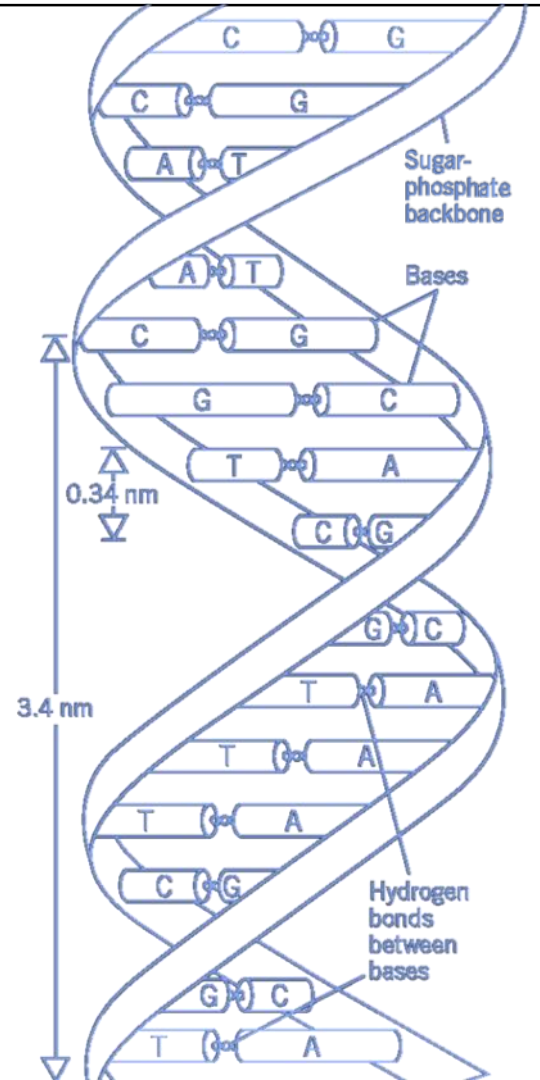
COVID-19 (coronavirus)

Overview Including the Potential Role of IL-6 and Roche-sponsored Clinical Trials

Revised: 18 September 2020

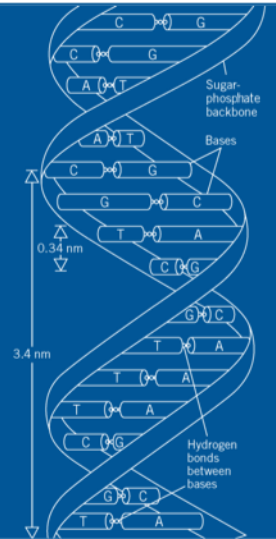


Disclaimer

- Actemra® (tocilizimab) is not FDA-approved for use in the treatment of COVID-19 pneumonia. There is no intent to promote any non-approved product or indication.
- This information is provided solely to enable physicians to make informed individual patient treatment decisions during the COVID-19 pandemic.
- Refer to the Actemra USPI for Prescribing Information, Warnings and Precautions

SARS-CoV-2 and COVID-19

Clinical and epidemiological overview and immune response



Coronavirus Disease of 2019 (COVID-19)

Pandemic declared by World Health Organization and U.S. Department of Health and Human Services

As of September 18, 2020,

World Health Organization

- **>30 million confirmed cases of COVID-19 infection have been reported worldwide with over 943,000 deaths[1]**
- **Current WHO COVID-19 data can be accessed here**

CDC Centers for Disease Control and Prevention

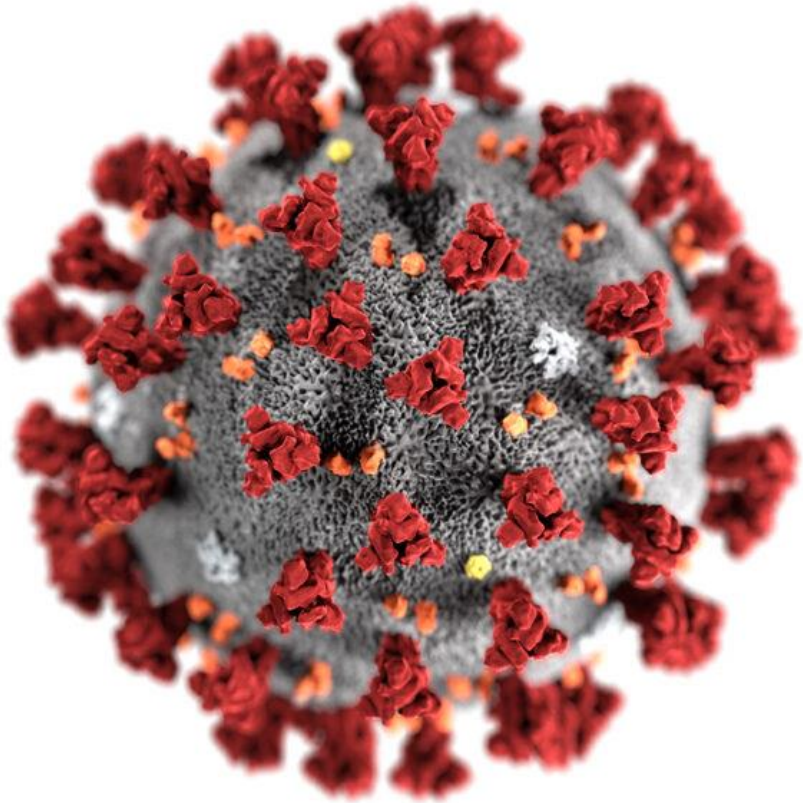
- **>6 million confirmed cases have been reported in the United States, with over 197,000 deaths[2]**
- **Current CDC COVID-19 data can be accessed here**

1. WHO Coronavirus Disease (COVID-19) Dashboard (https://covid19.who.int/). Accessed on September 18, 2020. 2. US Centers for Disease Control Coronavirus Disease 2019 (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html). Accessed on September 18, 2020.

Coronavirus Disease of 2019 (COVID-19)

Caused by novel coronavirus SARS-CoV-2

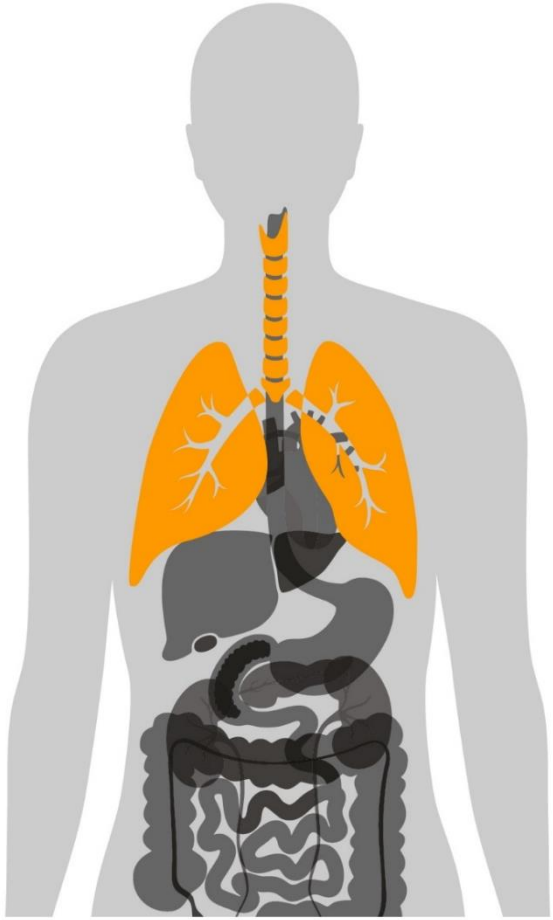
- **Coronaviruses (CoVs) are positive-stranded RNA viruses** with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope[1]
  - **Common human CoVs:** cause common colds and self-limiting upper respiratory infections; in immunocompromised individuals and the elderly, lower respiratory tract infections can occur (e.g. HCoV-OC43 and HCoV-HKU1; HCoV-229E and HCoV-NL63)[2]
  - **Other human CoVs:** cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations (e.g. SARS-CoV, **SARS-CoV-2** and MERS-CoV)[2]
  - **Nucleotide identity[1]:** 89% with bat SARS-like-CoVZXC2[1], 82% with human SARS-CoV



1. Cascella M, Rajnik M, Cuomo A, et al. StatPearls Publishing. 2020. ePub; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/ 2. Chen Y, Liu Q, Guo D. *J Med Virol*. 2020;92:418–423.

Coronavirus Disease of 2019 (COVID-19)

Clinical presentation



Most common symptoms[1]

- Fever
- Fatigue
- Dry Cough

Some patients may also have:

- Aches and pains
- Runny nose
- Sore throat
- Shortness of breath
- Diarrhea

Two clinical scenarios:

Based on Chinese Centers for Disease Control report on 72,314 patients[2]

Mild disease: non-pneumonia and mild pneumonia

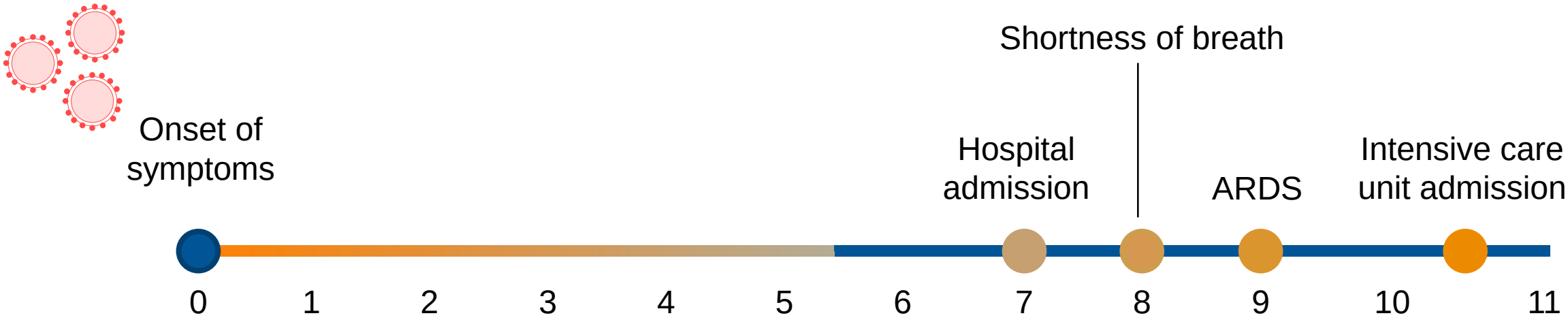
Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio*< 300 and/or lung infiltrates > 50% within 24 to 48 hours

Critical disease: respiratory failure, septic shock and/or multiple organ dysfunction (MOD) or failure (MOF)

1. Wang D, et al. *JAMA*. 2020;323:1061-1069. 2. Wu Z, et al. *JAMA*. 24 February 2020. doi:10.1001/jama.2020.2648
* the ratio between the blood pressure of the oxygen (PaO2) and the percentage of oxygen supplied (FiO2)

COVID-19

Timeline of onset to ICU admission in severely and critically ill patients



Number of days (median time from onset of symptoms, including fever [in 98% of patients], cough [75%], myalgia or fatigue [44%] and others)

Abbreviations: ARDS=acute respiratory distress syndrome.
Huang C, et al. *Lancet.* 2020; 395:497–506.

Risk Factors for Severe Disease

COVID-19 is a new disease and there is limited information regarding risk factors for severe disease. Patients who may be at high-risk for severe illness from COVID-19 include:


People aged 65 years and older


People who live in a nursing home or long-term care facility

Other high-risk conditions could include:


- People with chronic lung disease or moderate to severe asthma


- People who have heart disease with complications


- People who are immunocompromised* including cancer treatment


- People of any age with severe obesity (body mass index [(BM]I)≥40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or liver disease might also be at risk


People who are pregnant should be monitored since they are known to be at risk with severe viral illness, however, to date data on COVID-19 has not shown increased risk

*Many conditions can cause a person to be immunocompromised, including cancer treatment, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, and prolonged use of corticosteroids and other immune weakening medications

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html accessed April 2, 2020

COVID-19

Dysregulated immune response

- Some viral infections can lead to an accentuated immune response[1]
- Features of critically ill patients infected with COVID-19 suggest the presence of an accentuated immune response resulting in acute respiratory distress syndrome and multi-organ failure[2-4]

Clinical	Laboratory
Fever Confusion	Hyperferritinemia, Lymphopenia, Prolonged prothrombin time, **elevated interleukin-6**, lactate dehydrogenase, C-reactive protein, soluble CD25

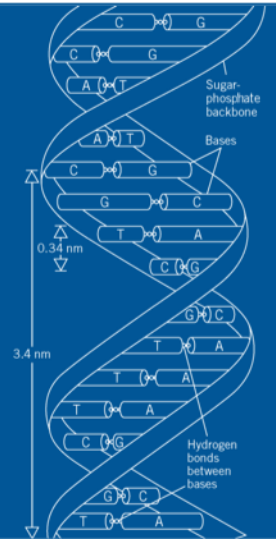
1. Crayne CB, et al. *Front Immunol.* 2019 Feb 1;10:119 2. Chen N, et al. *Lancet*. 2020;395:P507–P513. 3. Lei C, et al. *Chin J Tuberc Respir Dis*. 2020 Feb;43:E005 [Epub ahead of print].
4. Wang D, et al. *JAMA*. 2020;323:1061-1069.

Actemra® (tocilizumab)

- Tocilizumab is a humanized monoclonal antibody that targets the IL-6 receptor
- The role of IL-6 in the cytokine storms seen in some critically ill COVID-19 patients has led to the clinical investigation of tocilizumab as a treatment for COVID-19 pneumonia
- Actemra (tocilizumab) is indicated for use in:
  - Adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs
  - Adults with GCA
  - Patients 2 years of age and older with active pJIA
  - Patients 2 years of age and older with active sJIA
  - Adults and pediatric patients 2 years of age and older with CAR T-induced severe or life-threatening CRS
- Actemra is not indicated for use in patients with COVID-19 pneumonia and results from some studies have shown no benefit in COVID-19 pneumonia patients
- Refer to the Actemra USPI for Prescribing Information, Warnings and Precautions

Abbreviations: CAR T=chimeric antigen receptor T-cell; CRS=cytokine release syndrome; GCA=giant cell arteritis; IL-6=interleukin-6; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systemic juvenile idiopathic arthritis

Randomized Controlled Clinical Trials of Tocilizumab in COVID-19



COVACTA: A Randomized, Double-Blind, Placebo-Controlled, Phase III Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia

N	• 450 hospitalized adult patients with severe COVID-19 pneumonia	
Intervention	**Patients randomized to:** • TCZ 8 mg/kg IV (maximum dose = 800 mg) + standard-of-care or placebo + standard-of-care An additional dose of Actemra could be given 8-12 hours after the first dose if clinical signs and symptoms worsened or did not improve	
Patient Selection	**Key Inclusion Criteria** • ≥ 18 years old; • Hospitalized with confirmed COVID-19 pneumonia • SpO2 ≤ 93% or PaO2/FiO2 < 300 mmHg	**Key Exclusion Criteria** • Known severe allergic reactions to TCZ or other monoclonal antibodies • Active (e.g., TB) or suspected active infection (besides COVID-19) • In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments • Oral anti-rejection or immunomodulatory drugs within the past 6 months • Pregnant or lactating women • Participating in other drug clinical trials (anti-viral trials are acceptable) • ANC < 1000 /mL; Platelet count < 50,000 / mL; ALT or AST > 10 x ULN
Primary Outcome Measure	• Improvement in clinical status as measured by a 7-category ordinal scale, which tracked patients' clinical status based on the need for intensive care and/or ventilator use, as well as supplemental oxygen requirements.	
Key Secondary Outcome Measures	• Mortality rate • Incidence of mechanical ventilation • Time to hospital discharge • Safety	

Abbreviations: ARDS=Acute Respiratory Distress Syndrome; COVID-19=Coronavirus Disease 2019; CI=confidence Interval; CRP=C-reactive protein; GI=gastrointestinal; HTN=hypertension; IL-6=interleukin-6

1. https://www.clinicaltrials.gov/ct2/show/NCT04320615?term=covacta&cond=Covid19&draw=2&rank=1

COVACTA Primary and Secondary Outcome Measures*

Outcome Measures	Actemra (n=295)	*
Primary Endpoint - Clinical status based on 7-category ordinal scale at Day 28, median (95% CI)**	1 (1 to 1)	2 (1 to 4)
–Difference (95% CI), p value†	-1 (-2.5 to 0), p=0.36	
–Odds ratio (95% CI)‡	1.19 (0.81 to 1.76)	
Clinical status at Day 14 based on 7-category ordinal scale**, median (95% CI)	3 (2 to 4)	4 (3 to 5)
–Difference (95% CI), p value†	-1 (-2 to 0.5), p=0.05	
–Odds ratio (95% CI)‡	1.42 (0.99 to 2.05)	
Mortality at Day 28, n (% [95% CI])	58 (19.7 [15.2 to 24.3])	28 (19.4 [13 to 25.9])
–Weighted difference in % (95% CI)§, p value	0.3 (-7.6 to 8.2), p=0.94	
Time to hospital discharge or ready for discharge in days, median (95% CI)	20 (17 to 27)	28 (20 to NE)
–p-value‖	p=0.04	
–Hazard ratio (95% CI) reference:placebo¶	1.35 (1.02 to 1.79)	
Time to improvement of ≥2 categories on 7-category ordinal scale** of clinical status in days, median (95%CI)	14 (12 to 17)	18 (15 to 28)
–p-value‖	p=0.08	
–Hazard ratio (95% CI), reference:placebo¶	1.26 (0.97 to 1.64)	
Ventilator-free days to Day 28, median (95% CI)	22 (18 to 28)	16.5 (11 to 26)
–Difference in medians (95% CI), p-value†	5.5 (-2.8 to 13), p=0.32	

Notes: *Study results are pending peer review, **Defined as: 1=discharged or ready for discharge, 2=non-ICU hospital ward, not requiring supplemental oxygen, 3=non-ICU hospital ward, requiring supplemental oxygen, 4=ICU or non-ICU hospital ward, requiring noninvasive ventilation/ high-flow oxygen, 5=ICU, requiring intubation and mechanical ventilation, 6=ICU, requiring ECMO or mechanical ventilation and additional organ support, 7=death, † Based on van Elteren test, stratified by mechanical ventilation and region at randomization, ‡ Based on ordinal logistic regression analysis, adjusted for mechanical ventilation and region at randomization, § Based on extended Cochran-Mantel-Haenszel test, stratified by mechanical ventilation and region at randomization, ‖ Based on log-rank test, ¶ Cox proportional hazards model, stratified by mechanical ventilation and region at randomization

Summary COVACTA Safety Results Up to Day 28

Adverse Events, Serious Adverse Events, and Deaths

Events	Actemra (n=295)	Placebo (n=143)
Total AE, n	778	360
Patients with ≥1 AE, n (%)	228 (77.3)	116 (81.1)
Total SAE, n	160	101
Patients with ≥1 SAE, n (%)	103 (34.9)	55 (38.5)
Deaths, n (%)	58 (19.7)	28 (19.6)

Genentech Provides an Update on the Phase III COVACTA Trial of Actemra in Hospitalized Patients With Severe COVID-19 Associated Pneumonia. [press release]. South San Francisco, CA: Genentech, Inc.; July 28, 2020. Accessed July 28, 2020, from https://www.gene.com/media/pressreleases/14867/2020-07-28/genentech-provides-an-update-on-the-phas

COVACTA Safety Results Up To Day 28

Adverse Events of Special Interest (AESI)

AESI	Actemra (n=295)	Placebo (n=143)
Infections, n (%) –Serious infections, n (%) –Opportunistic infections*, n (%)	113 (38.3) 62 (21) 1 (0.3)	58 (40.6) 37 (25.9) 1 (0.7)
Medically confirmed malignancies, n (%)	1 (0.3)	0
Hypersensitivity†, n (%)	19 (6.4)	4 (2.8)
Anaphylaxis per Sampson criteria, n (%)	0	1 (0.7)
Hepatic events, n (%)	5 (1.7)	3 (2.1)
Laboratory criteria of Hy's Law‡, n (%)	3 (1)	2 (1.4)
Myocardial infraction, n (%)	3 (1)	2 (1.4)
Stroke, n (%)	3 (1)	2 (1.4)
Bleeding events, n (%) –Serious bleeding events, n (%)	45 (15.3) 13 (4.4)	16 (11.2) 5 (3.5)

Notes: *Candida sepsis occurred in the Actemra group, and respiratory moniliasis occurred in the placebo group, †Defined as all events that occurred within 24 hours of infusion and were not deemed "unrelated to study treatment" by the investigator, regardless of whether the events were clinically consistent with hypersensitivity, ‡Alanine aminotransferase or aspartate aminotransferase levels >3 times upper limit of normal with either bilirubin level >2 times upper limit of normal

Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. MedRxiv. E-pub Date: [published online ahead of print] September 2020. DOI # https://doi.org/10.1101/2020.08.27.20183442

COVACTA Safety Results to Day 28

Serious Infections Reported in >1% of Patients in Actemra- or Placebo-treated Patients

Serious Infections	Actemra (n=295)	Placebo (n=143)
Death caused by COVID-19, n (%)	39 (13.2)	18 (12.6)
Septic shock, n (%)	7 (2.4)	6 (4.2)
Pneumonia, n (%)	7 (2.4)	4 (2.8)
Bacterial pneumonia, n (%)	6 (2)	2 (1.4)
Sepsis, n (%)	3 (1)	4 (2.8)
Bacteremia, n (%)	2 (0.7)	3 (2.1)

Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. MedRxiv. E-pub Date: [published online ahead of print] September 2020. DOI # https://doi.org/10.1101/2020.08.27.20183442

EMPACTA: A Phase III Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients with COVID-19 Pneumonia

N	• 379 adult, hospitalized patients with confirmed COVID-19 pneumonia	
Intervention	**Patients randomized 2:1 to:** • TCZ 8 mg/kg IV (maximum dose = 800 mg) + SOC or placebo + SOC An additional dose of Actemra could be given 8-12 hours after the first dose if clinical signs and symptoms worsened or did not improve	
Patient Selection	**Key Inclusion Criteria** • Age ≥ 18 years old • Hospitalized with confirmed COVID-19 pneumonia • SpO2 <94%	**Key Exclusion Criteria** • Require CPAP or BIPAP, or invasive mechanical ventilation • Progression to death is imminent and inevitable within 24 hours • ANC <1000/mm^3, platelet count <50,000/mm^3 and/or ALT or AST >10x ULN
Primary Outcome Measure	• Cumulative proportion of patients requiring mechanical ventilation at Day 28	
Key Secondary Outcome Measures	• Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status • Mortality rate by Day 28	
Safety	• Incidence and severity of adverse events • Incidence of any post-treatment bacterial and/or fungal infection • Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)	

Abbreviations: ALT=; ANC=absolute neutrophil count; AST=; BIPAP=; CPAP=; COVID-19=Coronavirus Disease 2019; IV=intravenous; PCR=polymerase chain reaction; SOC=standard-of-care; SpO2=peripheral capillary oxygen saturation; TCZ=tocilizumab

1. https://clinicaltrials.gov/ct2/show/NCT04372186

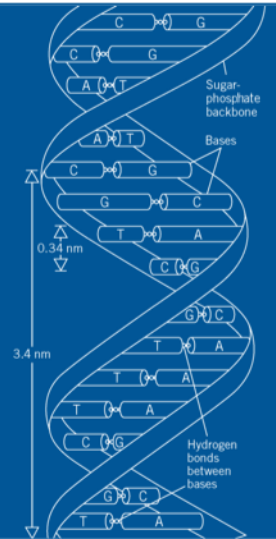
EMPACTA Primary and Secondary Outcome Measures

Outcome Measures	Result
Primary Endpoint	• The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the TCZ arm versus 19.3% in the placebo arm • Patients were 44% less likely to progress to mechanical ventilation or death when treated with TCZ + SOC vs. placebo + SOC (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97])
Key Secondary Endpoints	• Difference in time to hospital discharge or “ready for discharge” to day 28 was not significant – (median (days): TCZ = 6; PBO = 7.5; log-rank p-value = 0.2456; HR [95% CI] = 1.16 [0.90, 1.48]) • The difference in time to improvement in ordinal clinical status to day 28 was not significant – (median (days): TCZ = 6; PBO = 7; log-rank p-value = 0.2597; HR [95% CI] = 1.15 [0.90, 1.47]) • Time to clinical failure to day 28 was longer in the TCZ arm compared to the PBO arm – (median (days): TCZ = NE; PBO = NE; log-rank p = 0.0217; HR [95% CI] = 0.55 [0.33, 0.92]) – Difference cannot be considered statistically significant as other key secondary endpoints were not met • No statistical difference in mortality between patients who received TCZ or PBO by day 28 – TCZ = 10.4%; PBO = 8.6%, p-value = 0.5146, Difference [95% CI]: 2.0% [-5.2%, 7.8%]
Safety	• At day 28, the incidence of infections were 10% and 11% in the TCZ and placebo arms, respectively, and the incidence of serious infections were 5.0% and 6.3% in the TCZ and placebo arms, respectively • The most common adverse events in patients who received TCZ were constipation (5.6%), anxiety (5.2%), and headache (3.2%) • No new safety signals were identified for TCZ

Abbreviations: CI=confidence interval, HR=hazard ratio, Ne=not estimable, PBO=placebo, SOC=standard of care, TCZ=tocilizumab

1. Genentech’s Phase III EMPACTA Study Showed Actemra Reduced the Likelihood of Needing Mechanical Ventilation in Hospitalized Patients with COVID-19 Associated Pneumonia. [press release]. South San Francisco, CA: Genentech, Inc.; September 17, 2020. Accessed on September 17, 2020 at https://www.gene.com/media/press-releases/14881/2020-09-17/genentechs-phase-iii-empacta-study-showe

Selected (N≥50) Prospective Clinical Studies of Tocilizumab in COVID-19



Published Prospective Studies (N≥40)

Toniati et al, Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.[1]

N	• 100 patients with severe COVID-19 infection and acute respiratory distress syndrome
Intervention	• Actemra 8 mg/kg IV q12h x 2, followed by a third dose 24 hours after the second infusion based on clinical response
Outcome Measures	• Improvement in ARDS based on the Brescia COVID Respiratory Severity Score at 24-72 hours and 10 days after Actemra
Patient Demographics	• Median age = 62 years (IQR, 57-71 years); 88% male • Comorbidities included HTN (46%), obesity (31%), diabetes (17%), and cardiovascular disease (16%) • Majority of patients (87%) received 2 doses of Actemra with the remaining (13%) receiving 3 doses • All patients had elevated inflammatory markers (CRP, fibrinogen, ferritin and IL-6)
Results	<u>At 24-72 hours</u> • 58 patients demonstrated clinical and respiratory improvement, 37 were stable, and 5 deteriorated <u>By 10 days</u> • 15 patients were discharged and 23 patients had worsened • A total of 20 patients died • CRP, fibrinogen, and ferritin decreased in patients who had improved clinical status, while IL-6 and D-dimer increased in both improved and worsened patients
Safety	• Serious adverse events included septic shock (n=2; both died) and GI perforation (n=1)

Abbreviations: ARDS=Acute Respiratory Distress Syndrome; COVID-19=Coronavirus Disease 2019; CI=confidence Interval; CRP=C-reactive protein; GI=gastrointestinal; HTN=hypertension; IL-6=interleukin-6

1. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev. E-pub Date: [published online ahead of print] May 2020. DOI # 10.1016/j.autrev.2020.102568. https://www.ncbi.nlm.nih.gov/pubmed/32376398.

Published Prospective Studies (N≥40)

Somers EC, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19.[1]

N	• 154 patients with severe COVID-19 illness and whom required mechanical ventilation – 78 patients received TCZ – 76 patients were untreated
Intervention	• TCZ 8 mg/kg (max 800 mg) IV x 1 dose (additional doses were discouraged)
Outcome Measures	• Survival probability post-intubation (primary endpoint) • Secondary analyses included an ordinal illness severity scale integrating superinfections
Patient Demographics	• Baseline characteristics were well-balanced between both groups with the following exceptions: – TCZ-treated patients were younger (55 years vs 60 years; p=0.05); – TCZ-treated patients had lower median d-dimer (2.4 mg/dL vs 6.5 mg/dL; p=0.005); and, – TCZ-treated patients had higher mean serum albumin concentrations (3.5 g/dL vs 3.1 g/dL; p<0.001)
Results	• Based on Kaplan-Meier estimates, TCZ patients had an improved survival compared to those who did not (p=0.0189) • TCZ treatment was associated with a lower hazard of death when adjusted for demographics (HR=0.54, 95% CI, 0.29-1.00), complete laboratory data (n=116; HR=0.55; 95% CI, 0.33- 0.90), and missing laboratory data (HR=0.54; 95% CI, 0.35-0.84)
Safety	• TCZ patients were more than twice as likely to develop a superinfection compared with controls (54% vs. 26%, respectively; p<0.001) – No difference existed between the groups regarding the timing of infection, incidence of bloodstream infections, or in the development of ≥1 infection – Causes of superinfection were similar between groups with Staphylococcus aureus accounting for ~50% of infections in both TCZ-treated and control patients • Fatality rates at Day 28 were similar among TCZ-treated patients who had a superinfection and those who did not (8/37 [22%] vs. 6/41 [15%], respectively; p=0.42).

Abbreviations: CI=confidence interval; HR=hazard ratio; IV=intravenous; TCZ=tocilizumab

1. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clinical Infectious Diseases*, ciaa954, https://doi.org/10.1093/cid/ciaa954

Published Prospective Studies (N≥40)

Sciascia, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19.[1]

N	• 63 hospitalized patients with laboratory-confirmed COVID-19 infection
Intervention	• Actemra 8 mg/kg IV (n=34) or 324 mg SC (n=29)
Outcome Measures	• 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).
Patient Demographics	• Age 62.6±2.5 years; 89% male • Comorbidities include: HTN (38%), diabetes (9.5%), heart disease (7%), and COPD (4.7%) • 25/63 patients (39.7%) had a fever of >38°C • At baseline, 95.2% of patients had bilateral pulmonary infiltrates and 7.9% required invasive mechanical ventilation
Results	• Fever resolved within 24 hours after Actemra infusion in 24 of the 25 patients with fever at admission • Improvements in CRP, ferritin, D-dimer and lymphocyte counts were observed and respiratory parameters as measured by PaO2/FiO2, were also improved • 11% mortality at 14 days. No difference in mortality was observed between those who received intravenous (12.9%) vs subcutaneous (10.3%) administration. • The authors concluded that 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)
Safety	• No moderate to severe AEs directly related to Actemra were reported

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; COVID-19=Coronavirus Disease 2019; CRP=C-reactive protein; HTN=hypertension; IV=intravenous; SC=subcutaneous

1. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020. Available at https://www.clinexprheumatol.org/. Accessed on May 13, 2020. https://www.ncbi.nlm.nih.gov/pubmed/32359035.

Published Prospective Studies (N≥40)

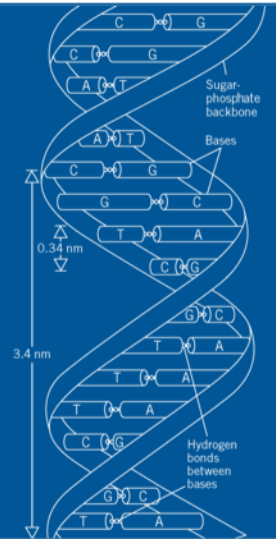
Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med.[1]

N	• 51 patients with confirmed, severe COVID-19 pneumonia
Intervention	• Actemra 400 mg IV q12h x2 or 8 mg/kg IV q12h x2 (for patients ≥60 kg) – 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)
Outcome Measures	• Death or hospital discharge (primary endpoint) • Change in disease severity and • Change in oxygen requirements at different time points after Actemra administration
Patient Demographics	• Age=60 years (IQR, 50-70) and 78.4% male • Comorbidities included: 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)
Results	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%) remained hospitalized • 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 • CRP levels returned to normal in 36 (71%) patients.
Safety	• Most common AEs were increased hepatic enzymes ≥3xULN (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).

Abbreviations: AE(s)=adverse event(s); COVID-19=Coronavirus Disease 2019; CRP=C-reactive protein; HTN=hypertension; IL-6=interleukin-6; IV=intravenous; ULN=upper limit of normal

1. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med. E-pub Date: [published online ahead of print] May 2020. DOI # 10.1016/j.ejim.2020.05.011. https://www.ncbi.nlm.nih.gov/pubmed/32448770

Actemra Investigator-Initiated Studies in COVID-19 Pneumonia



Italian Investigator-Initiated Study

An Open-label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of TCZ in 126 Hospitalized Patients With COVID-19 Pneumonia[1]

Interventions	**Experimental Arm** • TCZ (8 mg/kg IV; max dose of 800 mg) + standard-of-care – First TCZ dose within 8 hours of study entry – A second TCZ IV dose could be given 12 hours after the first if symptoms worsened (as defined by protocol)	**Control Arm** • Standard-of-care – If COVID-19 pneumonia symptoms worsened (as defined by protocol), patients could receive TCZ 8mg/kg x 1 dose (max. dose of 800 mg), followed by a second dose, as needed, 12 hours later
Outcome Measures	**Primary Endpoint** • Entry into Intensive Care with invasive mechanical ventilation or death from any cause at 2 weeks following study entry	**Secondary Endpoints** • Death from any cause • Correlation of IL-6 and CRP levels with treatment effectiveness • Changes from baseline in PaO2 / FiO2 ratio • Changes from baseline in lymphocyte count • Safety
Patient Selection	**Key Inclusion Criteria** • Age ≥18 years with PCR confirmed Sars-CoV2 infection • Hospitalized with PaO2 / FiO2 200-300 mm/Hg • Presence of exaggerated inflammatory response defined by the presence of at least 1 of the following criteria: – At least one body temperature measurement >38° C in the past two days; – Serum CRP greater than or equal to 10 mg/dl; – CRP increase of at least twice the basal value	**Key Exclusion Criteria** • PaO2 / FiO2 <200 mm/Hg • Required invasive or on-invasive ventilation support • Presence of shock or concomitant organ failure requiring ICU admission • Severe heart or kidney disease; • Patients who will not be moved to the ICU for any reason • Known hypersensitivity to TCZ or its excipients • Known active infections or other conditions that contraindicate TCZ • ALT or AST > 5 times the upper limit of the norm; Neutrophils <500 /mmc; Platelets <50.000 /mmc

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRP=C-reactive protein; FiO2=fraction of inspired oxygen; ICU=intensive care unit; IV=intravenous; PAO2=partial pressure of oxygen; PCR=polymerase chain reaction; TCZ=tocilizumab

1. https://www.clinicaltrials.gov/ct2/show/NCT04346355?term=Actemra&recrs=h&cond=COVID&fund=13&draw=2&rank=1

Italian Investigator-Initiated Study

An Open-label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of TCZ in 126 Hospitalized Patients With COVID-19 Pneumonia

- The study was terminated early after an interim analysis showed that, compared with standard-of-care, TCZ did not reduce the severity of respiratory symptoms, the number of intensive care visits, or death

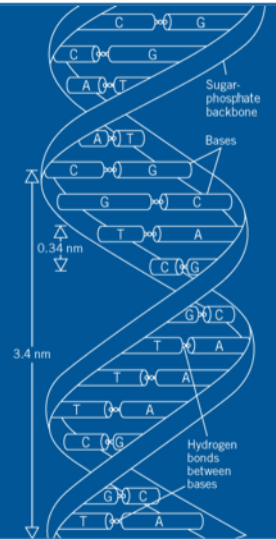
- 123 patients were included in the interim analysis which found:
  - 28.3% and 27% of TCZ and SOC patients, respectively, experienced an aggravation of symptoms
  - There was no significant difference between the groups in ICU admissions (10% and 7.9% for TCZ and SOC, respectively)
  - There was no significant difference in 30-day mortality between TCZ and SOC treated patients (3.3% vs. 3.2%, respectively)

- In a translated press release, the Italian Medicines Agency (Aifa) stated that the use of TCZ should be limited to the context of randomized clinical trials

Abbreviations: ICU=intensive care unit; SOC=standard-of-care; TCZ=tocilizumab

1. Agenzia Italiana del Farmaco (2020, June 17). COVID-19: Studio randomizzato italiano, nessun beneficio dal tocilizumab. [Press Release] Accessed at https://www.aifa.gov.it/web/guest/-/covid-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab

Ongoing Roche-Sponsored Clinical Trials of Tocilizumab in COVID-19 Pneumonia



Ongoing Roche-Sponsored Trials of TCZ in COVID-19 Pneumonia

REMDACTA: A Phase III Study to Compare the Efficacy and Safety of Remdesivir/TCZ with Remdesivir/Placebo in Hospitalized Patients With Severe COVID-19 Pneumonia (NCT04409262)

N	• 450 hospitalized patients with severe COVID-19 pneumonia	
Intervention	**Patients randomized to:** • Remdesivir + TCZ • Remdesivir + placebo	
Patient Selection	**Key Inclusion Criteria** • Age ≥ 12 years old • Hospitalized with COVID-19 pneumonia confirmed per WHO criteria • Requiring more than 6 L/min supplemental oxygen to maintain SpO2 > 93%	**Key Exclusion Criteria** • Known severe allergic reactions to monoclonal antibodies or hypersensitivity to remdesivir, its metabolites or formulation excipients • Known or suspected active bacterial, fungal, viral or other infection • Any immunosuppressive or immunomodulatory therapy within the past 3 months • Concurrent treatment with other agents with actual or possible direct-acting antiviral activity against SARS-CoV-2 within 24 hours prior to study drug dosing
Primary Outcome Measure	• Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 28	
Key Secondary Outcome Measures	• Time to Clinical Improvement • Proportion of Participants Requiring Initiation of Mechanical Ventilation Post-baseline • Mortality Rate on Days 7, 14, 21, 28, and 60	
Safety	• Percentage of participants with adverse events • Proportion of participants with post-treatment infection	

Abbreviations: COVID-19=Coronavirus Disease 2019; IV=intravenous; SOC=standard-of-care; SpO2=peripheral capillary oxygen saturation; TCZ=tocilizumab; WHO=World Health Organization

1. https://www.clinicaltrials.gov/ct2/show/NCT04409262?term=remdacta&draw=2&rank=1

Ongoing Roche-Sponsored Trials of TCZ in COVID-19 Pneumonia

MARIPOSA: A Phase II Study to Investigate Intravenous TCZ in Patients With Moderate to Severe COVID-19 Pneumonia (NCT04363736)

N	• 100 patients with moderate-to-severe, confirmed COVID-19 pneumonia	
Intervention	**Patients randomized to:** • TCZ 8 mg/kg IV • TCZ 4 mg/kg IV	
Patient Selection	**Key Inclusion Criteria** • Age ≥ 18 years old • Hospitalized with confirmed COVID-19 pneumonia – For **severe patients**, SpO2 ≤ 93% or PaO2/FiO2 <300 mmHg – For **moderate patients** (CRP >2x ULN is required)	**Key Exclusion Criteria** • Known severe allergic reactions to monoclonal antibodies • Suspected active bacterial, fungal, viral or other infection (besides COVID-19) • Patients who are on a mechanical ventilator >24 hours or ECMO, in shock, or a combination thereof with other organ failure requiring treatment in an ICU • Progression to death is imminent and inevitable within 24 hours • Long-term oral anti-rejection or immunomodulatory drugs
Primary Outcome Measure	• Pharmacodynamic response to TCZ treatment, as measured by CRP at Day 7	
Key Secondary Outcome Measures	• Clinical status, as assessed using a 7-category ordinal scale at Days 14 and 28 • Time to improvement in at least two categories relative to baseline on a 7-category ordinal scale of clinical status • Incidence of mechanical ventilation • Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first) • Mortality rate	
Safety	• Percentage of participants with adverse events • Proportion of participants with post-treatment infection	

Abbreviations: CRP=C-reactive protein; COVID-19=Coronavirus Disease 2019; ECMO=extracorporeal membrane oxygenation; ICU=intensive care unit; IV=intravenous; SpO2=peripheral capillary oxygen saturation; TCZ=tocilizumab; ULN=upper limit of normal

1. https://clinicaltrials.gov/ct2/show/NCT04363736

Summary

- As of September 18, 2020, The COVID-19 pandemic has affected over 30 million people worldwide with hundreds of thousands of deaths reported
- Features of critically ill patients infected with COVID-19 suggest the presence of an accentuated immune system resulting in acute respiratory distress syndrome and multi-organ failure
- The role of IL-6 in the cytokine storms seen in some critically ill COVID-19 patients has led to the clinical investigation of Actemra as a treatment for COVID-19 pneumonia
- Genentech and Roche have initiated four clinical trials to evaluate the role of Actemra in hospitalized patients with moderate to severe COVID-19 pneumonia: COVACTA, EMPACTA, REMDACTA, and MARIPOSA
- On July 28, 2020, it was announced that the Phase 3 COVACTA trial failed to meet its primary endpoint of improved clinical status in adult hospitalized patients with severe COVID-19 pneumonia treated with Actemra. The study also failed to meet the key secondary endpoint of reduced patient mortality
- On September 17, 2020, it was announced that the Phase 3 EMPACTA trial met its primary endpoint showing that the cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was less in Actemra-treated patients compared to placebo. The study also did not meet key secondary endpoints, including reduced patient mortality

Medical Resources

Click here to access the written Genentech Medical Response on Actemra Use in Coronavirus Disease 2019 (COVID-19)

Click here to access additional Genentech resources for Healthcare Providers

Doing now what patients need next