with 16 (48%) of patients who received SOC. Overall, 8 (25%) patients in the Actemra group experienced serious AEs, which included bacteremia ($n = 4$) and fungal infection ($n = 1$). Three patients were discharged home while the patient with the fungal infection remained hospitalized at Day 28. Patients who received 1 dose of Actemra experienced a lower rate of infections compared to those who received 2 doses (9% vs 33%; $p = 0.06$). Nine (27%) patients in the SOC group experienced serious AEs (4 had bacteremia). Among the 4 patients with bacteremia, 1 died, 1 remained in the ICU intubated, and 2 patients remained hospitalized. Additional adverse events in the Actemra group vs SOC alone group were: pulmonary thrombosis (6% vs 9%), transient elevation of AST or ALT (15% vs 18%), and neutropenia (5% vs 0%; $p = 0.02$). The median time to highest serum level of ALT increase was 11 days (range, 9-13 days). No patients experienced infections due to neutropenia.

A retrospective, case-control study conducted by Klopfenstein et al. compared the rate of survival and/or ICU admissions in patients with confirmed COVID-19 infections receiving Actemra plus SOC ($n = 20$) or SOC alone ($n = 25$).¹⁵ Patients in the SOC group received hydroxychloroquine or lopinavir/ritonavir, antibiotics, and less commonly, corticosteroids. Those with moderate disease (i.e., hospitalized for < 48

hours and/or who did not receive standard treatment and/or oxygen therapy) or those who received treatment not routinely administered at their hospital (e.g., remdesivir and immunoglobulins) were excluded. Patients in the Actemra group had a higher Charlson comorbidity index (5.3 [±2.4] vs 3.4 [±2.6]; p=0.14) and included more patients over 70 years of age (75% vs 44%; p=0.036) than the SOC group. On admission, lymphopenia (676/mm³ vs 914/mm³, p=0.037) and CRP levels (158 mg/L vs 105 mg/L, p=0.017) were more severe in the Actemra group vs the SOC group. Over the course of hospitalization, oxygen requirement was higher in the Actemra group compared to the SOC group (flow, 13L/min vs 6L/min [p<0.001]; duration, 12 days vs 4 days [p=0.009], respectively). Overall, the combined primary endpoint of death and/or ICU admission was higher in the SOC group compared to the Actemra group (72% vs 25%, p=0.002). More patients in the SOC group required mechanical ventilation (32% vs 0%, p=0.006) and died (48% vs 25%; p=0.066) compared with those in the Actemra group.

Additional Safety Experience

Preprinted Literature (N≥60)

Preliminary results shared in open repositories and distribution servers for unpublished but complete manuscripts (preprints) that provide information on adverse events of special interest related to Actemra following treatment for COVID-19 pneumonia are summarized below. Preprints are preliminary reports of work that have **not been peer-reviewed**. As such, results from preprints should be interpreted with caution.

Outcomes of 2,512 hospitalized, confirmed COVID-19 patients were reviewed in a retrospective, observational cohort study using electronic medical records data.¹⁶ The primary objective was to evaluate the effect of hydroxychloroquine in hospitalized patients. A secondary, exploratory objective was to evaluate the effect of Actemra in ICU patients. The primary endpoint was mortality. Data for the Actemra group are presented here. Age, gender, COPD, and renal failure were included in the propensity score model for Actemra using a multivariate logistic regression. Patients receiving Actemra in the ICU were compared to control patients in the ICU who did not receive Actemra. Out of 198 patients who received Actemra, 134 patients received the first dose of Actemra in the ICU and comprised the Actemra exploratory treatment cohort. A total of 413 patients served as the control group. The median age of patients in the Actemra group was 62 years (range, 53-70) and 28% were male. Actemra was administered as a single dose in 104 (78%) patients (400 mg, 96%; 800 mg, 1%, 4 mg/kg, 1%, missing dose, 1%). Treatment with Actemra in the ICU setting trended towards improved survival (HR=0.76; 95% CI, 0.57-1.00). The unadjusted mortality rate was 46% in the Actemra group and 56% in the control group. Eighteen (13%) patients in the Actemra group and 44 (11%) patients in the control group experienced secondary bacteremia. Twelve (9%) patients in the Actemra group and 25 patients (6%) in the control group developed secondary pneumonia.

The association between Actemra and secondary infections was investigated in a study conducted by Kimmig et al. the University of Chicago.¹⁷ Sixty critically ill COVID-19 patients were randomly selected for the analysis. Among those patients, 28 patients received 400 mg once and one patient received 800 mg once. A second dose was allowed based on clinical response. Secondary infections were defined as a positive culture or high clinical suspicion of infection requiring antibiotic therapy. A higher incidence of secondary bacterial infections (including hospital-acquired and ventilator-associated pneumonia) was observed in patients receiving Actemra compared to those who did not (64.3% vs 31.3%). In logistic regression analyses which include independent variables (age, gender, and CCI), Actemra was associated with an increase in secondary bacterial infections (OR=3.96; 95% CI, 1.35-11.6; p=0.033). Two patients developed fungal infections in the Actemra arm; none were reported in the control arm.

Clinical Trials

Genentech/Roche-Sponsored Clinical Trials

[Randomized, Double-blind, Placebo-controlled, Phase 3 Study \(REMDACTA\)](#)

REMDACTA (ClinicalTrials.gov Identifier: NCT04409262) is a randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of Actemra plus remdesivir in approximately 450 hospitalized patients with severe COVID-19 pneumonia.¹⁸ Key inclusion criteria include age ≥ 12 years old, confirmed COVID-19 infection by positive PCR and evidenced by radiographic imaging, body weight ≥ 40 kg, and $SpO_2 > 93\%$. Key exclusion criteria include suspected active bacterial, fungal, viral or other infection (besides COVID-19), concurrent treatment with other agents with actual or possible activity against SARS-CoV-2 within 24 hours of study drug dosing, treatment with immunosuppressive or immunomodulatory drugs (including Actemra) within the past 3 months, or any serious abnormality of clinical laboratory tests. Eligible patients will be randomized to receive a remdesivir loading dose, followed by 1 infusion of Actemra 8 mg/kg IV (maximum dose of 800 mg) on Day 1, and a once-daily maintenance dose of remdesivir from Days 2-10 or remdesivir plus placebo. The primary endpoint is clinical status on Day 28. Key secondary endpoints include time to improvement of clinical status, time to clinical failure, mechanical ventilation, ICU care, mortality, and time to discharge.

Additional information on REMDACTA, including inclusion and exclusion criteria, enrollment status, study sites, can be found at <https://clinicaltrials.gov/ct2/show/NCT04409262>.

[Randomized, Double-blind, Placebo-controlled, Phase 3 Study \(COVACTA\)](#)

COVACTA (ClinicalTrials.gov Identifier: [NCT04320615](#)) is a randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of Actemra plus SOC in approximately 450 hospitalized adult patients with severe COVID-19 pneumonia.¹⁹ The study is being conducted by Genentech in collaboration with the Biomedical Advanced Research and Development Authority (BARDA). Key inclusion criteria include ≥ 18 years of age, confirmed COVID-19 infection per the WHO criteria (including a positive PCR of any specimen) and evidenced by chest X-ray or CT scan, and $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg despite being on SOC. Key exclusion criteria includes active tuberculosis or suspected active bacterial, fungal, viral or other infection (besides COVID-19), oral anti-rejection or immunomodulatory drugs (including Actemra) within the past 6 months, or any serious abnormality of clinical laboratory tests. Eligible patients will be randomized to receive Actemra 8 mg/kg IV (maximum dose of 800 mg) or placebo with current SOC. One additional Actemra infusion can be given 8-12 hours after the initial infusion if the clinical signs and symptoms worsen or do not improve. The primary and secondary endpoints include clinical status, mortality, mechanical ventilation and additional ICU variables. Patients will be followed for 60 days post-randomization, and an interim analysis will be conducted to look for early evidence of efficacy.

Additional information on COVACTA, including inclusion and exclusion criteria, enrollment status, study sites, can be found at <https://clinicaltrials.gov/ct2/show/NCT04320615>.

[Randomized, Double-blind, Placebo-controlled, Phase 3 Study \(EMPACTA\)](#)

EMPACTA (ClinicalTrials.gov Identifier: [NCT04372186](#)) is a randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of Actemra plus SOC in approximately 379 hospitalized patients with COVID-19 pneumonia.^{20,21} It will focus on recruiting patients at trial sites known to provide critical care to underserved and minority populations that often do not have access to clinical trials. Key inclusion criteria include adults ≥ 18 years old, confirmed COVID-19 infection by positive PCR and evidenced by radiographic imaging, and $SpO_2 < 94\%$. Key exclusion criteria include requirement for continuous positive airway pressure, bi-level positive airway pressure, or invasive mechanical ventilation, suspected active bacterial, fungal, viral or other infection (besides COVID-19), oral anti-rejection or immunomodulatory drugs (including Actemra) within the past 3 months, or any serious abnormality of clinical laboratory tests. Eligible patients will be randomized to receive Actemra 8 mg/kg IV (maximum dose of 800 mg) or placebo with current SOC. One additional Actemra infusion can be given. The

primary endpoint is the cumulative proportion of patients requiring mechanical ventilation by Day 28. Key secondary endpoints include time to improvement of clinical status, time to clinical failure, mortality rate by Day 28, time to discharge, and adverse events.

Additional information, including inclusion and exclusion criteria, enrollment status, study sites, can be found at <https://clinicaltrials.gov/ct2/show/NCT04372186>.

[Randomized, Open-Label, Phase 2 Study \(MARIPOSA\)](#)

MARIPOSA (ClinicalTrials.gov Identifier: [NCT04363736](#)) is a randomized, open-label Phase 2 clinical trial investigating the pharmacodynamics, pharmacokinetics, safety and efficacy of Actemra in approximately 100 hospitalized patients with moderate to severe COVID-19 pneumonia.²² Key inclusion criteria include confirmed COVID-19 pneumonia (including a positive PCR of any specimen) and evidenced by chest X-ray or CT scan, SpO₂ ≤93% or PaO₂/FiO₂ <300 mmHg for severe patients, and CRP >2xULN for moderate patients. Key exclusion criteria include active tuberculosis or suspected active bacterial, fungal, viral or other infection (besides COVID-19), oral anti-rejection or immunomodulatory drugs (including Actemra) within the past 3 months, patients on mechanical ventilation >24 hours or extracorporeal membrane oxygenation, in shock, or combination thereof with other organ failure requiring treatment in an ICU, or any serious abnormality of clinical laboratory tests. Eligible patients will be randomized to receive Actemra 8 mg/kg or 4 mg/kg IV in addition to current SOC. The key primary and secondary endpoints include concentrations of CRP, IL-6, ferritin, clinical status, mortality, mechanical ventilation, and additional ICU variables.

Additional information on MARIPOSA, including inclusion and exclusion criteria, enrollment status, study sites, can be found at <https://clinicaltrials.gov/ct2/show/NCT04363736>.

Additional Clinical Trial Resources

Researchers around the world are independently exploring the efficacy and safety of Actemra for COVID-19. Interested clinicians can access the following website for additional clinical trials information:

- The World Health Organization International Clinical Trials Registry Platform (ICTRP), a searchable portal of COVID-19 trials at www.who.int/ictrp/en/.
- ClinicalTrials.gov, a web-based resource by the National Library of Medicine at the National Institutes of Health at <https://clinicaltrials.gov/>.

The WHO has also gathered and compiled the latest scientific findings and knowledge on COVID-19 in a database. Interested clinicians can search the WHO database of publications on COVID-19 at www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov.

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