SEE ATTACHED ADDENDUM

Emergency Use Authorization (EUA) for tocilizumab, FOR THE UNAPPROVED USE OF AN APPROVED PRODUCT
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	99
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Hoffmann-La Roche Ltd. C/O Genentech, Inc. 1 DNA Way, Bldg 45-1 South San Francisco, CA 94080 Dhushy Thambipillai Regulatory Program Management Phone: (b) (6) Fax: (b) (6) Email: (b) (6)
Submission Date(s)	April 20, 2021
Receipt Date(s)	April 20, 2021
OND Division / Office	Division of Pulmonology, Allergy, and Critical Care / Office of Immunology and Inflammation
Reviewer Name(s)/Discipline(s)	Clinical: Andrew Clerman, Robert Lim, Jessica Lee Stats: Cesar Torres, Xiaofeng (Tina) Wang, Rebecca Rothwell Clin Pharm: Ping Ji, Jiang Liu, Jianmeng Chen Nonclinical: Brett Jones, Eleni Salicru OBP: Zachary Kraus, Mate Tolnay, Gerald Feldman OBP Labeling: Koung Lee OPMA: Wendy Tan, Zhong Li, Max Van Tassell OMQ: Tara Gooen, Rick Friedman OPRO: Teshara Bouie, RBPM OND Policy: Andrew Leboeuf, Jagjit Grewal ORP: Stefanie Kraus DPMH: Amy Taylor, Shetarra Walker DMPP: Sharon Williams, Marcia Williams DMEPA: Lissa Owens, Idalia Rychlik DPV: Ida-Lina Diak OPDP: Adewale Adeleye, Kathleen Klemm
Integrated Review Completion Date	June 24, 2021
Proprietary Name	Actemra
Established Name/Other names used during development	Tocilizumab

Dosage Forms/Strengths	Intravenous Infusion; 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL
Therapeutic Class	IL-6 receptor antagonist
Intended Use or Need for EUA	Treatment of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

I. EUA Determination/Declaration

On February 4, 2020, the Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States (US) citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

The Division of Pulmonology, Allergy and Critical Care, Office of Immunology and Inflammation, Office of New Drugs, CDER recommends EUA issuance.

The EUA will authorize tocilizumab (tradename: ACTEMRA) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

B. Eligibility of the Product for an EUA

COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.

Based on the totality of the scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, it is reasonable to believe that tocilizumab may be effective for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic

corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; and when used under such conditions, the known and potential benefits of tocilizumab outweigh the known and potential risks of the product.
There is no adequate, approved, and available alternative to the emergency use of tocilizumab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Remdesivir (Veklury®) is the only drug approved by FDA to treat COVID-19 at the time of FDA's review of tocilizumab. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

Tocilizumab also has a different mechanism of action than remdesivir. Tocilizumab is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors. Severe COVID-19 has been associated with inflammation. In this context, high levels of IL-6, as well as other pro-inflammatory cytokines and inflammatory markers, have been observed in some patients with severe COVID-19 and have been associated with worse outcomes. Thus, a product inhibiting IL-6, such as tocilizumab, may potentially act on the COVID-19-associated inflammatory response. This is distinct from remdesivir, which acts as an antiviral agent. We also note that Remdesivir's FDA-approved indication is for a narrower population than the use authorized for Actemra under this EUA.

III. Proposed Use and Dosing of the Product Under the EUA

- Proposed use(s) under EUA: Use of tocilizumab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

- Proposed dosing regimen(s) for use under EUA

    - Adult patients: 8 mg/kg (max. 800 mg) given as a single 60-minute intravenous infusion. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered at least 8 hours after the initial infusion.

    - Pediatric patients 2 years of age and older: 8 mg/kg given as a single 60-minute intravenous infusion if body weight is greater than or equal to 30 kg and 12 mg/kg given as a single 60-minute intravenous infusion for body weight less than 30 kg. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered at least 8 hours after the initial infusion.

- Pregnant or lactating patients: Tocilizumab has not been studied in pregnant or lactating women with COVID-19.

- Other specific populations (e.g., geriatric patients, patients with renal or hepatic impairment): No dose adjustment is required in patients with mild or moderate renal impairment and hepatic impairment.

- Rationale for dosing regimen: The dosing of tocilizumab is based on the regimen that was evaluated in four randomized, [redacted]-controlled trials in adult patients hospitalized with COVID-19: WA42380 (COVACTA), RECOVERY, ML42528 (EMPACTA), WA42511 (REMDACTA) and one phase 2 trial CA42481 (MARIPOSA). In these trials, the proposed dosing regimen was used except in the RECOVERY trial, which used weight tiered dosing. Even though weight-tiered dosing was used in the RECOVERY trial, the difference in dose from the proposed dosing regimen of 8 mg/kg was less than 25% for any patient. The dosing rationale for pediatric patients 2 years of age or older is based on the consideration that the disease in adults and pediatric patients is sufficiently similar once patients progress to require supplemental oxygen, or invasive mechanical ventilation or ECMO. The proposed dosing regimen for pediatric patients is expected to have comparable PK exposure of tocilizumab as in adult patients with COVID-19. The pediatric dosing regimen is also informed by the accumulated PK and safety information with tocilizumab in multiple adult and pediatric populations including adult patients with COVID-19 and population PK modeling and simulation. Further details on the rationale for the dosing regimen is discussed in the section on Human Clinical Pharmacology.

SEE ATTACHED ADDENDUM

IV. Product Information (Dose Preparation and Administration)

Preparation and Administration

Tocilizumab (tradename: ACTEMRA) for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Use a sterile needle and syringe to prepare tocilizumab.
- Patients less than 30kg: use a 50 mL infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients at or above 30kg weight: use a 100 mL infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the tocilizumab injection required for the patient's dose from the infusion bag or bottle (0.4 mL/kg and 0.6mL/kg for 8mg/kg and 12mg/kg dosages, respectively)
- Step 2. Withdraw the amount of tocilizumab for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

- The fully diluted tocilizumab solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 2°C to 8°C (36°F to 46°F) or room temperature for up to 24 hours and should be protected from light.
- The fully diluted tocilizumab solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
- Tocilizumab solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
- Allow the fully diluted tocilizumab solution to reach room temperature prior to infusion.
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
- Tocilizumab should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of tocilizumab with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates or discolorations are noted, the product should not be used.
- Fully diluted tocilizumab solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

Storage and Handling

Do not use beyond expiration date on the container or package. Tocilizumab must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package until time of use.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

- Background information on the condition

  There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, approximately 173 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of June 7, 2021, including an estimated 3.7 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC), as of June 7, 2021, approximately 33.2 million cases of COVID-19 have been reported with 594,802 deaths.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. COVID-19 may result in hypoxemia, respiratory failure, multi-organ failure, and death.

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

- Therapeutic alternatives for the disease/condition

  There is no adequate, approved, and available alternative to the emergency use of tocilizumab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

  There is an approved drug for severe COVID-19. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This medication was initially authorized for emergency use on May 1, 2020, and was ultimately approved on October 22, 2020, under NDA 214787. At the time of this review, remdesivir remains authorized for emergency use for treating suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

  There are other COVID-19 treatments authorized for emergency use in hospitalized patients, including baricitinib. Baricitinib, an inhibitor of Janus kinases, is authorized for emergency use in combination with remdesivir for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplementary oxygen, invasive mechanical ventilation, or ECMO.

Tocilizumab also has a different mechanism of action than remdesivir. Tocilizumab is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors. Severe COVID-19 has been associated with inflammation. In this context, high levels of IL-6, as well as other pro-inflammatory cytokines and inflammatory markers, have been observed in some patients with severe COVID-19 and have been associated with worse outcomes. Thus, a product inhibiting IL-6, such as tocilizumab, may potentially act on the COVID-19-associated inflammatory response. This is distinct from remdesivir, which acts as an antiviral agent. We also note that Remdesivir's FDA-approved indication is for a narrower population than the use authorized for Actemra under this EUA

VI. Related Regulatory Submission(s)

- Related NDAs or BLAs
  - BLA 125276 for tocilizumab
    - Applicant: Genentech, Inc.
    - Initial US approval: 2010
    - Dosage form: injection for intravenous (IV) use
    - Approved indications:
      - Rheumatoid Arthritis (RA) - 4mg/kg – 8mg/kg every 4 weeks
      - Polyarticular juvenile idiopathic arthritis (PJIA) - 10mg/kg IV every 4 weeks for patients <30kg; 8mg/kg every 4 weeks for patients ≥30kg
      - Systemic juvenile idiopathic arthritis (SJIA) – 12mg/kg IV every 2 weeks for patients <30kg; 8mg/kg IV every 2 weeks for patients ≥30kg
      - Cytokine release syndrome (CRS) - 12mg/kg IV for patients <30kg; 8mg/kg IV for patients ≥30kg

  - BLA 125472 for tocilizumab
    - Applicant: Genentech, Inc.
    - Initial US approval: 2013
    - Dosage form: injection for subcutaneous (SC) use
    - Approved indications:
      - RA – 162 mg SC every other week for patients <100kg; 162mg every week for patients >100kg
      - Giant Cell Arteritis – 162 mg SC every to every other week
      - Systemic sclerosis-associated interstitial lung disease – 162 mg SC every week.
      - PJIA – 162 mg SC every 3 weeks for patients <30kg; 162 mg SC every 2 weeks for patients ≥30kg
      - SJIA – 162 mg SC every 2 weeks for patients <30kg; every week for patients ≥30kg

- Related INDs
  - Tocilizumab, in various formulations and routes of administration, has been studied for multiple indications under multiple INDs. These include INDs 011972, 112406, 113654, (b) (4) 148225, (b) (4).

    Under IND 148225, tocilizumab was studied for the treatment of hospitalized patients with COVID-19. COVACTA, EMPACTA, and REMDACTA were conducted under this IND. Under this IND, patients received up to two doses of tocilizumab 8mg/kg intravenously, an approved dose.

- Related Master Files
  - DMF (b) (4)
    - (b) (4)
    -
  - DMF (b) (4)
    - (b) (4)
    -

VII. Summary of Clinical Data

To support this EUA, the sponsor submitted results from four trials. These included the RECOVERY trial and the Sponsor-conducted trials: COVACTA, EMPACTA, and REMDACTA. In all the Sponsor-conducted trials, study treatment was administered on a background of local standard-of-care (SOC). The RECOVERY trial, conducted by the RECOVERY Collaborative Group, was an open-label trial comparing tocilizumab to usual care alone. The Sponsor has also submitted results from two meta-analyses; one based on patient level data from the Sponsor-conducted trials and one based on study-level summary data from the Sponsor-conducted trials and RECOVERY. At the time of EUA request, trials investigating the use of tocilizumab for treatment of COVID-19 are ongoing (www.clinicaltrials.gov); however, there are no ongoing trials under IND 148225 and no plan for additional Sponsor-conducted trials in COVID-19. Key design features of the trials used to support the EUA for tocilizumab in treatment of COVID-19 are summarized in Table 1.

Table 1. COVID -19 Clinical Trials

Study Identifier or Protocol Number	IND	Type of Study	Sample Size and Treatment Arms (N)	Study Design and Type of Control	Enrolled Population	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration
RECOVERY NCT04381936 Study dates: April 2020 – January 2021	Not conducted under IND	Efficacy and safety	4116 underwent second randomization 1:1 to TCZ+usual care (N=2022) or usual care alone (N=2094)	Randomized, open-label, controlled, platform trial (tocilizumab sub-study)	Hospitalized patients age ≥18 years with suspected or laboratory confirmed SARS-CoV-2 infection, oxygen saturation <92% on ambient air or receiving oxygen therapy, and CRP ≥75 mg/L	TCZ IV dose was determined by four body weight categories (800 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8mg/kg if weight ≤40 kg). A second dose could be given 12−24 hours after the initial dose.
WA42380 (COVACTA) NCT04320615 Study dates: April 2020 – May 2020	IND 148225	Efficacy and safety	452 randomized 2:1 to TCZ + SOC (N=301), or PBO + SOC (N=151)	Randomized, double-blind, placebo-controlled trial	Hospitalized patients age ≥18 years with positive SARS-CoV-2 PCR, radiographic evidence of pneumonia, hypoxemia (oxygen saturation ≤93% or PaO2/FiO2 <300 mmHg)	TCZ 8 mg/kg (max. 800 mg) given IV. Patients could receive one additional dose between 8-24 hours after the initial infusion.
ML42528 (EMPACTA) NCT04372186 Study dates: May 2020 - July 2020	IND 148225	Efficacy and safety	388 randomized 2:1 to TCZ + SOC (N=259), or PBO + SOC (N=129)	Randomized, double-blind, placebo-controlled trial	Hospitalized patients age ≥18 years with positive SARS-CoV-2 PCR, radiographic evidence of pneumonia, hypoxemia (oxygen saturation <94% on ambient air) excluding patients on CPAP, BPAP, or MV	TCZ dose is the same as in COVACTA
WA42511 (REMDACTA) NCT04409262 Study dates: June 2020 – January 2021	IND 148225	Efficacy and safety	649 randomized 2:1 to TCZ+RDV+SOC (N=434) or PBO+RDV+SOC (N=215)	Randomized, double-blind, placebo-controlled trial	Hospitalized patients age ≥12 years with positive SARS-CoV-2 PCR hypoxemia (>6 L/min supplemental oxygen to maintain oxygen saturation >93%)	TCZ dose is the same as in COVACTA. RDV 200 mg IV on Day 1 followed by 100 mg IV on Days 2-10.

TCZ=tocilizumab; RDV=remdesivir; PBO=placebo; SOC=Standard of care; NA=not applicable; PCR=polymerase chain reaction; PaO2=arterial oxygen partial pressure; FiO2=fraction of inspired oxygen; CPAP=continuous positive airway pressure; BPAP=bilevel positive airway pressure; MV=mechanical ventilation; IV=intravenous

VIII. Human Clinical Efficacy

RECOVERY

Study Design and Primary Endpoint Analysis Plan

RECOVERY is a multicenter, adaptive, randomized, controlled, open-label, platform trial to evaluate the effects of potential treatments in patients hospitalized with COVID-19. The trial was conducted entirely in the United Kingdom (UK) by the RECOVERY Collaborative Group. Roche Products Ltd (UK) provided tocilizumab but was otherwise not involved in the trial design or conduct. To facilitate trial conduct and rapid large-scale enrollment in the setting of an ongoing pandemic, trial procedures and data collection were simplified.

The RECOVERY trial enrolled hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history, in the opinion of the attending clinician, that might put them at substantial risk if they were to participate. Patients with known hypersensitivity to tocilizumab, evidence of active tuberculosis, or clear evidence of active bacterial fungal, viral, or other infection (besides SARS-CoV2) were not eligible for the RECOVERY tocilizumab cohort. Once enrolled, patients underwent an initial randomization to receive either an active treatment or usual care. The initial randomization included a variety of products that changed over time given the adaptive design, but tocilizumab was not included in the initial randomization at any point during the trial. Up to 21 days after the initial randomization and regardless of treatment allocation, patients could qualify for the tocilizumab cohort and undergo a second randomization to tocilizumab + usual care versus usual care alone if they had "progressive COVID-19" defined as having both of the following: 1) oxygen saturation <92% on room air or receiving oxygen therapy and 2) C-reactive protein (CRP) ≥75 mg/L. Patients were not eligible for the second randomization if tocilizumab was unavailable at the hospital or if the attending clinician determined that tocilizumab was either definitely indicated or definitely contraindicated.

Patients randomized to tocilizumab received an intravenous (IV) dose of 800 mg if >90kg; 600 mg if >65 and ≤90 kg; 400 mg if >40 and ≤65 kg; and 8mg/kg if ≤40 kg). This is in contrast to the FDA approved dosing of intravenous tocilizumab which is on a mg/kg basis only. Tocilizumab was administered as a single IV infusion and a second dose could be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

The primary objective of the overall RECOVERY trial was to provide estimates of the effect of study treatments on all-cause mortality within 28 days of the relevant randomization. The prespecified primary analysis indicated that the primary efficacy endpoint would be evaluated as time to death through Day 28. The secondary endpoints were [redacted] and, for patients not on invasive mechanical ventilation at baseline, the composite endpoint of death or need for invasive mechanical ventilation or ECMO. SEE ATTACHED ADDENDUM

Throughout the RECOVERY trial, interim trial results were monitored by an independent Data Monitoring Committee (DMC). At each interim analysis, the DMC could recommend stopping the trial for efficacy if a reduction in mortality of at least 3 to 3.5 standard errors was observed.

Baseline Patient Characteristics

A total of 4116 (19%) of the 21,550 patients enrolled in the RECOVERY trial underwent the second randomization with 2022 patients allocated to receive tocilizumab and 2094 patients allocated to usual care alone. In both the tocilizumab and usual care alone arms, most patients underwent the second randomization very soon after the first randomization, with median days since the first randomization being zero; and soon after hospitalization with median days since hospitalization of 2 days. The mean age of patients enrolled was 63.6 years old and a majority were male (67.4%). In terms of respiratory support at baseline, 45% were receiving simple oxygen (with 9 patients reported to not be receiving oxygen at baseline), 41% were receiving non-invasive positive pressure ventilation or high flow nasal oxygen, and 14% were receiving invasive mechanical ventilation (with 14 patients on ECMO at baseline). A summary of key baseline patient characteristics is shown in Table 2. Overall, there were no major imbalances in baseline patient characteristics between the tocilizumab and usual care arms that would be expected to impact the trial outcome.

Table 2. RECOVERY baseline characteristics by randomized allocation

Characteristic	Tocilizumab (N=2022)	Usual care (N=2094)
Age, Mean (SD), years	63.3 (13.7)	63.9 (13.6)
Sex n(%)		
Male	1337 (66%)	1437 (69%)
Female	685 (34%)	657 (31%)
Race/ethnicity n(%)		
White	1530 (76%)	1597 (76%)
Black, Asian, or minority ethnic	354 (18%)	378 (18%)
Unknown	138 (7%)	119 (6%)
Days since symptom onset, median (IQR)	9 (7-13)	10 (7-14)
Days since hospitalization, median (IQR)	2 (1-5)	2 (1-5)
Days since first randomization, median (IQR)	0 (0-1)	0 (0-1)
Respiratory support at second randomization n(%)		
Supplemental oxygen*	935 (46%)	933 (45%)
Non-invasive ventilation or high-flow oxygen**	819 (41%)	867 (41%)
Invasive mechanical ventilation***	268 (13%)	294 (14%)
Receiving systemic corticosteroids n(%)	1664 (82%)	1721 (82%)
C-reactive protein, mg/L, median (IQR)	143 (107-203)	144 (106-205)
Previous diseases n(%)		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease n(%)	473 (23%)	484 (23%)

N=number of randomized subjects, SD= standard deviation, IQR= interquartile range
*Includes 9 patients not receiving any oxygen
**Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation
***Includes 14 patients on ECMO
Source: RECOVERY Collaborative Group, 2021

Efficacy Results

Mortality

The primary endpoint for the RECOVERY study was 28-day mortality, evaluated using time-to-event statistical methodology (a log-rank test) in the study's primary analysis. The analysis results for this endpoint are described by the RECOVERY Collaborative Group as a "rate ratio" (RECOVERY Collaborative Group, 2021). To avoid confusion with describing the ratio of probabilities of dying by Day 28 and the statistical relationship of this summary measure to the hazard function, the primary analysis results in this review are described as a comparison between treatment arms on the hazard ratio scale.[1,2]

Among the 2022 patients in the tocilizumab + usual care treatment arm, 621 (31%) died within 28 days. Among the 2094 patients in the usual care treatment arm, 729 (35%) died within 28 days. The hazard ratio comparing the two treatment arms with respect to time to death through Day 28 was estimated to be 0.85 (95% CI: 0.76 to 0.95), with there being statistically significant evidence tocilizumab has an effect on time to death through Day 28 when compared to usual care (p = 0.0028).

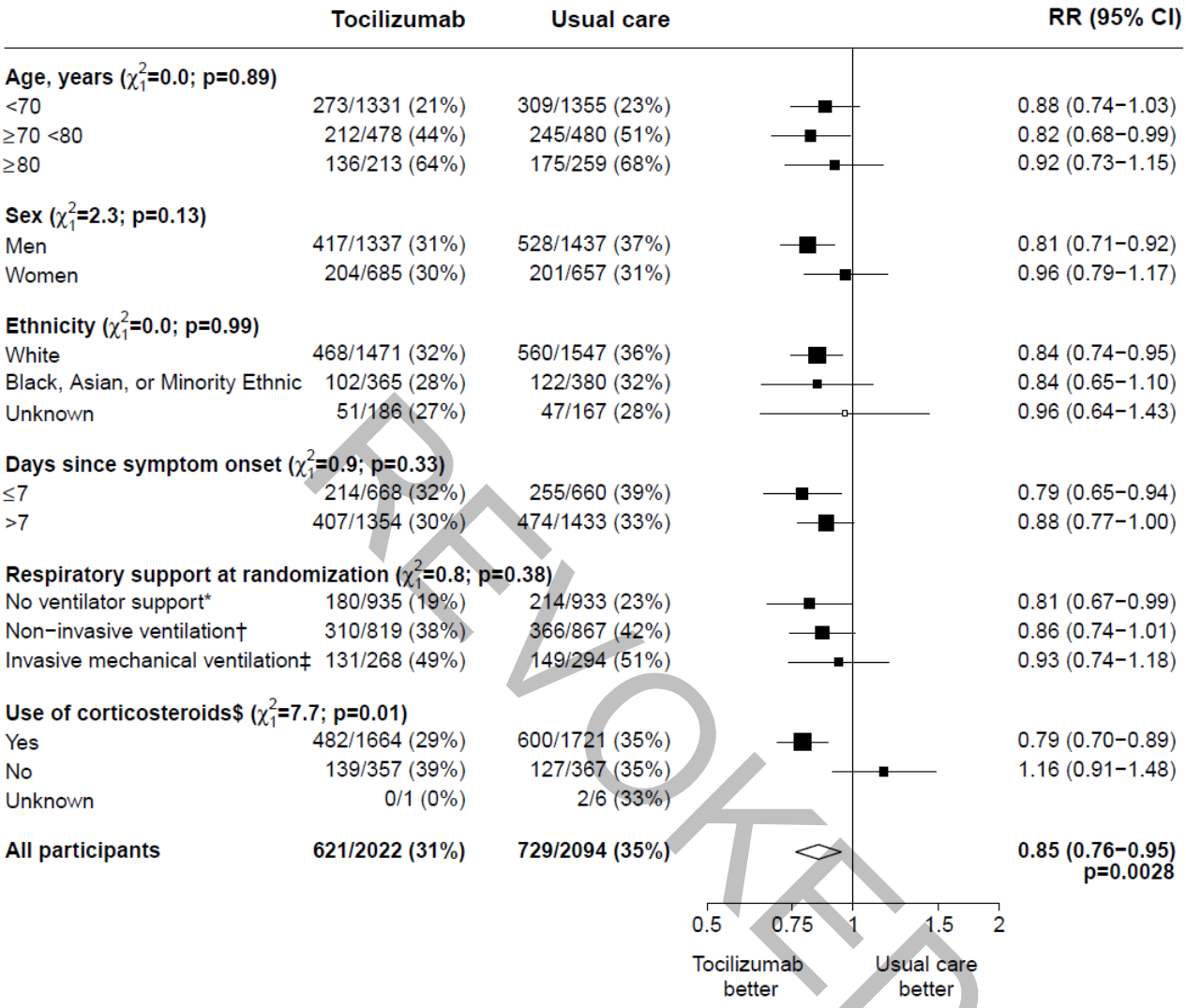
Numerous interim analyses occurred during which tocilizumab's effect was evaluated to allow for the possibility of stopping further evaluation for efficacy. The DMC did not recommend stopping for efficacy based on the reduction of mortality at any of these interim analyses. When adjusting for the interim analyses that occurred, changes to the primary analysis results of all-cause mortality were minimal (point estimate of 0.86, 95% CI of 0.76 to 0.97, and p-value of 0.0097).

The analysis results of all-cause mortality within pre-specified subgroups are presented in Figure 1. For the majority of subgroups, results are consistent with the overall population. However, when examining the results within subgroups of patients defined by corticosteroid use at baseline, the point estimate favors usual care alone in patients who did not use corticosteroids. While tests for heterogeneity in subgroups are exploratory and can lack reliability, there is preliminary evidence of an interaction with baseline steroid use.

[1] The RECOVERY website (accessed 13 June 2021) and publication state the treatment comparisons as rate ratios. This review uses hazard ratios.

[2] For a Cox proportional hazards model with a binary variable as the single covariate in the model, the log-rank test can be derived as the score test for this model. When fitting this study's data to such a model, the analysis results were numerically equivalent to those from the prespecified primary analysis.

Figure 1: RECOVERY Study Primary Analysis Results (28-Day Mortality), by Subgroup



Source: RECOVERY Collaborative Group, 2021
*Includes nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only. †Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation. ‡Includes patients receiving invasive mechanical ventilation and extracorporeal membranous oxygenation.
Note: The header for the rightmost column reflects that the results are presented on the rate ratio scale. However, these results can also be interpreted on the hazard ratio scale.

Given that extending the time to death in one treatment group within 28 days would be of questionable clinical meaningfulness if ultimately similar proportions of patients died in this timeframe, an analysis evaluating 28-day mortality as a binary endpoint was requested to supplement the time-to-event primary analysis. The probability of dying by Day 28 was estimated to be 30.7% and 34.9% in the tocilizumab and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis.

Time to Hospital Discharge

The probabilities of being discharged from the hospital by Day 28 were estimated to be 57% and 50% among patients in the tocilizumab and placebo groups, respectively. The median time to hospital discharge with tocilizumab was estimated to be 19 days, while with usual care, it was estimated to be greater than 28 days.[3] The hazard ratio comparing the two treatment groups for time to hospital discharge was estimated to be 1.22 (95% CI: 1.12 to 1.33). As this represents time to a positive event, a hazard ratio greater than 1 favors tocilizumab.

SEE ATTACHED ADDENDUM

Mechanical Ventilation (MV) or Death

Among those not on MV at baseline, the probabilities of progression to MV or death by Day 28 were estimated to be 35% and 41% in the tocilizumab and placebo groups, respectively. The ratio comparing the two treatment groups for MV or death was estimated to be 0.85 (95% CI: 0.78 to 0.92).

Early Study Withdrawal and Missing Data

Among the 2022 patients randomized to tocilizumab, 1964 (97%) had complete follow-up through Day 28. Among the 2094 patients randomized to usual care, 2049 (98%) had complete follow-up through Day 28. Follow-up for the primary and secondary outcomes was complete for 99% of randomized participants.

Efficacy Conclusion for the RECOVERY Trial

In the RECOVERY trial, a statistically significant reduction in 28-day mortality was observed for patients treated with tocilizumab compared to usual care alone. Additionally, there were benefits in probability of discharge from the hospital within 28 days and reduction in the composite outcome of invasive mechanical ventilation or death among patients not on invasive mechanical ventilation at baseline. Across these clinically meaningful endpoints, the subgroup of patients who used baseline systemic corticosteroids showed a treatment effect consistent with the overall population. However, there is a trend favoring usual care alone for the outcome of 28-day mortality in the subgroup of patients not on baseline corticosteroids.

Issues affecting interpretation include the open-label design, which may introduce bias, and that the trial was conducted entirely in the U.K., which raises concerns regarding generalizability to the U.S. population. An additional issue with the interpretation of RECOVERY is the “progressive COVID-19” criteria used for enrollment. Only 19% of patients enrolled in RECOVERY underwent the second randomization; however, it is likely that many more would have met the hypoxemia and CRP criteria. This raises the concern as to whether this population was limited in other ways (e.g., additional clinical judgement in determining whether a patient had “progressive COVID-19”). While there are limitations, it is reasonable to conclude from RECOVERY that tocilizumab may be effective in hospitalized patients with COVID-19, particularly in patients receiving corticosteroids.

[3] A non-parametric point estimate for the median time to hospital discharge with usual care is not available due to the limited number of events relative to the sample size in this arm prior to Day 28.

WA42380 (COVACTA)

Study Design and Primary Endpoint Analysis Plan

COVACTA was a phase 3, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of tocilizumab in adult patients hospitalized with severe COVID-19. Patients could be enrolled if they had radiographic evidence of pneumonia and hypoxemia (SpO2 ≤ 93% or PaO2/FiO2 <300 mmHg), which included patients on invasive mechanical ventilation. Once enrolled, patients were randomized 2:1 to receive tocilizumab 8 mg/kg or placebo, respectively, with both randomized treatments administered in addition to SOC. One additional dose of blinded treatment could be given 8-24 hours after the first treatment if clinical signs or symptoms worsened or did not improve.

The primary efficacy endpoint was the difference in distributions in clinical status assessed using a 7-category ordinal scale at Day 28. The ordinal scale was defined as follows:

1. Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen)
2. Non-ICU hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen
3. Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Key secondary endpoints included mortality at Day 28 (proportion of subjects who died by Day 28), ordinal scale clinical status at Day 14, ventilator-free days (VFD) to Day 28, time to improvement from baseline in ≥2 categories on the ordinal scale, and time to hospital discharge (or “ready for discharge”). No interim analyses were performed for this study.

Baseline Patient Characteristics

A total of 452 patients were randomized at 62 centers across Europe and North America, and more than half of patients were randomized in the US (55.8%). Patients were randomized at a 2:1 ratio, resulting in 301 patients in the tocilizumab arm and 151 patients in the placebo arm. A summary of key baseline patient characteristics for the modified intent-to-treat (mITT) population, which is defined as all randomized patients who received at least one dose of study treatment, is shown in Table 3. Groups were generally well-balanced; however, a greater proportion of patients in the placebo arm received corticosteroids at baseline compared to the tocilizumab arm, with 22% of all subjects receiving steroids at baseline.

Table 3. COVACTA patient baseline characteristics (mITT population)

Characteristic	Tocilizumab (N=294)	Placebo (N=144)
Age, Mean (SD), years	60.9 (14.6)	60.6 (13.7)
Sex n(%)		
Male	205 (69.7%)	101 (70.1%)
Female	89 (30.3%)	43 (29.9%)
Race n(%)		
American Indian or Alaska Native	8 (2.7%)	5 (3.5%)
Asian	28 (9.5%)	10 (6.9%)
Black or African American	40 (13.6%)	26 (18.1%)
Native Hawaiian or other Pacific Islander	3 (1.0%)	5 (3.5%)
White	176 (59.9%)	76 (52.8%)
Multiple	0	1 (0.7%)
Unknown	39 (13.3%)	5 (3.5%)
Ethnicity n(%)		
Hispanic or Latino	94 (32.0%)	47 (32.6%)
Not Hispanic or Latino	181 (61.6%)	86 (59.7%)
Not stated	12 (4.1%)	6 (4.2%)
Unknown	7 (2.4%)	5 (3.5%)
Days since symptom onset (SD)	11.4 (6.9)	12.1 (6.6)
Ordinal scale clinical status* n(%)		
2	9 (3.1%)	6 (4.2%)
3	78 (26.5%)	44 (30.6%)
4	94 (32.0%)	39 (27.1%)
5	45 (15.3%)	15 (10.4%)
6	68 (23.1%)	39 (27.1%)
7	0	1 (0.7%)
Receiving systemic corticosteroids n(%)	57 (19.4%)	41 (28.5%)
C-reactive protein, mg/L, mean (SD)	168 (101)	173 (114)
Previous diseases n(%)		
Hypertension	168 (56.9%)	90 (62.9%)
Type 2 diabetes	69 (23.4%)	35 (24.5%)
Obesity	63 (21.4%)	27 (18.9%)

N= number of subjects in the modified intent-to-treat population, SD = standard deviation
*Ordinal scale for clinical status: 1) discharged or “ready for discharge” 2) non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3) non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4) ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5) ICU, requiring intubation and mechanical ventilation 6) ICU, requiring ECMO or mechanical ventilation and additional organ support 7) death
Source: Adapted from Tables 9, 10, and 11 (pg. 70-75) of COVACTA CSR

Efficacy Results

Primary Endpoint

In the analysis of the primary endpoint, there was not statistically significant evidence that tocilizumab has an effect on the 7-category ordinal scale at Day 28 when compared to placebo (p = 0.36). The median outcomes with respect to the 7-category ordinal scale were estimated to be 1 (discharged or “ready for discharge”) and 2 (non-ICU hospital ward, or "ready for hospital ward", not requiring supplemental oxygen) in the tocilizumab and usual care groups, respectively. The difference in medians was estimated to be -1.0 (95% CI: -2.5 to 0.0).

Key Secondary Endpoints

Results for the key secondary endpoints were not statistically significant. To control the family-wise type I error rate, the secondary endpoints were to be tested in a sequential manner after the primary endpoint. However, because the hypothesis test for the primary efficacy endpoint failed, the analysis results for the subsequent secondary endpoints are descriptive only. The key secondary endpoints are summarized in Table 4.

Table 4. COVACTA secondary endpoints, mITT Population

	Tocilizumab (n=294)	Placebo (n=144)	Treatment Effect
28-Day Mortality*, n (%)	58 (19.7%)	28 (19.4%)	0.3% (95% CI: -7.6% to 8.2%)[a]
Number of Ventilator-Free Days at Day 28*, Median	22.0	16.5	5.5 (95% CI: -2.8 to 13.0)[b]
Time to Improvement in ≥2 categories on the ordinal scale Through Day 28*, Median	14.0	18.0	1.26 (95% CI: 0.97 to 1.64)[c]
7-Category Ordinal Scale at Day 14*, Median	3.0	4.0	-1.0 (95% CI: -2.0 to 0.5)[d]
Time to Hospital Discharge Through Day 28*, Median	20.0	28.0	1.35 (95% CI: 1.02 to 1.79)[c]
MV or Death by Day 28, Among Those not on MV at Baseline, n (%)	51 (27.9%)	33 (36.7%)	-8.9% (95% CI: -20.7% to 3.0%)[a]

Source: Adapted from Table 18 (pg. 87) of COVACTA CSR
Note: The hypothesis test for the primary endpoint in the sequential testing procedure failed, so p-values are not presented for secondary endpoints.
*Multiplicity controlled endpoint
[a]Summary contrast is a difference in probabilities
[b]Summary contrast is a difference in medians
[c]Summary contrast is a hazard ratio
[d]Summary contrast is a difference in medians

While results for the key secondary endpoints were not statistically significant, across the majority of endpoints, point estimates numerically favor tocilizumab treatment over placebo.

Mortality

As shown in Table 4, for 28-day mortality, similar proportions of patients treated with tocilizumab and placebo died by day 28 [58 (19.7%) and 28 (19.4%), respectively] with a difference of 0.3% (95%CI: -7.6, 8.2%). Given the importance of mortality, additional analyses were performed based on day 60 status. By Day 60, 24.5% of patients in the tocilizumab arm and 25.0% of the patients in the placebo arm were observed to have died. The difference in probabilities of dying by Day 60 comparing tocilizumab to placebo was estimated to be -0.5% (95% CI: -9.1% to 8.0%).

. SEE ATTACHED ADDENDUM

Early Study Withdrawal and Missing Data

Among the 301 patients randomized to tocilizumab, 281 (93.4%) completed the study through Day 28 or died by Day 28. Among the 151 patients randomized to placebo, 137 (90.7%) completed the study through Day 28 or died by Day 28. Table 5 provides further information on reasons for withdrawal from the study. The amount of missing data is low

enough through Day 28 that the results are likely to be robust to violations of assumptions in the analyses regarding the missing data.

Table 5. COVACTA patient disposition to Day 28 (all randomized patients)

	Tocilizumab (n=301)	Placebo (n=151)	All patients (n=452)
Alive and completed to Day 28	224 (74.4%)	108 (71.5%)	332 (73.5%)
Death observed on or prior to Day 28	57 (18.9%)	29 (19.2%)	86 (19.0%)
Withdrew alive from study on or prior to Day 28	20 (6.6%)	14 (9.3%)	34 (7.5%)
Reason for withdrawing alive from study			
Lost to follow-up	7 (2.3%)	5 (3.3%)	12 (2.7%)
Other	2 (0.7%)	1 (0.7%)	3 (0.7%)
Physician decision	4 (1.3%)	4 (2.6%)	8 (1.8%)
Withdrawal of consent by subject	7 (2.3%)	4 (2.6%)	11 (2.4%)
Source: Adapted from Table 4 (pg. 64) of COVACTA CSR			

Efficacy Conclusion for COVACTA

COVACTA does not provide substantial support for efficacy, given the trial failed on its primary endpoint and the secondary endpoint analysis results were not statistically significant. However, there is some suggestion of a treatment benefit based on numerical trends favoring tocilizumab over placebo for the key secondary endpoints of ventilator free days, time to improvement in ≥ 2 categories on the ordinal scale, and time to hospital discharge. With regard to mortality, in contrast to RECOVERY, no effect was observed. However, the relatively small sample size of 452 patients resulted in limited power and considerable uncertainty around important endpoints such as mortality. Additionally, COVACTA was conducted before systemic corticosteroids were considered SOC for treatment of COVID-19, and there was an imbalance in baseline corticosteroid use.

ML42528 (EMPACTA)

Study Design and Primary Endpoint Analysis Plan

EMPACTA was a phase 3, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of tocilizumab in adult hospitalized patients with COVID-19 who had hypoxemia (SpO2<94% on room air) but were not on mechanical ventilation. Additionally, EMPACTA sought to prioritize enrollment of patients belonging to racial and ethnic minorities. Once enrolled, patients were randomized 2:1 to receive tocilizumab 8 mg/kg or placebo, respectively, with both randomized treatments administered in addition to SOC. One additional dose of blinded treatment could be given 8-24 hours after the first treatment if clinical signs or symptoms worsened or did not improve.

The primary efficacy endpoint was the cumulative proportion of patients who required invasive mechanical ventilation (defined as invasive mechanical ventilation or ECMO) or died by Day 28. Key secondary endpoints included time to hospital discharge or ready for discharge by Day 28, time to improvement in clinical status up to Day 28 in the 7-category ordinal scale, time to clinical failure up to Day 28 (defined as death, invasive mechanical

ventilation, ICU admission, 2-category worsening in the 7-category ordinal scale from baseline, or withdrawal), and mortality rate by Day 28 (proportion of subjects who died by Day 28).

Baseline Patient Characteristics

A total of 388 patients were randomized at 72 centers with a large majority of patients being randomized in the US (81.2%). Note that one additional patient was randomized, however, this patient was randomized prior to IRB approval of the study site and did not receive study drug or have data collected. Patients were randomized at a 2:1 ratio, resulting in 259 patients in the tocilizumab arm and 129 patients in the PBO arm. A summary of key baseline patient characteristics for the mITT population, which is limited to patients who received any amount of study treatment, is shown in Table 6. Patients were generally well-balanced between arms in terms of baseline demographics and baseline ordinal scale clinical status. Patients in the placebo arm had a higher mean and median CRP. In this study, over 70% of patients received steroids at baseline.

Table 6. EMPACTA patient baseline characteristics (mITT population)

Characteristic	Tocilizumab (N=249)	Placebo (N=128)
Age, mean (SD), years	56.0 (14.3)	55.6 (14.9)
Sex		
Male	150 (60.2%)	73 (57.0%)
Female	99 (39.8%)	55 (43.0%)
Race n(%)		
American Indian or Alaska Native	52 (20.9%)	25 (19.5%)
Asian	5 (2.0%)	1 (0.8%)
Black or African American	35 (14.1%)	22 (17.2%)
Native Hawaiian or other Pacific Islander	0	1 (0.8%)
White	134 (53.8%)	65 (50.8%)
Multiple	4 (1.6%)	2 (1.6%)
Unknown	19 (7.6%)	12 (9.4%)
Ethnicity n(%)		
Hispanic or Latino	143 (57.4%)	68 (53.1%)
Not Hispanic or Latino	106 (42.6%)	60 (46.9%)
Days since symptom onset, mean (SD)	7.8 (4.4)	8.6 (6.1)
Ordinal scale clinical status*		
2	24 (9.6%)	11 (8.6%)
3	161 (64.7%)	81 (63.3%)
4	64 (25.7%)	36 (28.1%)
Receiving systemic corticosteroids	183 (73.5)	91 (71.1)
C-reactive protein		
Mean (SD), mg/L	149 (171)	203 (405)
Median	124.5	143.4

N= number of subjects in the modified intent-to-treat population, SD = standard deviation
*Ordinal scale for clinical status: 1) discharged or “ready for discharge” 2) non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3) non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4) ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5) ICU, requiring intubation and mechanical ventilation 6) ICU, requiring ECMO or mechanical ventilation and additional organ support 7) death
Source: Adapted from Tables 6 and 7 (pg. 56-61) of EMPACTA CSR

Efficacy Results

Primary Endpoint

In the primary analysis, the cumulative proportion of patients who required invasive mechanical ventilation/ECMO or died by Day 28 for the tocilizumab and placebo groups were 12.0% (95% CI: 8.52% to 16.86%) and 19.3% (95% CI: 13.3% to 27.4%), respectively. The hazard ratio when comparing the two treatment arms was estimated to be 0.56 (95% CI: 0.33 to 0.97). This result was statistically significant and favored tocilizumab (p = 0.0360). The median times to MV or death through Day 28 were not estimable for either of the treatment arms due to the limited number of events relative to the sample size prior to the end of the follow-up time.

Key Secondary Endpoints

Results for the key secondary endpoints were not statistically significant. To control the family-wise type I error rate, the secondary endpoints were to be tested in a sequential manner in the order presented in Table 7. The hypothesis test for the first secondary efficacy endpoint failed, so the analysis results for the subsequent secondary endpoints are descriptive only.

Table 7. Results for key secondary endpoints in EMPACTA, mITT Population

	Tocilizumab (n=249)	Placebo (n=128)	Treatment Effect
Time to hospital discharge or "ready for discharge" up to Day 28, median	6.0	7.5	1.16 (95% CI: 0.91 to 1.48) p = 0.2417[a]
Time to ≥ 2 category improvement in ordinal clinical status through Day 28 relative to baseline based on 7-category ordinal scale, median	6.0	7.0	1.15 (95% CI: 0.90 to 1.48)[a]
Time to clinical failure up to Day 28, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first), median	NE*	NE*	0.55 (95% CI: 0.33 to 0.93)[a]
Mortality rate by Day 28, n (%)	26 (10.4%)	11 (8.6%)	2.0% (95% CI: -5.2% to 7.8%)[b]

Source: Adapted from Tables 14, 15, 16, and 17 (pgs. 72, 76, 80, and 82) of EMPACTA CSR
Note: The hypothesis test for the first secondary endpoint in the sequential testing procedure failed, so p-values are not presented for subsequent secondary endpoints.
*NE=Not estimable due to limited number of events prior to Day 28
[a]Summary contrast is a hazard ratio
[b]Summary contrast is a risk difference

While there were some favorable trends in terms of the point estimates for the time to event analyses, overall these key secondary endpoint data provide minimal additional support for efficacy.

Mortality

As shown in Table 7, for mortality rate by day 28, a numerically higher proportion of tocilizumab patients died by day 28 [26 (10.4%)] versus placebo [11 (8.6%)] with a risk difference of 2.0% (95%CI: -5.2 to 7.8%). The EMPACTA study design did not plan to collect Day 60 vital status, and the Day 60 follow-up was required to collect AEs only.

Early Study Withdrawal and Missing Data

All 249 patients randomized to tocilizumab (mITT) either completed the study through Day 28 or died by Day 28. Among the 128 patients randomized to placebo (mITT), 126 (98.4%) either completed the study through Day 28 or died by Day 28. Table 8 provides further information on reasons for withdrawal from the study. Overall, the amount of missing data through Day 28 was sufficiently low across both arms such that the results are likely to be robust to violations of assumptions in the analyses regarding the missing data.

Table 8. EMPACTA patient disposition to Day 28 (mITT population)

	Tocilizumab (n=249)	Placebo (n=128)	All patients (n=377)
Alive and completed to Day 28	225 (90.4%)	115 (89.8%)	340 (90.2%)
Death observed on or prior to Day 28	24 (9.6%)	11 (8.6%)	35 (9.3%)
Withdrew alive from study on or prior to Day 28*	0	2 (1.6%)‡	2 (0.5%)
*Reasons for withdrawing alive from study not all available ‡One patient transferred to long-term care facility and one patient transferred to another hospital Source: Adapted from Table 2 (pg. 52) of EMPACTA CSR			

Efficacy Conclusion for EMPACTA

EMPACTA met its primary efficacy endpoint, showing a reduction in the likelihood of progressing to mechanical ventilation or death by Day 28 with a time-to-event analysis; however, statistical significance was not reached across the key secondary endpoints. As such, the clinical benefit shown in EMPACTA is primarily avoidance of invasive mechanical ventilation. EMPACTA excluded patients requiring the highest levels of respiratory support (i.e., noninvasive ventilation or mechanical ventilation), and avoidance of mechanical ventilation is a clinically meaningful benefit in this population. Additionally, a majority of patients in EMPACTA were receiving systemic corticosteroids at baseline, and unlike COVACTA, the arms were well-matched in this regard. With regard to mortality, while proportions were similar between treatment arms, this study was not sufficiently powered to demonstrate a mortality benefit. Overall, results from EMPACTA support that tocilizumab may be effective in treating hospitalized patients with COVID-19.

WA42511 (REMDACTA)

Study Design and Primary Endpoint Analysis Plan

REMDACTA was a phase 3, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of tocilizumab in combination with remdesivir compared with matching placebo in combination with remdesivir in adult patients hospitalized with severe COVID-19. Patients could be enrolled if they required >6 L/min supplemental oxygen to maintain an oxygen saturation >93%. Once enrolled, patients were randomized 2:1 to receive either tocilizumab (8 mg/kg) and remdesivir (TCZ+RDV) or placebo and remdesivir (PBO+RDV), respectively, with both randomized treatments administered in addition to SOC. One additional dose of blinded treatment could be given 8-24 hours after the first treatment if clinical signs or symptoms worsened or did not

improve. Remdesivir was administered to both arms at a dose of 200 mg on Day 1 and 100 mg daily for the next 9 days (10 days total treatment).

The primary efficacy endpoint was time from randomization to hospital discharge/ready for discharge up to Day 28. Hospital discharge/ready for discharge was defined as an ordinal scale score of 1 on the 7-category ordinal scale (see COVACTA section for definition). Key secondary endpoints included time to mechanical ventilation or death up to Day 28, clinical status on the 7-category ordinal scale on Day 14, and time to death up to Day 28.

Baseline Patient Characteristics

A total of 649 patients were randomized at 53 centers across four countries (United States, Brazil, Spain and Russia). Approximately 67% of the patients were recruited from the United States. Patients were randomized at a 2:1 ratio, resulting in 434 patients in the TCZ+RDV arm and 215 patients in the PBO+RDV arm. A summary of key baseline patient characteristics for the mITT population, which is limited to patients who received any amount of study treatment, is shown in Table 9. There was a larger proportion of patients on mechanical ventilation (ordinal scale scores 5 and 6) in the TCZ+RDV arm compared to the PBO+RDV arm (15.1% versus 10.5%, respectively). Other baseline characteristics were generally well-matched. Overall, approximately 84% of subjects were receiving steroids at baseline.

Table 9. REMDACTA patient baseline characteristics (mITT population)

Characteristic	TCZ+RDV (N=430)	PBO+RDV (N=210)
Age, mean (SD), years	60.1 (13.3)	58.2 (13.3)
Sex		
Male	266 (61.9%)	139 (66.2%)
Female	164 (38.1%)	71 (33.8%)
Race n(%)		
American Indian or Alaska Native	4 (0.9%)	4 (1.9%)
Asian	17 (4.0%)	5 (2.4%)
Black or African American	51 (11.9%)	19 (9.0%)
Native Hawaiian or other Pacific Islander	7 (1.6%)	3 (1.4%)
White	279 (64.9%)	150 (71.4%)
Multiple	9 (2.1%)	2 (1.0%)
Unknown	63 (14.7%)	27 (12.9%)
Ethnicity n(%)		
Hispanic or Latino	208 (48.4%)	122 (58.1%)
Not Hispanic or Latino	207 (48.1%)	86 (41.0%)
Not stated	10 (2.3%)	1 (0.5%)
Unknown	5 (1.2%)	1 (0.5%)
Days since symptom onset, mean (SD)	8.8 (4.8)	8.9 (4.7)
Ordinal scale clinical status*		
3	29 (6.7%)	13 (6.2%)
4	336 (78.1%)	175 (83.3%)
5	39 (9.1%)	9 (4.3%)
6	26 (6.0%)	13 (6.2%)
Receiving systemic corticosteroids	358 (83.3%)	181 (86.2%)
C-reactive protein		
Mean (SD), mg/L	114.4 (86.0)	116.2 (85.0)
Median	97.4	101.7

TCZ=tocilizumab; RDV=remdesivir; PBO=placebo; SD = standard deviation
*Ordinal scale for clinical status: 1) discharged or “ready for discharge” 2) non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3) non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4) ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5) ICU, requiring intubation and mechanical ventilation 6) ICU, requiring ECMO or mechanical ventilation and additional organ support 7) death
Source: Adapted from Tables on pages 5-8 of WA42511 (REMDACTA) Primary Analysis Output

Efficacy Results

Primary Endpoint

In the primary analysis of time to discharge/ready for discharge, both treatment arms had an estimated median time to event of 14 days. The hazard ratio comparing the two treatment arms was estimated to be 0.97 (95% CI: 0.78 to 1.19). These results were not statistically significant (p=0.7414). They do not provide support for efficacy.

Key Secondary Endpoints

Results for the key secondary endpoints were also not statistically significant. To control the family-wise type I error rate, the secondary endpoints were to be tested in a sequential manner after the primary endpoint. However, because the hypothesis test for the primary efficacy endpoint failed, formal hypothesis tests were not conducted for any of the secondary endpoints. Descriptive results for key secondary endpoints are summarized in Table 10.

Table 10. Results for key secondary endpoints in REMDACTA, mITT Population

	TCZ+RDV (n=430)	PBO+RDV (n=210)	Treatment Effect
Time to mechanical ventilation or death up to Day 28, Median	NE*	NE*	0.98 (95% CI: 0.72 to 1.34)[a]
7-Category Ordinal Scale at Day 14, Mean	2.8	2.9	-0.07 (95% CI: (-0.42 to 0.29)[b]
Time from randomization to death up to Day 28, Median	NE*	NE*	0.95 (95% CI: 0.65 to 1.39)[a]
TCZ=tocilizumab; RDV=remdesivir; PBO=placebo Source: Adapted from EUA Application, Section 3.3.5.4 (pg. 64) *Not estimable due to limited number of events prior to Day 28 [a]Summary contrast is a hazard ratio [b]Summary contrast is a difference in means			

As with the primary endpoint results, key secondary endpoint results are not suggestive of efficacy, with point estimates for the difference between treatment arms at approximately the null value.

Mortality

The probability of dying by Day 28 was estimated to be 18.1% and 19.5% in the TCZ+RDV and PBO+RDV arms, respectively. The risk difference was estimated to be -1.3% (95% CI: -7.8% to 5.2%). Given the importance of mortality, additional analyses were conducted based on day 60 status. By Day 60, 22.6% of patients in the TCZ+RDV arm and 25.7% of the patients in the PBO+RDV arm were observed to have died. The difference in probabilities of dying by Day 60 comparing TCZ+RDV to PBO+RDV was estimated to be -3.0% (95% CI: -10.1% to 4.0%).

[redacted]. SEE ATTACHED ADDENDUM

Early Study Withdrawal and Missing Data

Among the 434 patients randomized to TCZ+RDV, 414 (95.4%) either died by Day 28 or completed the study through Day 28. Among the 215 patients randomized to PBO+RDV, 202 (94.0%) either died by Day 28 or completed the study through Day 28. Table 11 provides further information on reasons for withdrawal from the study. Overall, the amount of missing data through Day 28 was sufficiently low across both arms such that the results are likely to be robust to violations of assumptions in the analyses regarding the missing data.

Table 11. REMDACTA patient disposition to Day 28 (all randomized patients)

	TCZ+RDV (n=434)	PBO+RDV (n=215)	All patients (n=649)
Alive and completed to Day 28	336 (77.4%)	160 (74.4%)	496 (76.4%)
Death observed on or prior to Day 28	78 (18.0%)	42 (19.5%)	120 (18.5%)
Withdrew alive from study on or prior to Day 28	20 (4.6%)	13 (6.0%)	33 (5.1%)
Reason for withdrawing alive from study			
Adverse event	2 (0.5%)	0	2 (0.3%)
Lost to follow-up	9 (2.1%)	7 (3.3%)	16 (2.5%)
Other	1 (0.2%)	0	1 (0.2%)
Protocol deviation	1 (0.2%)	3 (1.4%)	4 (0.6%)
Withdrawal of consent by subject	7 (1.6%)	3 (1.4%)	10 (1.5%)

TCZ=tocilizumab; RDV=remdesivir; PBO=placebo
Source: Adapted from Table on page 1 of WA42511 (REMDACTA) Primary Analysis Output

Efficacy Conclusion for REMDACTA

REMDACTA did not result in a statistically significant treatment effect in the primary endpoint and the secondary endpoints provided no supportive evidence of efficacy. Furthermore, and in contrast to COVACTA, there were no notable numerical trends to suggest a treatment benefit of TCZ+RDV over PBO+RDV. It is possible that REMDACTA was underpowered to detect a small treatment benefit. It is also possible that required concurrent remdesivir use obscured a potential tocilizumab treatment effect as was observed in the other trials (i.e. RECOVERY and EMPACTA) given remdesivir's established efficacy in treatment of COVID-19. Nonetheless, the results of REMDACTA were inconclusive.

Meta-analyses

Two meta-analyses were conducted to further investigate the effect of tocilizumab on mortality and subgroup effects. In the first, meta-analyses of data from the three Sponsor-conducted trials (COVACTA, EMPACTA and REMDACTA) were performed to evaluate efficacy using pooled patient-level data from the three trials and a stratified Cox proportional hazards model, with study being a stratification factor. When comparing the two treatments, which were given on a background of SOC, for the outcome of time to death through Day 28, the estimated hazard ratio was 1.02 (95% CI: 0.77 to 1.33), with a hazard ratio >1 favoring placebo. The estimated probabilities of dying by Day 28 were 18.1% and 17.6% for tocilizumab and placebo, respectively. The estimated risk difference was 0.5% (95% CI: -3.9% to 4.8%).

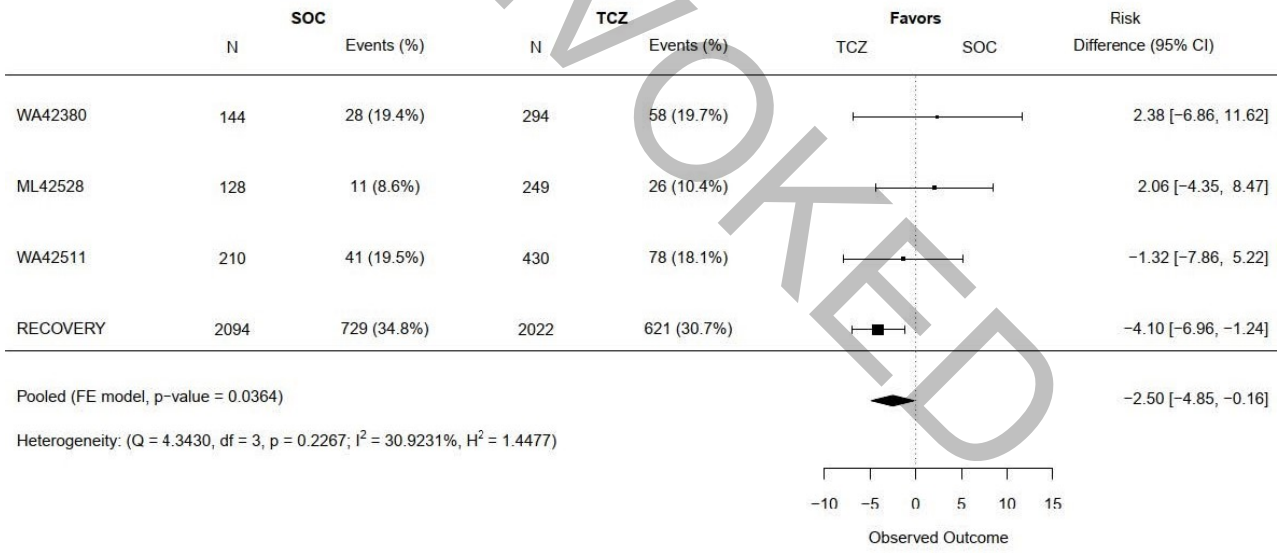
Subgroup meta-analysis results using data from the Sponsor-conducted trials for time to death up to Day 28 were also reviewed. When comparing the two treatments for patients on baseline systemic corticosteroids, the hazard ratio was estimated to be 0.88 (95% CI: 0.64 to 1.22), favoring tocilizumab. For patients not on baseline corticosteroids, the hazard ratio was estimated to be 1.33 (95% CI: 0.79 to 2.25), favoring SOC. A subgroup analysis based on baseline CRP tertiles was also pre-specified and evaluated. For patients with baseline CRP <80.40 mg/L, >80.40 mg/L and <171.10 mg/L, and ≥171.10 mg/L the hazard ratios were estimated to be 1.00 (95% CI: 0.56 to 1.79), 1.07 (95% CI:

0.64 to 1.82), and 0.96 (95% CI: 0.63 to 1.46), respectively, with hazard ratios <1 favoring tocilizumab. For patients with missing baseline CRP value, the hazard ratio was 0.68 (95% CI: 0.25 to 1.82), with the favorable trend toward tocilizumab likely reflecting an unreliable estimate given a small sample size and no obvious underlying clinical rationale. For patients <65 years old and ≥65 years old, the hazard ratios were estimated to be 0.91 (95% CI: 0.58 to 1.43) and 1.07 (95% CI: 0.76 to 1.50), respectively.

Meta-analyses were also performed using study-level results from COVACTA, EMPACTA, REMDACTA, and RECOVERY. As shown in Figure 2, when leveraging the mortality data from all four studies, the pooled estimate for the risk difference comparing tocilizumab to standard of care treatment is -2.5% (95% CI: -4.9% to -0.2%).

While the meta-analyses of the Sponsor-conducted trials show no effect on time to death by Day 28, the subgroup on baseline corticosteroids does show a trend favoring tocilizumab, though the 95% CI does not exclude the null. This finding is generally consistent with RECOVERY analysis of the same subgroup. Additionally, the treatment effect for time to death was similar across subgroups defined by baseline CRP levels.

Figure 2: 28-Day Mortality Meta-Analysis, Using Results from Studies COVACTA, EMPACTA, REMDACTA, and RECOVERY



Source: EUA Application, Section 3.3.7 (pg. 92)

In the meta-analysis of the Sponsor-conducted trials and RECOVERY, there is an overall observed reduction in mortality with tocilizumab compared to placebo/standard of care. Due to the large sample size of RECOVERY compared to the Sponsor-conducted trials, the treatment effect observed in the RECOVERY trial largely dominates the meta-analysis estimate despite lack of observed effects from the Sponsor-conducted trials. The Sponsor-conducted trials were not powered for this evaluation of mortality. However, as noted above, positive trends were observed in the meta-analysis of the Sponsor-conducted trials for the subgroup of patients on corticosteroids at baseline is generally consistent with RECOVERY.

Integrated Analysis of Efficacy

To support this EUA request, the sponsor submitted data from 4 randomized, concurrently-controlled, prospective clinical trials in hospitalized COVID-19 patients: RECOVERY, COVACTA, EMPACTA, and REMDACTA. There were fundamental differences across the 4 trials, including dates of trial conduct in the course of the pandemic, blinding, population, background therapy, and endpoints, that resulted in variability in response to study treatment and patient outcomes across trials. As such, in determining whether tocilizumab may be effective for the proposed intended use, it is important to weigh the strength of evidence from each trial, both from a statistical perspective as well as the clinical importance of observed treatment effects.

RECOVERY had the largest sample size of the reviewed trials and demonstrated a statistically significant reduction in 28-day mortality. The mortality reduction was consistent in the subgroup of patients on baseline systemic corticosteroids while there was a trend favoring usual care alone for patients not on baseline systemic corticosteroids. Additionally, benefits in discharge from the hospital and avoidance of invasive mechanical ventilation for those not on invasive mechanical ventilation at baseline were observed. While results were positive, RECOVERY was designed as a randomized, open-label trial comparing tocilizumab plus SOC to SOC alone. The open-label design is a limitation and introduces the potential for bias that impacts interpretation of these results. However, the relatively objective nature of a mortality endpoint may limit the impact of bias, and the pragmatic approach facilitated the enrollment and randomization of a large sample size necessary to evaluate this meaningful endpoint. These factors taken together, in the context of an EUA, alleviate concerns regarding the impact of the design limitations of RECOVERY on the conclusions drawn regarding the potential benefit of tocilizumab.

One notable difference in RECOVERY compared to the Sponsor-conducted trials is the higher 28-day mortality rate across arms observed in RECOVERY, which in the absence of substantial differences in baseline patient characteristics is of unclear cause and importance. Only a fraction of patients enrolled in RECOVERY underwent the second randomization for patients with “progressive COVID-19” despite a high likelihood that most patients enrolled would have met the oxygenation and CRP criteria. This raises the concern that there may have been investigator-driven selection for a subset of perceived high-risk or rapidly progressive patients — an issue noted in the NIH COVID-19 Treatment Guidelines.

Though not a limitation of RECOVERY’s design, the fact that it was conducted entirely in the UK raises concerns regarding applicability to the US population. To support applicability, the clinical guidelines from the NIH and the UK’s National Institute for Health and CARE Excellence (NICE) were reviewed and are generally similar. Additionally, the availability of advanced supportive therapies (e.g., high-flow oxygen devices, non-invasive ventilation, invasive mechanical ventilation, ECMO) is similar between the US and UK. Given the similarity between clinical care for COVID-19 in the US and UK, it is reasonable to conclude that tocilizumab would likely be used in a similar clinical context in the US population compared to the UK population.

Overall, while there are some limitations due to trial design, as well as concerns with how "progressive COVID-19" was determined and the generalizability to the U.S. population, RECOVERY provides sufficient evidence that tocilizumab may be effective in treating COVID-19.

EMPACTA provides further support that tocilizumab may be effective. EMPACTA was unique among the Sponsor-conducted trials in that it included the least severe COVID-19 population, enrolling a majority of patients with ordinal scale score 3 (non-ICU wards on supplemental oxygen) and excluding [redacted]. EMPACTA was the only Sponsor-conducted trial to show a statistically significant result in its primary endpoint, showing a reduced likelihood of progressing to mechanical ventilation or death by Day 28. While EMPACTA did not have support from key secondary endpoints, the primary endpoint result provides evidence that tocilizumab may be effective in a less severe population (i.e., patients on simple supplemental oxygen who are not necessarily high-risk or rapidly progressing). The clinical benefit observed was primarily a reduction in progression to invasive mechanical ventilation, which is an important benefit in this population and is consistent with the RECOVERY results in the subgroup of patients not on invasive mechanical ventilation at baseline. While the secondary endpoint of mortality showed a trend in favor of placebo, the trial was not sufficiently powered to provide a precise estimate of the difference in mortality rates. Additionally, the positive EMPACTA results allay some of the concern regarding generalizability of the RECOVERY results to the U.S. population, as well as concerns regarding the 'progressive COVID-19' enrollment criteria in RECOVERY that may have selected for a more severe population.

SEE ATTACHED ADDENDUM

COVACTA and REMDACTA did not meet their primary endpoints, which does raise concerns about the clinical benefit observed in RECOVERY and EMPACTA. COVACTA had a relatively small sample size and enrolled patients across a wide spectrum of disease severity. The favorable, though not statistically significant, numerical trends across a variety of endpoints in COVACTA suggest the trial may have been underpowered to detect treatment benefits. Lack of power due to the small sample size may have been further exacerbated by including a wide spectrum of disease severity, leading to increased variability in the patient outcomes. Additionally, COVACTA was conducted early in the pandemic before systemic corticosteroids were considered SOC, and there was an imbalance in baseline steroid use, which in the context of RECOVERY's favorable results in the subgroup with baseline steroid use, may have led to an attenuated treatment effect. Therefore, while the COVACTA results were not statistically significant, they do not necessarily contradict RECOVERY and EMPACTA results.

The results for REMDACTA across primary and key secondary endpoints were consistently inconclusive. In contrast to COVACTA, numerical trends favoring tocilizumab were not observed. The reason for this is unclear. However, it is important to note that despite having the largest sample size of the Sponsor-conducted trials, it was still underpowered to detect the mortality reduction observed in RECOVERY. As such, the

results of REMDACTA do not necessarily contradict the conclusion that tocilizumab may be effective.

The result of the meta-analysis of the Sponsor-conducted trials with RECOVERY is consistent with a reduction in mortality, providing additional support that tocilizumab may be effective, though this result is clearly driven by RECOVERY. While the meta-analysis utilizing only the Sponsor-conducted trials was inconclusive regarding an effect on mortality, this result was not unexpected given the results of each individual trial and may have resulted from differing populations and baseline steroid use across trials. Nonetheless, the subgroup of patients on baseline corticosteroids in the Sponsor-conducted trials shows a favorable numerical trend for mortality with a point estimate similar to the primary analysis of RECOVERY, though the result was not statistically significant.

Based on review of the efficacy data included in the EUA application, it is reasonable to conclude that tocilizumab may be effective for the treatment of COVID-19. Subgroup analyses from RECOVERY and the meta-analysis of the Sponsor-conducted trials also suggest that this potential benefit may be more consistent in patients receiving systemic corticosteroids, compared to patients not receiving systemic corticosteroids. Therefore, the sponsor's proposed intended use of tocilizumab in patients who are receiving systemic corticosteroids is reasonable.

IX. Human Clinical Safety

Previous Human Experience

Tocilizumab is approved for treatment of RA, GCA, sJIA, pJIA, SSc-ILD, and CRS. The 8 mg/kg IV dose proposed in this EUA is consistent with the approved IV doses in RA, PJIA (patients ≥30kg), SJIA (patients ≥30kg), and CRS. As of April 2020, an estimated 24,940 patients have received tocilizumab (IV and SC dosing combined) in the context of a clinical trial, which includes 791 patients <18 years old. The estimated cumulative market exposure is (b) (4) patients (IV and SC dosing combined). While the previous human experience for approved indications are in populations different from COVID-19, this experience is still informative in terms of identifying the known and potential risks of tocilizumab for treatment of patients with COVID-19.

The United States Prescribing Information (USPI) for tocilizumab contains a boxed warning for the risk of serious infections leading to hospitalization or death, including tuberculosis, bacterial, invasive fungal, viral, and other opportunistic infections. Additional safety risks in the USPI Warnings and Precautions include risks for gastrointestinal perforations, hepatotoxicity, laboratory abnormalities (including treatment-related changes in neutrophils, platelets, lipids, and liver function tests), immunosuppression, hypersensitivity reactions, demyelinating disorders, use with active hepatic disease or hepatic impairment, and use with live vaccines.

Safety Database for COVID-19

In the clinical development program for COVID-19, 5571 patients were included in the trials to support the EUA with 2995 being randomized to receive tocilizumab. In RECOVERY, 2022 patients were allocated to the tocilizumab arm and 1647 patients received treatment with tocilizumab. In the Sponsor-conducted trials (COVACTA, EMPACTA, and REMDACTA), the safety population (all patients who received study drug) was comprised of 974 and 483 patients in the tocilizumab and placebo arms, respectively. In general, the population evaluated in the COVID-19 development program is consistent with the proposed intended use under this EUA. Safety results from each individual trial, as well as pooled safety data from the Sponsor-conducted trials is presented in the following sections.

RECOVERY

Safety data collection in RECOVERY was limited and did not include collection of all adverse events (i.e., adverse events defined as per 21 CFR 312.32). As such, data from this trial is of limited utility in the assessment of safety. However, prespecified safety outcomes that were collected included cause-specific mortality and major cardiac arrhythmia. All serious adverse reactions were not collected, only suspected serious adverse reactions were collected.

In the tocilizumab arm, of the 1964 patients who had a completed follow-up form, 1647 (84%) received at least 1 dose of study treatment and 565 (29%) received more than 1 dose. The 28-day cause-specific mortality results showed fewer deaths due to COVID-19 compared to usual care alone, consistent with the primary efficacy outcome. Deaths due to other causes (i.e., excluding COVID-19) were uncommon and similar between arms. Cause-specific 28-day mortality is shown in Table 12. Incidence of cardiac arrhythmia and types of arrythmia experienced were similar between the tocilizumab and usual care arms. There were 3 suspected serious adverse reactions observed with one case each of otitis externa requiring hospital admission, staphylococcus aureus bacteremia that was considered life-threatening, and pneumonia that prolonged hospital admission.

Table 12. RECOVERY cause-specific 28-day mortality

	Tocilizumab (n=2022)	Usual care (n=2094)	Absolute percent difference (95% CI)
All-cause	621 (30.7%)	729 (34.8%)	-4.10 (-6.97, -1.24)
COVID-19	595 (29.4%)	699 (33.4%)	-3.95 (-6.79, -1.12)
Other infection	1 (0.0%)	6 (0.3%)	-0.24 (-0.49, 0.01)
Cardiac	1 (0.0%)	3 (0.1%)	-0.09 (-0.28, 0.09)
Stroke	2 (0.1%)	2 (0.1%)	0.00 (-0.19, 0.19)
Other vascular	1 (0.0%)	2 (0.1%)	-0.05 (-0.21, 0.12)
Cancer	6 (0.3%)	3 (0.1%)	0.15 (-0.13, 0.44)
Other medical	14 (0.7%)	12 (0.6%)	0.12 (-0.37, 0.60)
External	0 (0.0%)	0 (0.0%)	-
Unknown cause	1 (0.0%)	2 (0.1%)	-0.05 (-0.21, 0.12)

N=number of subjects randomized, CI=confidence interval
Source: Adapted from Webtable 2 of the Supplementary Appendix (RECOVERY Collaborative Group, 2021)

The limited safety data from the RECOVERY trial are generally consistent with the known safety profile of tocilizumab. No new safety signals were identified. Given the limited safety data collection, safety data from this trial will not be included in the EUA factsheets.

WA42380 (COVACTA)

Safety analyses were conducted using a safety population consisting of all patients who received any amount of study medication, which included 295 patients who received tocilizumab and 143 patients who received placebo. One patient randomized to the placebo arm was mistakenly treated with tocilizumab and was included in the tocilizumab group for the safety population. Of the patients who received tocilizumab, 230 (78.0%) received 1 dose and 65 (22.0%) received 2 doses. Patients who completed the study were followed for 60 days. Deaths during the study were similar between treatment arms with 72/295 (24.4%) patients dying in the tocilizumab arm and 36/143 (25.2%) dying in the placebo arm. The most common AEs leading to death were COVID-19 pneumonia followed by COVID-19 and respiratory failure. In general, while there were some numerical differences in AE leading to death, differences were small. Specifically, COVID-19 and multiple organ dysfunction syndrome (MODS) more frequently led to death in tocilizumab-treated patients, but given the high baseline severity of disease in this patient population and the small number of events, this finding is of unclear significance. Fewer patients experienced at least 1 SAE in the tocilizumab arm (39.3%) compared to the placebo arm (44.8%). The tocilizumab arm had more SAE COVID-19, but when combined with SAE COVID-19 pneumonia, the imbalance between arms is less pronounced. The only AE to occur in more than 10% of patients in either arm was COVID-19 pneumonia. More urinary tract infections, acute kidney injury, and hypertension AEs were observed in the tocilizumab arm compared to placebo. However, these risks were not reflected in the SAE data and would be monitorable in a hospitalized setting. A summary of AEs is shown in Table 13.

Table 13. Summary of Adverse Event in COVACTA through Day 60 (Safety population)

Patients with	Tocilizumab n=295 n (%)	Placebo n=143 n (%)
At least 1 Adverse Event	240 (81.4)	118 (82.5)
At least 1 Serious Adverse Event	116 (39.3)	64 (44.8)
Deaths	72 (24.4)	36 (25.2)
Adverse Events Leading to Death (≥1% of patients in either arm)		
COVID-19 pneumonia	36 (12.2)	20 (14)
COVID-19	13 (4.4)	2 (1.4)
Respiratory failure	3 (1)	3 (2.1)
Acute Respiratory Distress Syndrome	2 (0.7)	2 (1.4)
Acute Respiratory Failure	1 (0.3)	2 (1.4)
Multiple Organ Dysfunction Syndrome	5 (1.7)	0
Septic Shock	2 (0.7)	1 (0.7)
Serious Adverse Events (≥2% of patients in either arm)		
COVID-19 pneumonia	36 (12.2)	20 (14)
COVID-19	14 (4.7)	2 (1.4)
Septic Shock	7 (2.4)	7 (4.9)
Pneumonia	7 (2.4)	4 (2.8)
Pneumonia Bacterial	6 (2.0)	2 (1.4)
Sepsis	3 (1.0)	4 (2.8)
Bacteremia	3 (1.0)	3 (2.1)
Respiratory Failure	5 (1.7)	6 (4.2)
Pneumothorax	4 (1.4)	3 (2.1)
Hypoxia	0	3 (2.1)
Cardiac Arrest	4 (1.4)	5 (3.5)
Acute Kidney Failure	10 (3.4)	4 (2.8)
Common Adverse Events (≥3% of patients in either arm)		
COVID-19 pneumonia	36 (12.2)	20 (14.0)
Pneumonia	17 (5.8)	12 (8.4)
Urinary tract infection	24 (8.1)	5 (3.5)
Anemia	17 (5.8)	10 (7.0)
Diarrhea	18 (6.1)	3 (2.1)
Acute kidney injury	21 (7.1)	7 (4.9)
Hypertension	21 (7.1)	3 (2.1)
Constipation	18 (6.1)	8 (5.6)
Hypotension	11 (3.7)	8 (5.6)
Septic shock	8 (2.7)	8 (5.6)
Delirium	14 (4.7)	3 (2.1)
Atrial fibrillation	12 (4.1)	6 (4.2)
Bacteremia	5 (1.7)	6 (4.2)
Hypokalemia	7 (2.4)	6 (4.2)
Insomnia	12 (4.1)	5 (3.5)
Thrombocytopenia	11 (3.7)	2 (1.4)
Bradycardia	7 (2.4)	5 (3.5)
Cardiac arrest	5 (1.7)	5 (3.5)
Pulmonary embolism	10 (3.4)	5 (3.5)
Deep vein thrombosis	10 (3.4)	3 (2.1)
Alanine aminotransferase increased	10 (3.4)	2 (1.4)
Anxiety	9 (3.1)	4 (2.8)
Source: COVACTA CSR tables 56,63, 64; pg 152, 162, 165		

Known safety issues related to tocilizumab use include infections, gastrointestinal perforations, laboratory abnormalities, hypersensitivity reactions, demyelinating disorders and hepatotoxicity. AEs and laboratory abnormalities consistent with the known safety

profile of tocilizumab were observed in some patients. SAEs in the infections and infestations SOC (i.e., serious infections) occurred more frequently in the placebo arm (29.4%) compared to the tocilizumab arm (24.1%). Gastrointestinal perforations were infrequent and occurred more frequently in the placebo arm (1.4%) compared to tocilizumab (0.3%). SAE neutropenia occurred in 4/295 (1.4%) of patients in the tocilizumab arm with no occurrences in the placebo arm. SAE thrombocytopenia was rare with only 1 event in each arm. Hypersensitivity reactions occurred more frequently in the tocilizumab arm (6.4%) compare to placebo (2.8%), but anaphylactic reactions were rare with 1 patient in the tocilizumab arm experiencing anaphylaxis across the whole trial. While elevations in transaminases occurred more frequently with tocilizumab compared to placebo, adverse event of special interest (AESI) hepatic events were similar between treatment arms, and more patients in the placebo arm (4.9%) compared to the tocilizumab arm (2.0%) met the laboratory criteria for potential Hy's Law (defined as having a >3X the upper limit of normal (ULN) ALT or AST elevation concurrently with a >2X the ULN total bilirubin elevation). No demyelinating events were observed in the trial.

Overall, the safety data from COVACTA are consistent with the known safety profile of tocilizumab as described in the approved label.

ML42528 (EMPACTA)

Safety analyses were conducted using a safety population consisting of all patients who received any amount of study medication, which included 250 patients who received tocilizumab and 127 patients who received placebo. Of the patients who received tocilizumab, 182/250 (72.8%) received 1 dose and 62/250 (27.2%) received 2 doses. Patients who completed the study were followed for 60 days. Deaths during the study were similar between treatment arms with 29/250 (11.6%) patients dying in the tocilizumab arm and 15/127 (11.8%) patients dying in the placebo arm. AEs leading to death were generally comparable between arms, though there were numerically more tocilizumab patients with acute respiratory distress syndrome (ARDS) leading to death compared to placebo. However, given the disease process, small number of cases, and small difference, this is of unclear clinical significance. A similar number of patients experienced at least 1 SAE in each treatment arm, with 15.2% and 19.7% of patients experiencing at least 1 SAE in the tocilizumab and placebo arms, respectively. Consistent with AEs leading to death, the SAE of ARDS occurred more commonly in TCZ compared to placebo patients. These appear to be the same patients who experience ARDS leading to death. The only AEs to occur in more than 5% of patients in either arm were constipation and anxiety. Constipation and anxiety were observed more frequently in the tocilizumab arm, but the risk difference was small. A summary of AEs is shown in Table 14.

Table 14. Summary of Adverse Events in EMPACTA through Day 60 (Safety population)

Patients with	Tocilizumab n=250 n (%)	Placebo n=127 n (%)
At least 1 Adverse Event	127 (50.8)	67 (52.8)
At least 1 Serious Adverse Event	38 (15.2)	25 (19.7)
Deaths	29 (11.6)	15 (11.8)
Adverse Events Leading to Death (>1% of patients in either arm)		
Acute Respiratory Distress Syndrome	5 (2.0)	1 (0.8)
Acute Respiratory Failure	4 (1.6)	2 (1.6)
Respiratory Failure	4 (1.6)	2 (1.6)
COVID-19 pneumonia	2 (0.8)	3 (2.4)
Serious Adverse Events (≥2% of patients in either arm)		
Septic shock	5 (2.0)	3 (2.4)
Acute respiratory failure	4 (1.6)	3 (2.4)
COVID-19 pneumonia	2 (0.8)	3 (2.4)
Acute respiratory distress syndrome	5 (2.0)	1 (0.8)
Acute kidney injury	1 (0.4)	3 (2.4)
Pneumonia	0	3 (2.4)
Common Adverse Events (≥3% of patients in either arm)		
Constipation	16 (6.4)	4 (3.1)
Anxiety	15 (6.0)	4 (3.1)
Headache	8 (3.2)	3 (2.4)
Pneumonia	2 (0.8)	4 (3.1)
Hyperglycemia	3 (1.2)	4 (3.1)
Acute kidney injury	4 (1.6)	4 (3.1)
Fatigue	3 (1.2)	5 (3.9)
Source: EMPACTA CSR Tables 27, 31, 32; pg 105, 114, 116		

Laboratory abnormalities and AEs consistent with the known safety profile of tocilizumab were observed. SAE infection incidence was similar between arms (5.2% and 7.1% in the tocilizumab and placebo arms, respectively). Gastrointestinal perforations were rare with 2 patients (0.8%) in the tocilizumab arm and 0 patients in the placebo arm experiencing the event. While more patients experienced AEs related to low neutrophil count when treated with tocilizumab, no patients experienced SAE neutropenia in either treatment arm. SAE thrombocytopenia occurred in one patient in the trial, and that patient received tocilizumab. One patient (0.4%) in the tocilizumab arm experienced an anaphylactic reaction compared with 0 patients in the placebo arm. Hypersensitivity events occurred in 4.4% of patients receiving tocilizumab and 2.4% of patients receiving placebo. AESI hepatic events were rare with 2 patients (0.8%) in the tocilizumab arm and 0 patients in the placebo arm having these events. [redacted] criteria were met by 2 patients in the tocilizumab arm and 0 patients in the placebo arm, and these cases are separate from the aforementioned AESI hepatic events. No demyelinating events occurred in the trial.

SEE ATTACHED ADDENDUM

The safety data from EMPACTA are consistent with the known safety profile of tocilizumab as described in the approved label.

WA42511 (REMDACTA)

Safety analyses were conducted using a safety population consisting of all patients who received any amount of study medication, which included 429 patients who received TCZ+RDV and 213 patients who received PBO+RDV. Of the patients who received tocilizumab, 344 (80.2%) received 1 dose and 85 (19.8%) received 2 doses. Patients who completed the study were followed for 60 days. Deaths during the study were similar between treatment arms with 97/429 (22.8%) patients dying in the TCZ+RDV arm and 55/213 (25.8%) patients dying in the PBO+RDV arm. The most common AEs leading to death were COVID-19 pneumonia followed by COVID-19 and septic shock, and the causes of death were similar between arms. A similar number of patients experienced at least 1 SAE in each treatment arm, with 32.9% and 35.7% of patients experiencing at least 1 SAE in the TCZ+RDV and PBO+RDV arms, respectively. The only SAEs to occur in more than 5% of patients in either arm were COVID-19 pneumonia, acute kidney injury, and septic shock. More patients experienced SAE and AE pneumonia with TCZ+RDV compared to PBO+RDV, but the differences were small and of unclear clinical significance. Overall, AEs were generally balanced between treatment groups. A summary of AEs is shown in Table 15.

Table 15. Summary of Adverse Events in REMDACTA through Day 60 (Safety population)

Patients with	TCZ+RDV n=429 n (%)	PBO+RDV n=213 n (%)
At least 1 Adverse Events	332 (77.4)	153 (71.8)
At least 1 Serious Adverse Events	141 (32.9)	76 (35.7)
Deaths	98 (22.8)	55 (25.8)
Adverse Events Leading to Death (>1% of patients in either arm)		
COVID-19 pneumonia	35 (8.2)	26 (12.2)
COVID-19	14 (3.3)	8 (3.8)
Septic shock	13 (3.0)	3 (1.4)
Pneumonia	6 (1.4)	1 (0.5)
Sepsis	5 (1.2)	2 (0.9)
Serious Adverse Events (≥2% of patients in either arm)		
COVID-19 pneumonia	36 (8.4)	27 (12.7)
Acute kidney injury	21 (4.9)	14 (6.6)
Septic shock	23 (5.4)	10 (4.7)
Pneumonia	21 (4.9)	6 (2.8)
COVID-19	14 (3.3)	8 (3.8)
Sepsis	11 (2.6)	6 (2.8)
Renal impairment	1 (0.2)	5 (2.3)
Common Adverse Events (≥3% of patients in either arm)		
Constipation	54 (12.6)	25 (11.7)
Acute kidney injury	44 (10.3)	24 (11.3)
COVID-19 pneumonia	36 (8.4)	27 (12.7)
Pneumonia	33 (7.7)	10 (4.7)
Transaminases increased	26 (6.1)	13 (6.1)
Hyperglycemia	22 (5.1)	9 (4.2)
Hypotension	23 (5.4)	16 (7.5)
Septic shock	24 (5.6)	14 (6.6)
Urinary tract infection	24 (5.6)	14 (6.6)
Anemia	15 (3.5)	14 (6.6)
Insomnia	21 (4.9)	7 (3.3)
Hyperkalemia	13 (3.0)	10 (4.7)
Atrial fibrillation	19 (4.4)	9 (4.2)
Nausea	19 (4.4)	7 (3.3)
COVID-19	17 (3.3)	8 (3.8)
Delirium	14 (3.3)	8 (3.8)
Sepsis	12 (2.8)	7 (3.3)
Anxiety	14 (3.3)	4 (1.9)
Bradycardia	8 (1.9)	7 (3.3)
Pneumonia bacterial	8 (1.9)	7 (3.3)
Hypoglycemia	14 (3.3)	2 (0.9)
Thrombocytopenia	14 (3.3)	2 (0.9)
Pneumothorax	13 (3.0)	6 (2.8)
Pain	13 (3.0)	2 (0.9)
Source: Response to IR received May 17, 2021, pg. 7-27		

Similar to COVACTA and EMPACTA, safety findings consistent with the known safety profile of tocilizumab were observed. SAE infection incidence was similar between arms (20.0% and 24.9% in the TCZ+RDV and PBO+RDV arms, respectively). Gastrointestinal perforations were rare, occurring in 2 patients (0.5%) in the TCZ+RDV arm and 1 patient (0.5%) in the PBO+RDV arm. There were no cases of SAE neutropenia in the trial. SAE thrombocytopenia occurred in 2 patients in the trial, both in the TCZ+RDV arm (0.5%). Two patients experienced anaphylactic reaction events, both in the TCZ+RDV arm

(0.5%). Hypersensitivity events were similar between arms (9.3% and 14.1% in the TCZ+RDV and PBO+RDV arms, respectively). Hepatic events were infrequent and similar between arms (1.9% and 1.4% in the TCZ+RDV and PBO+RDV arms, respectively). Similarly, [redacted] cases were also infrequent and similar between arms (0.9% and 2.3% in the TCZ+RDV and PBO+RDV arms, respectively). No demyelinating events occurred in the trial.

SEE ATTACHED ADDENDUM

The safety data from REMDACTA are consistent with the known safety profile of tocilizumab and no additional safety concerns were identified when used in combination with remdesivir.

Pooled Safety Data

A safety analysis was also conducted using pooled data from COVACTA, EMPACTA, and REMDACTA (excluding RECOVERY). While these trials were not identical in design or trial population and this analysis was based on simple pooling across studies, the pooled analysis is still informative in terms of evaluating overall safety. It should also be noted that while complete Day 60 safety data was available for all patients in COVACTA and EMPACTA, complete day 60 data was not available for REMDACTA patients at the time of EUA submission. The pooled population included 974 patients who received tocilizumab and 483 patients who received placebo. Incidence of death was similar between treatment arms with 199 (20.4%) patients dying who received tocilizumab and 106 (21.9%) patients dying who received placebo. The most common AEs leading to death were COVID-19 pneumonia, COVID-19, septic shock, and respiratory failure with similar occurrence between arms. A similar number of patients in the tocilizumab and placebo arms experienced at least 1 SAE (30.3% and 34.2% in the tocilizumab and placebo arm, respectively) with the most common SAEs being COVID-19 pneumonia, acute kidney injury, and septic shock. The only AE to occur in more than 10% of patients in either arm was COVID-19 pneumonia. The most common AEs reported with tocilizumab (≥3%) and at least 1% greater incidence compared to placebo were constipation, anxiety, diarrhea, insomnia, hypertension, and nausea. The previously noted numerical differences in AE COVID-19, ARDS, MODS, pneumonia, urinary tract infections, acute kidney injury, hypertension, constipation, and anxiety are absent or less pronounced in the pooled safety analysis. A summary of AEs is shown in Table 16.

Table 16. Summary of Adverse Events in all treated patients * (Safety population)

Patients with	Tocilizumab n=974 n (%)	Placebo n=483 n (%)
At least 1 Adverse Events	699 (71.8)	338 (70.0)
At least 1 Serious Adverse Events	295 (30.3)	165 (34.2)
Deaths	199 (20.4)	106 (21.9)
Adverse Events Leading to Death (>1% of patients in either arm)*		
COVID-19 pneumonia	72 (7.4)	49 (10.1)
COVID-19	28 (2.9)	10 (2.1)
Septic shock	17 (1.7)	5 (1.0)
Respiratory failure	7 (0.7)	5 (1.0)
Serious Adverse Events (≥2% of patients in either arm)*		
COVID-19 pneumonia	73 (7.5)	50 (10.4)
Acute kidney injury	32 (3.3)	21 (4.3)
Septic shock	35 (3.6)	20 (4.1)
COVID-19	29 (3.0)	10 (2.1)
Pneumonia	27 (2.8)	13 (2.7)
Sepsis	15 (1.5)	10 (2.1)
Common Adverse Events (≥3% of patients in either arm)*		
COVID-19 pneumonia	73 (7.5)	50 (10.4)
Constipation	88 (9.0)	37 (7.7)
Acute kidney injury	69 (7.1)	35 (7.2)
Hypotension	38 (3.9)	27 (5.6)
Pneumonia	52 (5.3)	26 (5.4)
Anemia	32 (3.3)	26 (5.4)
Urinary tract infection	49 (5.0)	21 (4.3)
Septic shock	37 (3.8)	21 (4.3)
Transaminases increased	39 (4.0)	17 (3.5)
Anxiety	38 (3.9)	12 (2.5)
Hypokalemia	37 (3.8)	15 (3.1)
Diarrhea	37 (3.8)	12 (2.5)
Atrial fibrillation	36 (3.7)	18 (3.7)
Insomnia	36 (3.7)	13 (2.7)
Hypertension	35 (3.6)	7 (1.4)
Hyperglycemia	31 (3.2)	17 (3.5)
Nausea	33 (3.4)	11 (2.3)
COVID-19	29 (3.0)	10 (2.1)

*Excludes RECOVERY. For patients in REMDACTA, only AEs starting on or prior to the clinical cutoff date (1 Feb 2021) are reported. This includes all events through Day 28 but may not include events through Day 60 for all patients. For COVACTA and EMPACTA AE data was available for all patients through Day 60
Source: Adapted from EUA Application meta-analysis outputs, pgs. 44-84; Response to IR received May 21, 2021, pg. 41

In the pooled safety analyses, AEs consistent with the known safety profile of tocilizumab were observed. SAE infections were similar between arms and occurred in 179 patients (18.4%) who received tocilizumab and in 110 patients (22.8%) who received placebo. Gastrointestinal perforations were rare with 5/974 (0.5%) patients experiencing the event who received tocilizumab and 3/483 (0.6%) patients experiencing the event who received placebo. SAE neutropenia was similarly rare across trials, occurring in 4/974 (0.4%) patients who received tocilizumab and 0 patients who received placebo. While thrombocytopenia was more common in patients receiving tocilizumab (2.8%) compared to placebo (0.8%), SAE thrombocytopenia was rare (0.4% and 0.2% in the tocilizumab and placebo arms, respectively). Anaphylactic reactions were rare and similar between

arms (0.3% and 0.2% in the tocilizumab and placebo groups, respectively). Hypersensitivity events were similar between treatment groups, occurring in 66/974 (6.8%) of patients receiving tocilizumab and 32/483 (6.6%) of patients receiving placebo. AESI hepatic events occurred in 17/974 (1.7%) of patients who received tocilizumab and 6/483 (1.2%) of patients who received placebo. [redacted] criteria were met by 12/974 (1.2%) and 12/483 (2.5%) of patients in the tocilizumab and placebo groups, respectively. No demyelinating events occurred in any of the Sponsor-conducted trials.

SEE ATTACHED ADDENDUM

Overall, the pooled safety data are consistent with the known safety profile of tocilizumab as described in the approved label and no new safety signals were identified.

Integrated Analysis of Safety

The safety of tocilizumab for the treatment of COVID-19 is supported primarily by data from COVACTA, EMPACTA, and REMDACTA given that RECOVERY collected very limited safety information. No new safety signals were identified in the COVID-19 development program. Safety signals that were observed were generally consistent with known risks of tocilizumab that were identified in prior approvals and are consistent with labeled warnings and precautions. Important known safety issues that were observed in the COVID-19 trials include laboratory abnormalities (primarily thrombocytopenia and neutropenia) and hypersensitivity reactions; however, the imbalances between treatment arms were small, the AEs were generally not serious, and patients can be closely monitored for adverse reactions while hospitalized. Notably, secondary infections were not observed more frequently with tocilizumab compared to placebo, but it should be noted that patients with secondary infections were excluded from the trials. Overall, no new potential risks of tocilizumab were identified in the COVID-19 development program, and the safety profile appears consistent with the current approved label.

X. Specific Populations

- No data are currently available for children or pregnant or lactating women with COVID-19 treated with tocilizumab. Although REMDACTA allowed for enrollment of patients age ≥12 years, no patients <18 years were enrolled.

- The recommended dose for pediatric patients 2 to 17 years of age is 8 mg/kg given intravenously if body weight is equal to or greater than 30 kg. The recommended dose for pediatric patients 2 to 17 years of age is 12 mg/kg given intravenously if body weight is less than 30 kg. For specific details, see Human Clinical Pharmacology section below.

- No dose adjustment is required in elderly patients >65 years of age or in patients with mild or moderate renal impairment.

- Embryo-fetal toxicities were not observed in animal studies with intravenous administration of tocilizumab. An increase in the incidence of abortion/embryo-fetal

deaths was observed at doses 1.25 times and higher the maximum recommended human dose.

XI. Human Clinical Pharmacology

- Pharmacokinetics (PK)

The PK of tocilizumab administered intravenously (IV) in patients with RA, pJIA, sJIA and CRS is available in the approved label of tocilizumab (BLA125276). In this review, we summarized the PK of IV tocilizumab in patients with COVID-19 based on the PK data collected from clinical studies WA42380 (COVACTA) and CA42481 (MARIPOSA).

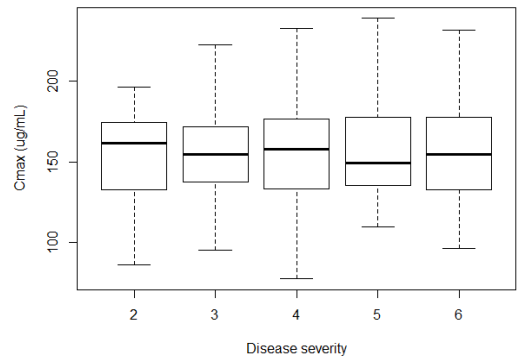
Distribution
Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In patients with COVID-19, based on the population PK model developed for tocilizumab, the estimated central volume of distribution was 4.52 L and the estimated peripheral volume of distribution was 4.23 L.

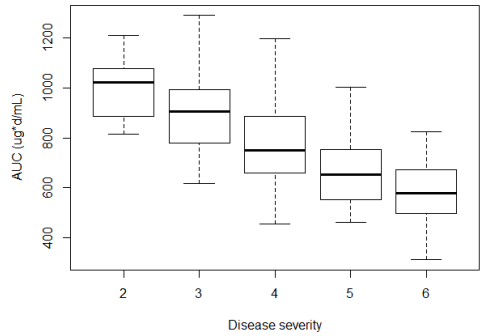
Elimination
Tocilizumab is eliminated by a combination of linear clearance and nonlinear elimination. The concentration-dependent nonlinear elimination plays a major role at low tocilizumab concentrations. Once the nonlinear pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The saturation of the nonlinear elimination leads to an increase in exposure that is more than dose proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration level. In COVID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of IV 8 mg/kg.

- Specific Populations

Linear clearance was found to increase with body size and disease severity. In COVID-19 patients, as with other diseases, tocilizumab exposure is positively correlated with the body weight based on body weight-based dosing regimen. With the maximum dose of tocilizumab capped at 800 mg, patients less than 100 kg and greater than 100 kg were comparable in mean tocilizumab exposure (Table 18). For an 80 kg patient, while Cmax remains constant, there is a consistent decreasing trend in AUC as disease severity increases (Figure 3).

Figure 3. Estimates of tocilizumab exposure by ordinal scale



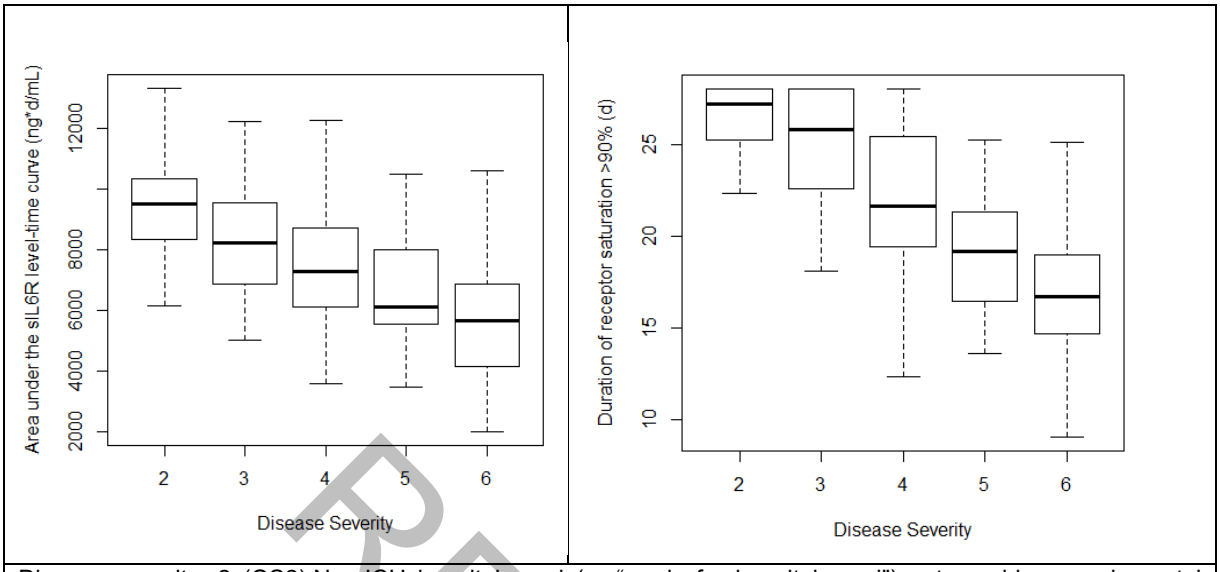


Disease severity: 2 (OS2):Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen; 3 (OS3): non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen; 4 (OS4): ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5 (OS5): ICU, requiring intubation and mechanical ventilation; 6 (OS6): ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy).
Source: Reviewer analysis

- Pharmacodynamics (PD)

  The PD (sIL-6R) of tocilizumab in patients with COVID-19 was also evaluated in the two clinical studies (WA42380 and CA42481). Similar to AUC, there was a trend of lower level of sIL-6r and lower duration of receptor saturation above 90% from day 0 to day 28 in patients with more severe disease at 8 mg/kg single IV dose (Figure 4).

Figure 4. Estimates of sIL-6R by ordinal scale



Disease severity: 2 (OS2):Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen; 3 (OS3): non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen; 4 (OS4): ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5 (OS5): ICU, requiring intubation and mechanical ventilation; 6 (OS6): ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy).
Source: Reviewer analysis

- Drug Interactions

  The interaction potential of tocilizumab has not been evaluated in patients with COVID-19. Refer to label of tocilizumab.

- Immunogenicity

  In incidence of antibodies to tocilizumab in patients with COVID-19 has not been evaluated.

- Dosing Regimen

  Adult patients with COVID-19
  The proposed dosing regimen was 8 mg/kg given intravenously (max. 800 mg) and likely one additional infusion at least 8 hours after initial infusion in adult patients with COVID-19.

  This proposed dosing regimen was evaluated in studies WA42380 (COVACTA), ML42528 (EMPACTA), CA42481 (MARIPOSA), WA42511 (REMDACTA) and is also the same as the approved dosing regimen for tocilizumab in CRS patients. In the RECOVERY trial, however, a weight tiered dosing regimen was used and the dose was determined by four body weight categories, i.e., 800 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8mg/kg if weight ≤40 kg. A second dose could be given 12−24 hours later if, in the opinion of the attending

clinician, the patient's condition had not improved. Although different from the proposed dosing regimen, this weight-tiered dosing regimen is comparable to the proposed dosing regimen of 8 mg/kg with the maximum difference of 25%.

At this proposed dosing regimen, tocilizumab exposure in patients with COVID-19 for body weight >=100 kg is comparable to that in patients for body weight <100 kg and is also overlapping with that in patients with other approved indications, even though the mean exposure is numerically less than that in RA patients and higher than that in CRS patients (Table 17). Refer to clinical and statistical sections for further benefit/risk evaluation.

Table 17. Exposure of tocilizumab in patients with COVID-19, pJIA, sJIA, RA, and CRS

Exposure after chronic IV dosing				
Patients	BW	Dose	Cave,ss (mcg/mL)	Cmax,ss (mcg/mL)
pJIA[1]	>=30 kg	8 mg/kg IV every 4 weeks	38.6 (22.2–83.8)	181 (114–331)
	<30 kg	10 mg/kg IV every 4 weeks	30.8 (16.0–48.0)	167 (125–220)
sJIA[1]	>=30 kg	8 mg/kg IV every 4 weeks	117 (37.6–199)	253 (120– 404)
	<30 kg	12 mg/kg IV every 2 weeks	124 (60–194)	274 (149–444)
RA[1]		8 mg/kg IV every 4 weeks	54.0 (17–260)	176 (75.4–557)
Exposure after single IV dose or two IV doses				
			Cmax, 1st	Cmax, 2nd
RA[2]	Adults	10 mg/kg single dose	273 (121)	-
CRS[3]	Adults	8 mg/kg IV 2 doses 8 hours apart	99.5 (36.8%)	160.7 (113.8%)
COVID-19[4]	Adults	8 mg/kg IV (<100 kg) 2 doses 8 hours apart	151 (78-296)	288 (152-553)
		800 mg (WT>=100 kg) 2 doses 8 hours apart	150 (89-319)	290 (172-604)

Data Source:
[1]BLA125276 package insert for pJIA, sJIA and RA patients; median (range)
[2]Study LRO300; mean (SD)
[3]Le et al. 2018 for CRS patients; mean (%CV)
[4]PopPK model prediction; median (range)

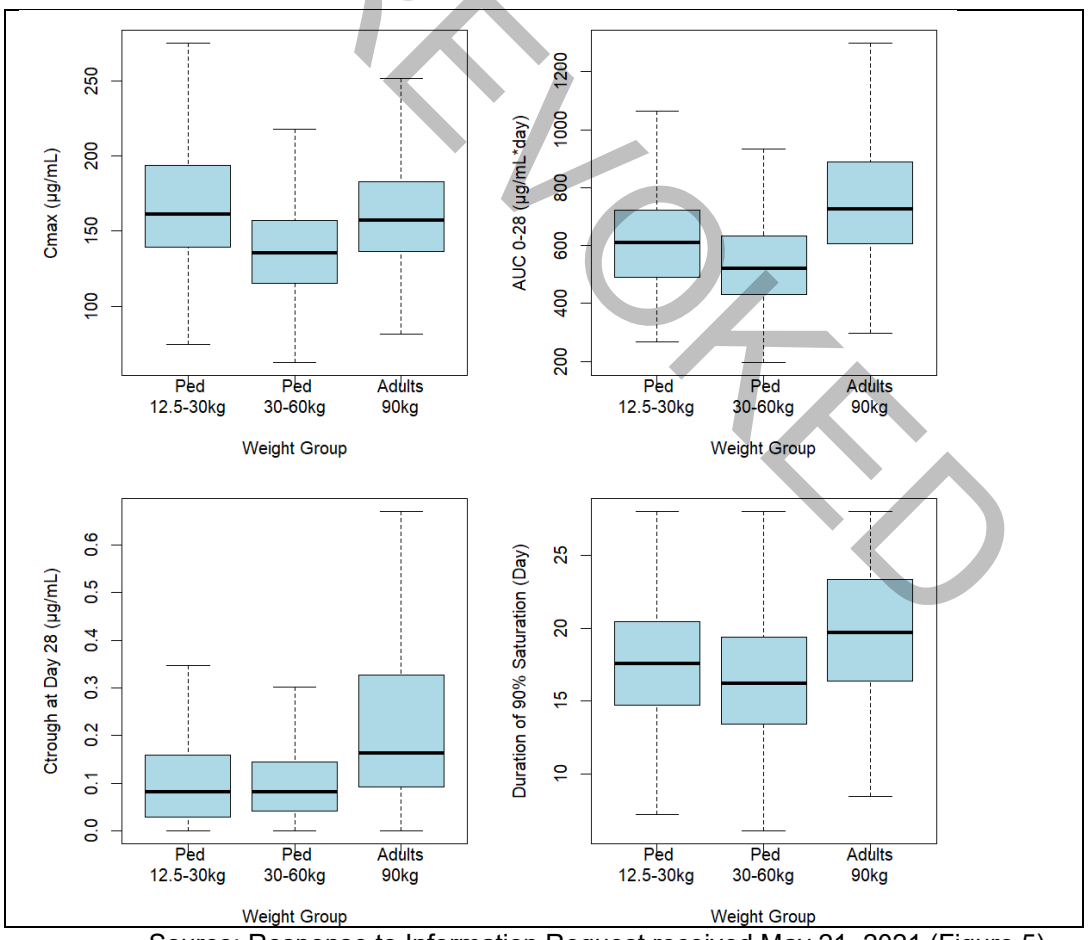
Pediatric patients with COVID-19

The proposed dose regimen for pediatric patients with COVID-19 is 8 mg/kg IV in pediatric patients greater than or equal to 30 kg and 12 mg/kg IV in pediatric patients less than 30 kg.

The PK of tocilizumab is not available in pediatric patients with COVID-19. However, tocilizumab has been approved in pediatric patients with pJIA, sJIA, CRS 2 years of

age and above. As shown in Table 18, the dose was higher for children less than 30 kg because of the higher weight-adjusted clearance in these children than children greater than 30 kg and adults. At the approved dosing regimens in these pediatric patients, the exposure of tocilizumab is within the same range with that in adult patients in the respective indications. Further, there are no known COVID-19-specific pathophysiological differences which can significantly impact the disposition profile of tocilizumab between adult and pediatric patients with COVID-19. As such, the PK in pediatric patients with COVID-19 was simulated based on the PKPD model established in adults with COVID-19 while varying the body weight to reflect the median weight that corresponds to a particular pediatric age according to the CDC growth tables. The simulated exposure and PD response of tocilizumab in pediatrics was in the range of those in adults with COVID-19 (Figure 5).

Figure 5. Comparison of PK and PD parameters between Adults (8 mg/kg TCZ IV) and Pediatrics (12 mg/kg TCZ IV for BW < 30 kg or 8 mg/kg TCZ IV for BW ≥ 30 kg) with COVID-19 pneumonia



Source: Response to Information Request received May 21, 2021 (Figure 5)

Considering that the disease in adults and pediatric patients is sufficiently similar once patients progress to require supplemental oxygen, invasive mechanical ventilation, or ECMO, that there are no known COVID-19-specific pathophysiological differences

which can significantly impact the disposition profile of tocilizumab between adult and pediatric patients with COVID-19, and that the simulated pediatric exposure and PD response following the proposed dose are within the adults' reference range and overlapping tocilizumab exposure with that in pediatric patients with other approved indications, the proposed dose in pediatric patients with COVID-19 (i.e., 8 mg/kg IV in pediatric patients greater than 30 kg and 12 mg/kg IV in pediatric patients less than 30 kg in pediatric patients 2 years to < 17 years of age) is reasonable.

XII. Nonclinical Data to Support Safety

- Nonclinical studies with tocilizumab were previously reviewed under BLAs 125276 (injection for intravenous use) and 125472 (injection for subcutaneous use) to support the approval of tocilizumab (BLA 125276 reviews dated in DARRTS August 15, 2008 and December 17, 2009 and BLA 125472 reviews dated in DARRTS January 23, 2013 and September 9, 2013; Authored by Dr. Asoke Mukherjee).

- No juvenile animal studies have been conducted with tocilizumab. However, there are no nonclinical safety concerns as the proposed age range matches that of the approved indication under the BLA.

- A chronic repeat-dose intravenous toxicology study in adult monkeys identified reversible slight granulomas in the liver and irreversible degeneration of the skeletal muscle as the major treatment-related toxicities. Although no effects on creatinine phosphokinase activity were observed, clinical monitoring of liver enzymes and creatinine phosphokinase was recommended for chronic treatment with tocilizumab based on nonclinical data. However, this risk is not considered clinically meaningful with the currently proposed treatment regimen. No dose-limiting toxicities were identified in a single-dose monkey study or a 28-day repeat-dose toxicology study in rats.

- In a non-human primate embryofetal development study with tocilizumab, an increase in the incidence of abortion/embryo-fetal deaths was observed at doses 1.25 times and higher the maximum recommended human dose. No evidence of teratogenicity was observed at any dose. A mechanistic concern detailing the potential effects of inhibiting IL-6 during pregnancy is included in the label for tocilizumab.

- Intravenous testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre-and postnatal development phase with treatment every three days from implantation until weaning. There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

- The nonclinical data provides coverage for the use of tocilizumab as an intravenous therapy for the treatment of patients with COVID-19 at a single-dose intravenous infusion of 8 mg/kg (up to 800 mg) with a second dose after 7 days, if needed.

XIII. Nonclinical Data to Support Efficacy

- IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. Inhibition of IL-6 is a therapeutic strategy for treatment of this condition.
- Tocilizumab is a recombinant humanized monoclonal antibody that selectively binds to both soluble and membrane-bound human IL-6 receptors (sIL-6R and mIL-6R) and subsequently inhibits IL-6-mediated signaling through these receptors. Tocilizumab did not exhibit any effects on the transduction of IL-1, IL-15, and TNF.
- In *in vitro* pharmacology studies, tocilizumab neutralized human IL-6R in cell membranes and in plasma at K_D values of 2.5 and 0.7 nmol/L, respectively.
- There are no directly relevant animal studies showing that tocilizumab inhibits cytokine release in the context of SARS-CoV-2 infection.

XIV. Supply Information

The dose of tocilizumab drug product proposed is a single dose of 8 mg/kg to not exceed 800 mg. An additional 8 mg/kg dose can be given 8-24 hr following the initial dose as an option if there is no improvement following the first dose. As of June 14, 2021, the Sponsor has approximately (b) (4) treatment courses available [assuming two treatments with maximum dose (800mg)] for distribution and expects to receive an additional (b) (4) by June 18, 2021. The exact timeframe for (b) (4) increases in production capacity are not provided. However, a new tocilizumab drug product manufacturing site at (b) (4) has been established and (b) (4) approved. (b) (4)

These expansions in tocilizumab (b) (4) manufacturing are designed to meet the projected increase in demand.

XV. Chemistry, Manufacturing, and Controls Information

- This EUA is for licensed commercial tocilizumab (tradename: ACTEMRA) at its approved dosage and route of administration. The new tocilizumab drug product facility at (b) (4) has recently been approved ((b) (4)). There are no product quality concerns. Standard infusion sets are to be used for dosing

- There is no change from the approved product and each vial of tocilizumab for intravenous infusion contains:
    - Polysorbate 80
    - Sucrose
    - Disodium phosphate dodecahydrate

- Sodium dihydrogen phosphate dihydrate
- Water for injection

XVI. Manufacturing Site Inspections

Table 18. Manufacturing Sites

Mfg. Site Identifier	Site Responsibilities	Location (US and Non-US)	Associated Submissons	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
Genentech OCN FEI: 3006129086	DS Mfg.	Oceanside CA, USA	BLA 125276	Roche/Genentech	Oct. 2017	Acceptable
Chugai Pharma Utsunomyia FEI: 3006942691	DS and DP Mfg.	Utsunomyia, Japan	BLA 125276	Roche/Genentech	Feb. 2020	Acceptable
Genentech Vacaville FEI: 3002902534	DS Mfg. and DP Release testing	Vacaville CA, USA	BLA 125276	Roche/Genentech	Mar. 2020	Acceptable
Genentech HTO FEI: 3007232634	DP Mfg.	Hillsborough OR, USA	BLA 125276	Roche/Genentech	May 2021	Acceptable
Roche Diagnostics GmbH FEI: 3002806559	DP Endotoxin and Sterility Testing	Manheim, Germany	BLA 125276	Roche/Genentech	Aug. 2019	Acceptable

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following condition(s) to the authorization as necessary to protect the public health[4]:

- Genentech will manufacture Actemra (tocilizumab) 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL Injection for Intravenous Infusion to meet all quality standards and per the manufacturing process and control strategy as detailed in Genentech's EUA request. Genentech will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

[4] See the evaluation documented in OMQ's EUA Recommendation Memo in CMS Case# 615423, OPMA's Product Quality Microbiology/Facility Assessment Memo associated with EUA 0099, and OBP's Chemistry, Manufacturing, and Controls Assessment Memo associated with EUA 0099 all dated June 24, 2021.

- Genentech will submit information to the Agency within three working days of receipt concerning significant quality problems with drug product distributed under this emergency use authorization for Actemra (tocilizumab) 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL Injection for Intravenous Infusion that includes the following:

    - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
    - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

    If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

    Genentech will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

    If not included in its initial notification, Genentech must submit information confirming that Genentech has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Genentech must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

XVII. Clinical Trial Site Inspections

No site inspection was performed or deemed necessary for the COVID-19 studies.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

No animal study site inspections were performed.

XIX. Recommendations From Treatment Guidelines and Other Sources

At the time of this review, the following treatment guidelines include tocilizumab for the treatment of COVID-19:

- The National Institutes of Health (NIH) COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/) recommend that tocilizumab be used in patients who were recently hospitalized with rapidly increase oxygen needs and systemic inflammation in conjunction with either dexamethasone or dexamethasone plus remdesivir. Additionally, the guidelines recommend tocilizumab in hospitalized patients who are within 24 hours of admission to the ICU and require

invasive mechanical ventilation or ECMO. The stated rationale for this recommendation is based on results of the RECOVERY trial, as well as Randomised, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). For children, the guidelines state that there is insufficient evidence to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19.

- The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) recommend tocilizumab in addition to SOC (i.e., steroids) rather than SOC alone in hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation. This recommendation is based on review of 8 randomized controlled trials (including pre-prints), including RECOVERY and REMAP-CAP.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Based on review of the 4 trials included in the EUA request — RECOVERY, COVACTA, EMPACTA, and REMDACTA — it is reasonable to believe that tocilizumab may be effective when used in hospitalized COVID-19 patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Despite some limitations and concerns, the results of RECOVERY suggest that treatment with tocilizumab may result in a reduction in mortality based on the statistically significant result for the primary endpoint, as well as increased chance of discharge from the hospital and avoidance of invasive mechanical ventilation based on secondary endpoints results. Patients on baseline systemic corticosteroids appeared to be most likely to benefit in RECOVERY. EMPACTA's primary endpoint data also suggests that tocilizumab treatment may reduce the need for invasive mechanical ventilation in a less severe hospitalized population than was studied in RECOVERY. Though COVACTA and REMDACTA did not meet their primary endpoints, these efficacy results do not necessarily contradict the positive findings of RECOVERY and EMPACTA. As noted in the Integrated Analysis of Efficacy, heterogeneity in disease severity and limited use of systemic corticosteroid in COVACTA may have impacted the observed treatment effect, and REMDACTA was underpowered to detect the mortality reduction observed in RECOVERY. It is also important to note that COVACTA and REMDACTA both did not raise any concerns for potential harm. Overall, the data suggest that tocilizumab may be effective for the proposed intended use.

In terms of risk, the safety issues identified in the COVID-19 development program are consistent with the approved product label and are monitorable. These risks include but are not limited to infection, hypersensitivity/anaphylaxis, and laboratory abnormalities. It is important to note that, consistent with the approved product label, tocilizumab should not be used in patients with known hypersensitivity to tocilizumab. Additionally, while excess secondary infections were not consistently observed in COVID-19 patients treated with tocilizumab, given the known safety concerns associated with tocilizumab, it should not be administered to patients with known or suspected infections other than COVID-19.

Overall, these potential risks do not outweigh the potential benefit of a reduction in mortality and avoidance of invasive mechanical ventilation.

The potential benefits and risks of tocilizumab use in adults observed in the clinical trials are expected to be similar for pediatric patients ≥2 years old based on considerations that the disease in adults and pediatric patients is sufficiently similar once patients progress to requiring supplemental oxygen, invasive mechanical ventilation, or ECMO. There are no known COVID-19-specific pathophysiological differences that can significantly impact the ADME profile of tocilizumab between adult and pediatric patients. The proposed dosing regimen for pediatric patients is expected to have comparable PK exposure to tocilizumab in adult patients with COVID-19, and is also informed by the accumulated PK and safety information with tocilizumab in multiple other adult and pediatric populations, as detailed in the sections on Human Clinical Pharmacology and Special Populations above.

In summation, it is reasonable to believe that tocilizumab may be effective and that the known and potential benefits of outweigh the known and potential risks for the proposed intended use. The Division concludes that tocilizumab meets the statutory criteria for EUA, and issuance of an EUA is recommended.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice. If used in clinical trials done under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where health care providers will have many competing priorities, adverse event reporting under this EUA will be streamlined through FDA's MedWatch system.

Genentech will report to FDA serious adverse events and all medication errors associated with the use of the authorized Actemra that are reported to Genentech.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to tocilizumab (tradename: ACTEMRA) within 7 calendar days from the onset of the event, using FDA Form 3500. The reports should include a statement "ACTEMRA use for COVID-19 under Emergency Use Authorization (EUA)" under the "Describe Event, Problem, or Product Use/Medication Error" heading. Healthcare providers will also be responsible for providing this form to Genentech via an established email at us_drug.safety@gene.com or an established telephone number at 1-888-835-2555.

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheets for Healthcare Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

Genentech plans to use commercially available product[5] upon initial issuance of the EUA. Upon issuance, the sponsor will provide a link to their website (https://www.actemrahcp.com/covid-19) to all full-line distributors and specialty pharmacies. Genentech's website will include the LOA and the authorized factsheets.

Per discussion with Genentech on June 23, 2021, Genentech intends to transition to an updated carton container label, which will include a QR code and reference to the EUA approximately 8 weeks after issuance of the EUA. The QR code will link directly to Genentech's website, which will include the authorized Fact Sheet and LOA. The revised carton container labeling is intended to be distributed as the commercially available product for Actemra under BLA 125276, and once authorized, may be distributed for the uses under the EUA. Upon authorization by the Agency, Genentech will issue a second notification to the full-line distributors and specialty pharmacies informing them of the new carton container labeling.

The authorized Fact Sheet for Healthcare Providers and Fact Sheet for Patients and Parents/Caregivers can be found in Section XXVI. Appendices

XXIV. Outstanding Issues/Data Gaps

Not applicable.

XXV. References

Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-661. doi:10.1016/S2352-4642(20)30177-2

RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-1645. doi:10.1016/S0140-6736(21)00676-0

XXVI. Appendices

1. Label for Approved Indications
2. Pharmacometrics Review
3. Fact Sheet for Healthcare Providers
4. Fact Sheet for Patients, Parents and Caregivers

[5] For the purposes of this authorization, commercially available Actemra refers to product in United States distribution under the approved Biologics License Application 125276.

Appendix 1: Label for Approved Indications
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf

Appendix 2: Pharmacometrics Review

Summary of Pharmacometrics Finding
The applicant performed a Population PKPD analysis to characterize the PK of tocilizumab and exposure of sIL-6r in subjects with COVID-19. The intrinsic factors which influence the PK-PD of tocilizumab were identified. The population model was subsequently used to predict tocilizumab exposure and PD response in pediatric patients with COVID-19. In this review, the pharmacometrics reviewer has validated the Applicant's population model and simulation.

The Applicant's Population PK-PD analysis
Population PK-PD (POP-PK-PD) analyses were conducted by the Applicant in subjects with COVID-19 with the objectives: 1) To establish a joint population PK-sIL6R model that describes the pharmacokinetics of tocilizumab and total sIL6R concentrations following intravenous administration in adult patients with COVID-19; 2) To describe dependence of tocilizumab PK- sIL6R model parameters on covariate factors, including severity of COVID-19 disease; 3)To perform model-based simulations of tocilizumab and sIL6R concentrations following clinically important dosing regimens in patients with COVID-19.

The Applicant's integrated POP-PK-PD analyses included data from Study WA42380 (COVACTA) and Study CA42481 (MARIPOSA) conducted in subjects with COVID-19.

Study WA42380 was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia. A total of 452 patients diagnosed with COVID-19 pneumonia were randomized at a 2:1 ratio to receive blinded treatment of either tocilizumab with one IV infusion of 8 mg/kg, with a maximum dose of 800 mg or a matching placebo. Serum samples were obtained according to the following schedule: Day 1 pre-dose, Day 1 end-of-infusion, 24 and 36 hours after infusion, and then at Day 3 (sIL-6 only), 7, 14, 21, 28, 35, and at study completion (Day 60) or discontinuation.

Study CA42481 was a Phase II, open-label, randomized, multicenter study to investigate the PD, PK, safety, and efficacy of 8 mg/kg or 4 mg/kg intravenous tocilizumab in patients with moderate to severe COVID-19 pneumonia. Approximately 100 patients diagnosed with COVID-19 pneumonia enrolled and randomized at a 1:1 ratio to receive one IV infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, or TCZ 4 mg/kg, both in addition to SOC. For both arms, if the clinical signs or symptoms worsened or did not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of TCZ (at the same dose as the

initial infusion) could be given, 8–24 hours after the initial infusion. Serum samples were obtained according to the following schedule: Day 1 pre-dose, Day 1 end-of-infusions, Days 2, 3 (sIL-6 only), 7, 14, 21, 28, 35, and at study completion (Day 60) or discontinuation.

Determination of tocilizumab concentrations in human serum samples was conducted using the established and validated enzyme-linked immunosorbent assay (ELISA) and so are for sIL-6R concentrations.

The final dataset for the POP-PK-PD analyses consists of a total of 1860 PK observations from 369 patients for PK analysis and a total of 2929 sIL-6R observations from 377 patients for the PK-sIL6R analysis. Missing observations (concentrations below the limit of quantification) were excluded from the analysis. The continuous covariates are summarized in Table 19. The categorical covariates are summarized overall and for each study in Table 20.

Table 19. Summary of continuous covariates

Covariate	Units	Mean (SD)			Median [Range]		
		Total	WA42380	CA42481	Total	WA42380	CA42481
N		378	284	94	378	284	94
AGE	years	59.9 (14.6)	60.6 (14.5)	58.1 (14.6)	62 [25-96]	62 [25-96]	58.5 [25-91]
WT	kg	89.6 (24.3)	89 (23.9)	91.6 (25.3)	85 [43.5-186]	84.6 [43.5-186]	88.6 [45.4-181]
CRCLN	mL/min /1.73m^2	88.7 (46.9)	86.2 (44.3)	96.1 (53.7)	85.4 [7.41-257]	85.2 [7.79-257]	85.7 [7.41-243]
ALB	g/L	28.5 (5.91)	28.2 (5.9)	29.3 (5.89)	28 [11-43]	28 [11-41]	30 [16-43]
PROT	g/L	64.2 (9.31)	63.7 (9.76)	65.5 (7.72)	64 [31-149]	64 [31-149]	65.5 [47-90]
SIL6R	ng/mL	36.8 (11.8)	36.7 (12.1)	37.1 (10.9)	35.6 [3.54-82.8]	35.6 [3.54-82.8]	35.6 [17.5-69.4]
FERRITIN	pmol/L	3360 (3710)	3260 (3060)	3650 (5230)	2340 [51.7-25600]	2450 [85.4-25600]	1830 [51.7-22000]
log(IL6)[a]	log (ng/L)	4.4 (1.36)	4.43 (1.43)	4.32 (1.14)	4.42 [1.14-11.5]	4.48 [1.14-11.5]	4.25 [1.35-7.84]
log (max IL6)	log (ng/L)	7.37 (1.55)	7.52 (1.55)	6.94 (1.46)	7.38 [1.77-12.9]	7.5 [3.74-12.9]	7.05 [1.77-10.3]
IL6	ng/L	481 (5380)	582 (6160)	157 (345)	82.2 [0-99700]	88 [3.12-99700]	67.9 [0-2540]
max IL6	ng/L	5670 (22800)	6710 (26100)	2510 (4110)	1610 [5.85-408000]	1800 [41.9-408000]	1150 [5.85-30800]

a: one subject from Study CA42481 with IL6=0 was excluded from the summary; SD=standard deviation

Source file: ContCovMean.csv, ContCovMedian.csv (Covacta_ReportPlots.R)

Subjects who did not have evaluable TCZ or sIL6R concentrations were excluded from the summary.
Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 4)

Table 20. Summary of categorical covariates: number (percent) of subjects

Two subjects from Study CA42481 who did not have evaluable TCZ or sIL6R concentrations were excluded from the summary.

Covariate	Level	Total (N=378)	Study WA42380 (N=284)	Study CA42481 (N=94)
Dose Group	1 = 4 mg/kg	35 (9.3%)	-	35 (37.2%)
	2 = 2 x 4 mg/kg	12 (3.2%)	-	12 (12.8%)
	3 = 8 mg/kg	262 (69.3%)	224 (78.9%)	38 (40.4%)
	4 = 2 x 8 mg/kg	69 (18.3%)	60 (21.1%)	9 (9.6%)
SEX	0 = female	126 (33.3%)	89 (31.3%)	37 (39.4%)
	1 = male	252 (66.7%)	195 (68.7%)	57 (60.6%)
RACE	1=White	205 (54.2%)	168 (59.2%)	37 (39.4%)
	2=Black	70 (18.5%)	38 (13.4%)	32 (34%)
	3=Asian	33 (8.7%)	29 (10.2%)	4 (4.3%)
	4=American Indian or Alaska Native	11 (2.9%)	8 (2.8%)	3 (3.2%)
	5=Native Hawaiian or Other Pacific Islander	4 (1.1%)	3 (1.1%)	1 (1.1%)
	6=Multiple	1 (0.3%)	-	1 (1.1%)
	Missing	54 (14.3%)	38 (13.4%)	16 (17%)
Ethnicity	1= Hispanic or Latino	113 (29.9%)	88 (31%)	25 (26.6%)
	2 = Not Hispanic or Latino	243 (64.3%)	178 (62.7%)	65 (69.1%)
	Missing	22 (5.8%)	18 (6.3%)	4 (4.3%)
SCALE7B	2	21 (5.6%)	8 (2.8%)	13 (13.8%)
	3	100 (26.5%)	75 (26.4%)	25 (26.6%)
	4	135 (35.7%)	91 (32%)	44 (46.8%)
	5	51 (13.5%)	42 (14.8%)	9 (9.6%)
	6	71 (18.8%)	68 (23.9%)	3 (3.2%)
Mechanical Ventilation	No	243 (64.3%)	175 (61.6%)	68 (72.3%)
	Yes	135 (35.7%)	109 (38.4%)	26 (27.7%)
sIL6R baseline	Not missing	362 (95.8%)	274 (96.5%)	88 (93.6%)
	Missing	16 (4.2%)	10 (3.5%)	6 (6.4%)

Source file: CatCov.csv (Covacta ReportPlots.R)

Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 5)

Reviewer comments: Given that each subject has 5 or 6 data points for PK analysis on average after dosing, the data can be analyzed via both modeling approach as well as noncompartmental approach. However, the population modeling allows simulation to predict various scenarios such as different dosing regimen and pediatric exposure given IV dosing of tocilizumab. The missing observations is less than 10% of the overall datasets so the impact of missing data on the PK assessment is considered not significant.

The PPO-PK data was modeled using non-linear mixed effects in NONMEM. The methodology included - 1) exploratory data analysis; 2) base structural model development; 3) evaluation of covariate effects; 4) model refinement; and 5) model evaluation.

The structural model developed by the Applicant consists of a two-compartment model with parallel linear and Michaelis-Menten elimination for tocilizumab and indirect response model with inhibition of elimination for sIL-6R. A log-normal distribution was assumed to describe interindividual variability (IIV) in clearance

(CL) and central volume of distribution (V) and a combined additive and proportional variance model was used to describe residual variability (RV).

Covariates evaluated in the Applicant's POP-PK model are described in Table 21. COVID-related effects were significant predictors of linear CL, Vc, kdeg and kint, respectively. Age was significant predictor for kdeg.

Table 21. Summary of NONMEM runs for model development

Run	Description [a]	Error code		OFV	Comment
		$EST	$COV		
001mar	Final model of prior analysis with fixed parameters	-	-	-4183.79	Initial model
003mar	As 001mar with COVID effects CL, V_C, V_P, V_M, k_{int}, and k_{deg}; SCALE7 effects on CL and k_{int}; Age effect on k_{deg} (for age > 50)	0	0	-8357.14	Accepted
004mar	As 003mar with removed effects of ALB and PROT on V_C and V_P	0	0	-8384.56	Accepted
018mar	As 004mar with removed COVID effects on CL, V_P and V_M	0	0	-8379.82	Final model
019mar	As 018mar with SCALE7B instead of SCALE7	0	0	-8157.06	Not as good
020mar	As 018mar with maximum IL6 instead of SCALE7	0	0	-8146.81	Not as good
021mar	As 018mar with IL6 instead of SCALE7	0	0	-8047.24	Not as good

In the $EST column, 0 indicates a successful run, error code 134 indicates rounding error. In the $COV column, 0 (1) indicates a successful (failed) covariance step.

Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 6).

The parameter estimates of the final POP-PK model including fixed and random effects parameters and their associated precisions (%RSE, relative standard error expressed as a percent) for the final tocilizumab model are presented in the Table 22. Parameter estimates of the tocilizumab population PK-sIL6R model 018mar.

Table 22. Parameter estimates of the tocilizumab population PK-sIL6R model 018mar

Parameters not listed in this table can be found in Table 2. Model was parameterized as follows: $CL=CL_{RA}\cdot(CL_{Scale7})^{Scale7}$; $V_C=V_{C,RA}\cdot V_{C,COVID}$; $k_{int}=k_{int,RA}\cdot k_{int,COVID,Scale7=4}\cdot(k_{int,Scale7})^{(Scale7-4)}$ $k_{deg}=k_{deg,RA}\cdot k_{deg,COVID}\cdot(\max(Age,50)/50)^{k_{deg,age}}$, where CL_{RA}, $V_{C,RA}$, $k_{int,RA}$, and $k_{deg,RA}$ are parameter estimates for patients with RA described by Table 2, with removed effects of albumin and total protein on central and peripheral volumes.

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
V_{ALB}	θ_{12}	0	Fixed			
V_{PROT}	θ_{13}	0	Fixed			
$CL_{COVID,Scale7=0}$	$\exp(\theta_{31})$	1	Fixed			
$V_{C,COVID}$	$\exp(\theta_{32})$	1.11	1.27	1.08 ; 1.14		
$k_{int,COVID,Scale7=4}$	$\exp(\theta_{33})$	2.45	1.69	2.37 ; 2.53		
$k_{deg,COVID}$	$\exp(\theta_{34})$	1.69	2.06	1.62 ; 1.76		
CL_{Scale7}	$\exp(\theta_{35})$	1.22	0.461	1.21 ; 1.23		
$k_{deg,age}$	θ_{36}	-0.539	14.2	-0.689 ; -0.389		
$k_{int,Scale7}$	$\exp(\theta_{37})$	1.07	0.656	1.05 ; 1.08		
ω^2_{CL}	$\Omega(1,1)$	0.0768	10.7	0.0606 ; 0.0929	CV=27.7%	18.3%
ω^2_{VC}	$\Omega(2,2)$	0.052	8.4	0.0435 ; 0.0606	CV=22.8%	7.1%
$R\omega_{VV}\omega_{VP}$	$\Omega(2,3)$	0.0729	13.6	0.0535 ; 0.0923	R=0.628	
ω^2_{VP}	$\Omega(3,3)$	0.259	13.9	0.189 ; 0.33	CV=50.9%	19.3%
ω^2_{Q}	$\Omega(4,4)$	0.01	Fixed		CV=10.0%	65.7%
ω^2_{VM}	$\Omega(5,5)$	0.01	Fixed		CV=10.0%	60.4%
ω^2_{KM}	$\Omega(6,6)$	0.01	Fixed		CV=10.0%	90.0%
ω^2_{sBASE}	$\Omega(9,9)$	0.381	Fixed		CV=61.7%	-
ω^2_{kint}	$\Omega(10,10)$	0.0218	26.3	0.0106 ; 0.0331	CV=14.8%	39.4%
ω^2_{kdeg}	$\Omega(11,11)$	0.0464	7.67	0.0394 ; 0.0533	CV=21.5%	4.7%
ω^2_{KSS}	$\Omega(12,12)$	0.0994	Fixed		CV=31.5%	48.8%
$\omega^2_{EPS,TCZ}$	$\Omega(13,13)$	0.128	Fixed		CV=35.7%	-11.6%
$\omega^2_{EPS,sIL6R}$	$\Omega(14,14)$	0.354	Fixed		CV=59.5%	6.1%
σ^2_{TCZ}	$\Sigma(1,1)$	1	Fixed		CV=100%	1.6%
σ^2_{sIL6R}	$\Sigma(2,2)$	0.015	Fixed		CV=12.2%	3.0%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·abs(SE/PE); 95% CI: 95% confidence interval; SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

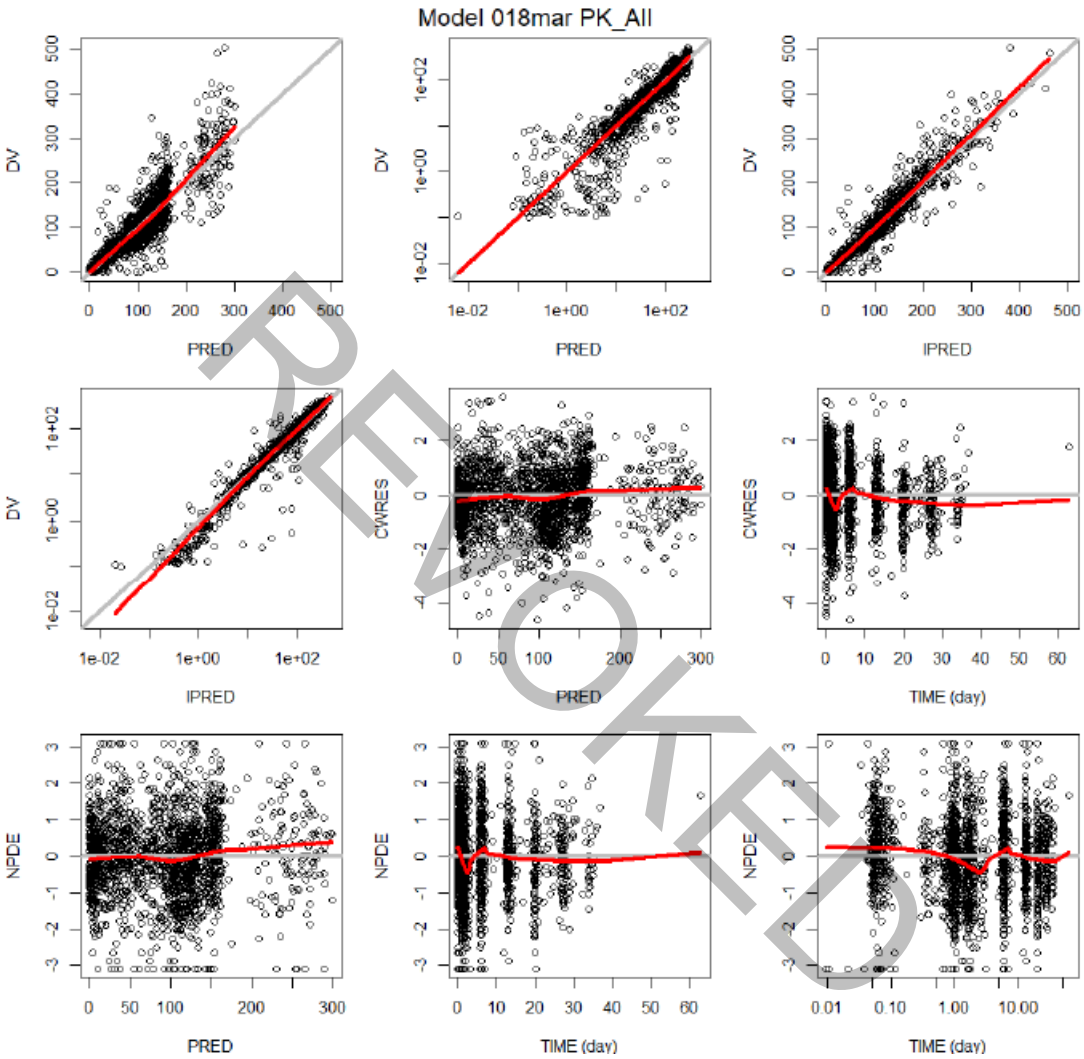
Source file: 018marParEst.csv (Covacta_DiagnosticPlots.R)

Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 7).

Figure 6 and Figure 7 show goodness-of-fit plots for the final model (Model 18mar) for TCZ and sIL-6R, respectively.

Figure 6. Goodness of fit for Model018mar: TCZ

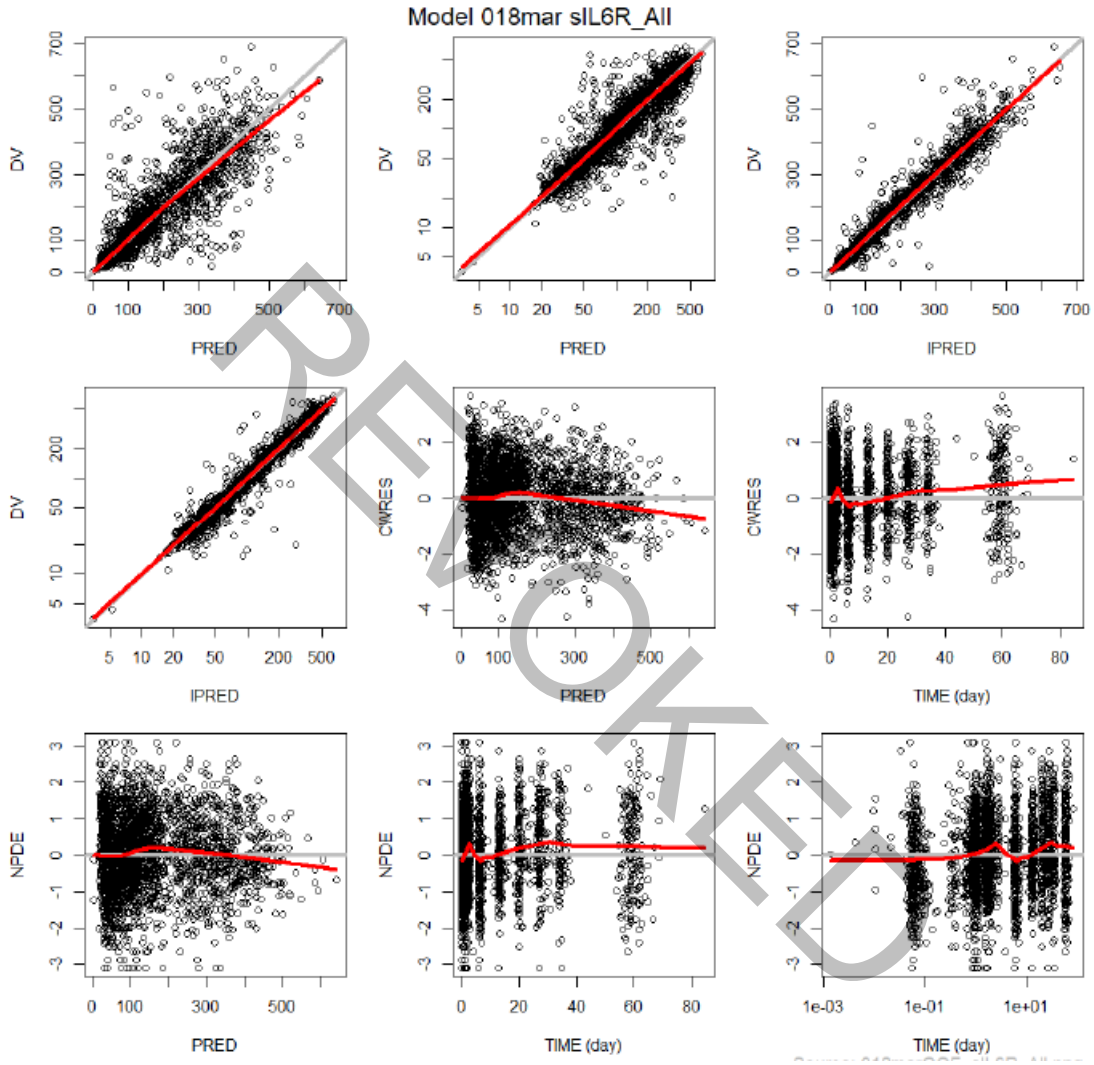
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **RES**: residuals; **TIME**: time after the first dose; **TAD**: time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.



Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Figure 14).

Figure 7. Goodness of fit for Model018mar: sIL6R

DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **RES**: residuals; **TIME**: time after the first dose; **TAD**: time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

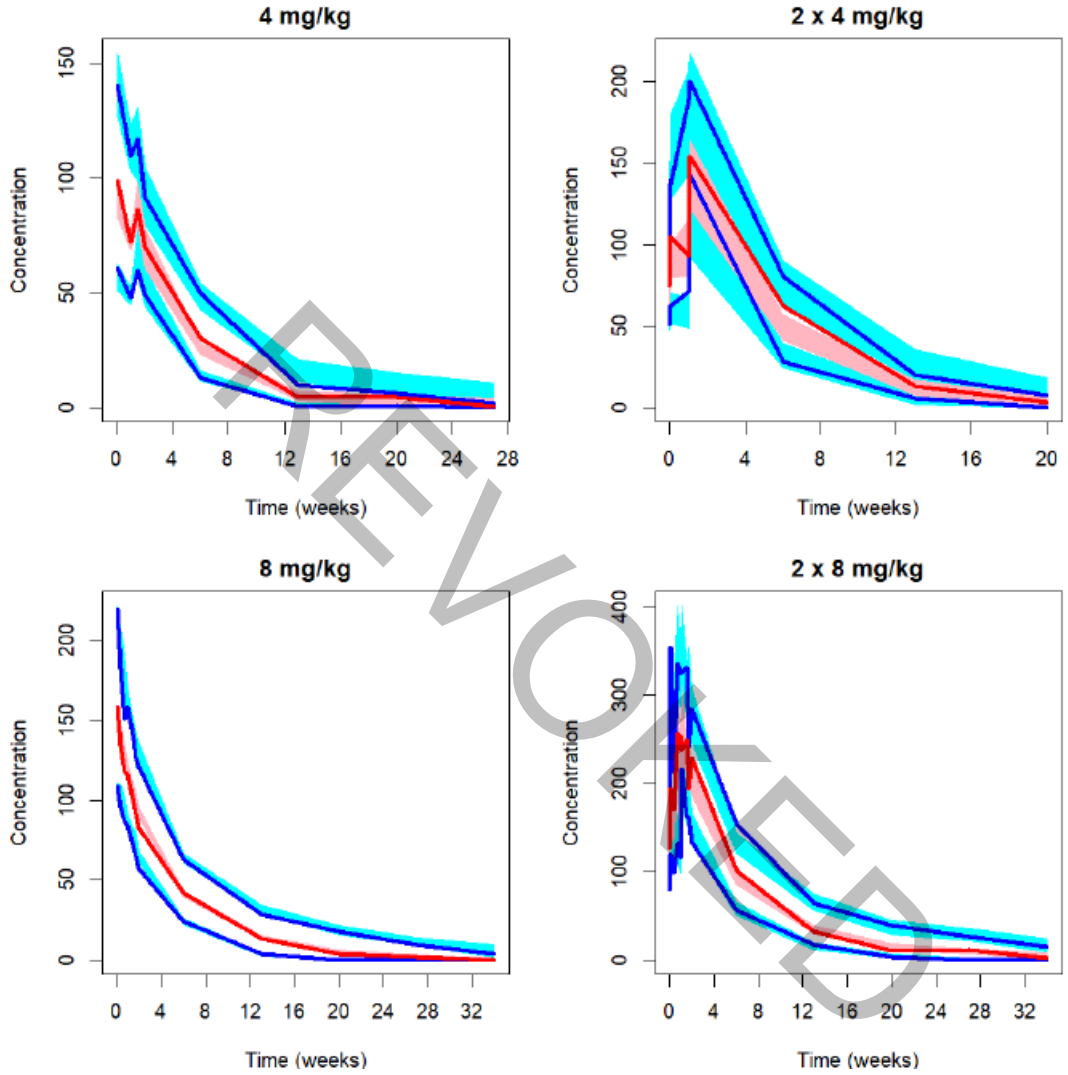


Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Figure 15).

Furthermore, a prediction-corrected visual predictive check (VPC) was used to evaluate the predictive performance of the tocilizumab model. The prediction from simulation of 1000 replicates with the same design (and overall population; as well as stratified by dose groups) using the estimates of the population means and variability from the final POP-PK model were overlaid with the observed data with the median values along with the 5th and 95th percentiles (with associated CIs) from the simulated concentration-time profiles. Visual predictive check for the final population pharmacokinetic model for tocilizumab serum concentrations and sIL6R level is presented in the Figure 8 and Figure 9, respectively.

Figure 8. Visual predictive check for model 018mar, by dose group: TCZ

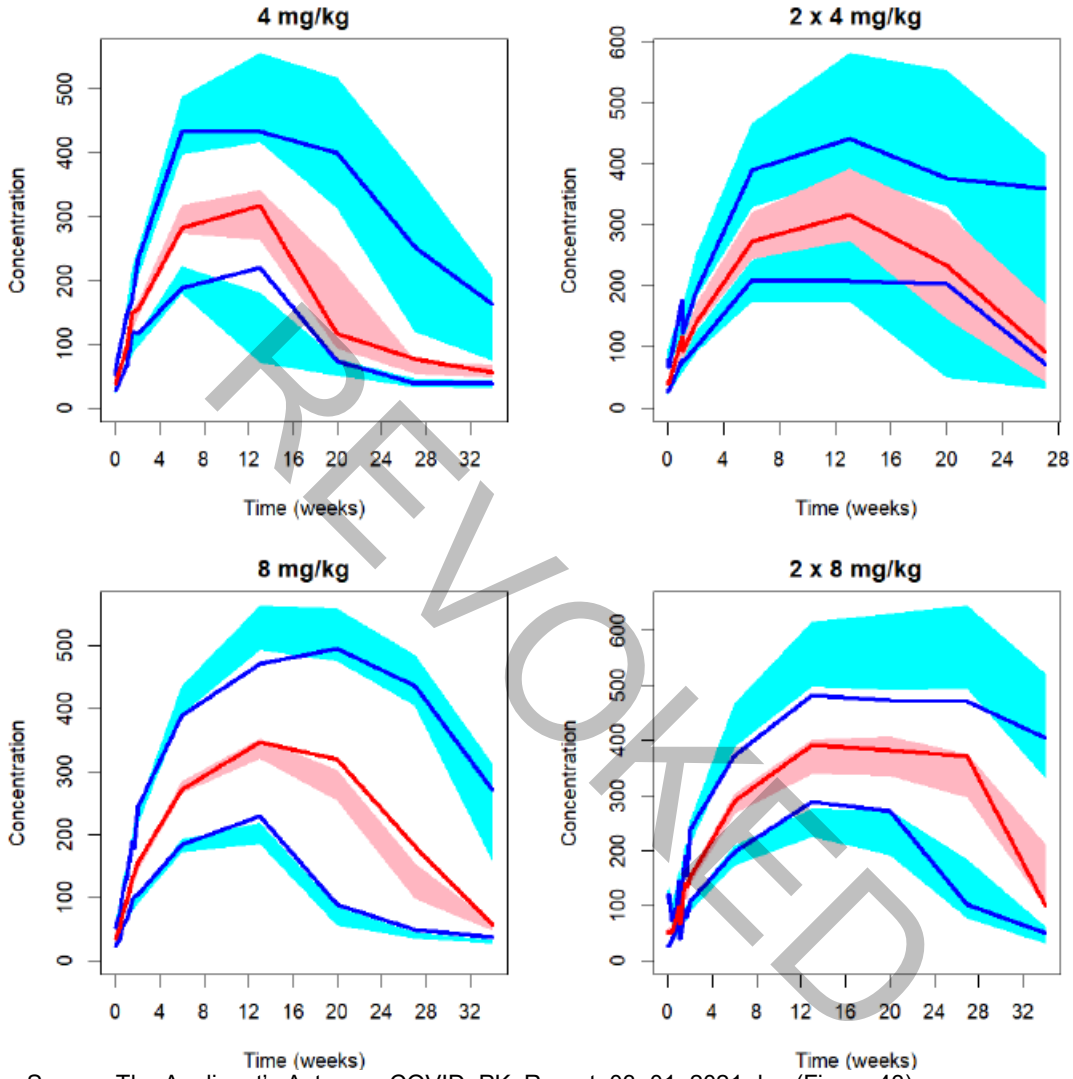
The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.



Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Figure 42).

Figure 9. Visual predictive check for Model 018mar, by dose group: sIL6R

The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.



Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Figure 43).

A summary of the estimated tocilizumab serum exposures and sIL-6R exposure for the COVDI-19 population using the final POP-PK model is described in Table 23 and Table 24, respectively.

Table 23. Estimates of tocilizumab exposure parameters

Dose group: 1 = 4 mg/kg; 2 = 2 x 4 mg/kg; 3 = 8 mg/kg; 4 = 2 x 8 mg/kg.

Study	Dose Group	N	AUC_{28} (µg/mL*day)	C_{max} (µg/mL)	C_{28} (µg/mL)
Mean (Standard Deviation)					
42380	3	224	776 (245)	152 (35.7)	1.41 (2.55)
42380	4	60	1710 (472)	280 (65)	9.54 (9.49)
42481	1	35	382 (143)	82.6 (19)	0.406 (1.86)
42481	2	12	903 (293)	159 (30.9)	1.96 (3.71)
42481	3	38	885 (251)	156 (32.1)	2.5 (3.92)
42481	4	9	1430 (268)	253 (51)	4.29 (3.86)
Median (Range)					
42380	3	224	732 (286-1630)	148 (82.3-318)	0.245 (0.0103-13.4)
42380	4	60	1660 (629-2850)	276 (145-464)	7.09 (0.0419-39.1)
42481	1	35	371 (196-1040)	82.2 (48.8-134)	0.0622 (0.00886-11.1)
42481	2	12	837 (592-1480)	150 (110-203)	0.407 (0.0946-12.9)
42481	3	38	849 (471-1500)	159 (101-234)	0.319 (0.00296-15.2)
42481	4	9	1330 (1130-1810)	228 (198-363)	3.5 (0.0229-12.4)
Geometric Mean (Coefficient of Variation)					
42380	3	224	739 (0.314)	148 (0.229)	0.38 (1.58)
42380	4	60	1650 (0.295)	273 (0.238)	4.08 (1.71)
42481	1	35	363 (0.31)	80.4 (0.233)	0.0719 (1.2)
42481	2	12	864 (0.309)	156 (0.2)	0.601 (1.48)
42481	3	38	851 (0.286)	153 (0.208)	0.604 (1.94)
42481	4	9	1410 (0.184)	249 (0.188)	2.05 (1.88)

Source file: 018marauc_exposureDataTable.csv.csv (Covacta_Exposure_Summary.R)

Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 9).

Table 24. Estimates of sIL6R parameters

Dose group: 1 = 4 mg/kg; 2 = 2 x 4 mg/kg; 3 = 8 mg/kg; 4 = 2 x 8 mg/kg.

Saturation: duration of receptor saturation above 90% or 95%, from day 0 to Day 28

Study	Dose Group	N	Baseline (ng/mL)	AUC_{28} (ng/mL*day)	$sIL6R_{max}$ (ng/mL)	$sIL6R_{28}$ (ng/mL)	Saturation (day)	
							>90%	>95%
Mean (Standard Deviation)								
42380	3	224	36 (11.8)	7750 (2460)	383 (101)	150 (137)	21.9 (4.9)	20 (5.33)
42380	4	60	38.5 (13.2)	9070 (1980)	395 (80.3)	312 (131)	26.7 (2.89)	25.8 (3.8)
42481	1	35	38.2 (11)	5440 (1550)	335 (85.1)	63.2 (67.7)	15.6 (3.68)	13.6 (3.53)
42481	2	12	35 (10.6)	8520 (2340)	398 (117)	167 (120)	23.8 (3.24)	21.8 (4.11)
42481	3	38	36.5 (10.1)	7880 (2090)	372 (86)	187 (141)	23.6 (4.53)	22 (5.17)
42481	4	9	37.6 (14.4)	8230 (1130)	364 (69.9)	257 (82.8)	26.4 (3.4)	25.4 (3.96)
Median (Range)								
42380	3	224	34.8 (3.54-78.4)	7450 (1950-15500)	382 (156-651)	79 (5.47-631)	21.8 (8.63-28)	19.4 (7.08-28)
42380	4	60	37.5 (18-82.8)	9290 (4780-15700)	407 (223-667)	347 (51.9-636)	28 (12-28)	28 (8.94-28)
42481	1	35	38.6 (17.5-69.4)	5090 (2720-10200)	321 (174-559)	48.4 (21.6-430)	15.2 (9.61-28)	13.3 (8.33-28)
42481	2	12	32.3 (20.2-60)	9090 (4770-13400)	394 (237-656)	132 (53.8-434)	23.5 (18.2-28)	20.9 (15.8-28)
42481	3	38	35.2 (18.7-56.8)	8020 (3090-13400)	364 (170-582)	123 (32.7-551)	24.2 (13.7-28)	22.2 (11.8-28)
42481	4	9	38.2 (20.6-60)	8430 (6360-10400)	355 (269-503)	298 (65.7-324)	28 (17.8-28)	27.2 (16.4-28)
Geometric Mean (Coefficient of Variation)								
42380	3	224	34.1 (0.355)	7330 (0.347)	370 (0.276)	103 (0.862)	21.3 (0.246)	19.2 (0.288)
42380	4	60	36.4 (0.343)	8840 (0.234)	387 (0.213)	272 (0.601)	26.5 (0.136)	25.5 (0.189)
42481	1	35	36.7 (0.283)	5240 (0.273)	325 (0.247)	52.1 (0.508)	15.3 (0.222)	13.2 (0.232)
42481	2	12	33.7 (0.287)	8210 (0.29)	382 (0.294)	132 (0.711)	23.6 (0.14)	21.4 (0.189)
42481	3	38	35.1 (0.288)	7570 (0.298)	362 (0.252)	135 (0.85)	23.1 (0.21)	21.4 (0.252)
42481	4	9	35.1 (0.401)	8160 (0.138)	358 (0.185)	237 (0.506)	26.2 (0.15)	25.1 (0.18)

Source file: 018marauc_exposureDataTable.csv.csv (Covacta_Exposure_Summary.R)

Source: The Applicant's Actemra_COVID_PK_Report_03_01_2021.doc (Table 10).

Based on the model of tocilizumab in COVID-19, the model estimation and in comparison with the exposure in other diseases, the Applicant concluded that the infection with COVID-19 and severity of the disease had major effects on elimination rate of tocilizumab and sIL6R bound to tocilizumab. Specifically, linear clearance in patients with COVID-19 was on average 124% (95%CI: 116-132%) higher than those in patients with RA. Clearance increased by 22.3% (95%CI: 21.2-23.4%) for each point on a 7-level SCALE. Elimination rate of bound sIL-6R was on average 145% (95%CI:137-153%) higher in patients with COVID-19 than

in patients with RA. It increased by 7% (95%CI: 5-8%) for each point on a 7-level SCALE. Degradation rate of free (unbound) sIL-6R was 69% (95%CI: 62-76%) higher in patients with COVID-19 than in patients with RA, with no noticeable dependence on disease severity. Mechanical ventilation had no effect on tocilizumab PK parameters.

Reviewer's comments: The reviewer has reviewed and validated the Applicant's population model of tocilizumab PK and sIL-6r. The reviewer also agreed with the Applicant's parameter estimation on the population model and PK exposure estimation after IV dosing of tocilizumab at 8 mg/kg either as single dose or as two doses separated by 8 hours.

*The applicant compared the exposure of tocilizumab in COVID-19 with that in patients with RA patients, but not in patients with other disease such as CRS. There is overlap in the estimated exposure in patients with COVID-19 and that in patients with other approved indications, even though the mean exposure is numerically less than that in RA patients and higher than that in CRS patients (*Table 17*).*

The estimation of sIL6R parameters was summarized with area under the curve (AUC28), maximum level ($sIL6R_{max}$), level at day 28 ($sIL6R_{28}$), and duration of receptor saturation, calculated as a Michaelis-Menten formula, above 90% or above 95%. The predictability of the above PD estimation on clinical endpoints has not been evaluated at this point. Descriptive analysis showed that there was a trend of lower level of sIL-6r and lower duration of receptor saturation above 90% from day 0 to day 28 in patients with more severe disease at 8 mg/kg single IV dose (Figure 4).

As requested by the Agency, the Applicant proposed pediatric use of tocilizumab for 2 years of age and above at 12 mg/kg given intravenously for body weight less than 30 kg and 8 mg/kg given intravenously for body weight greater than or equal to 30 kg. This proposed dosing regimen of TCZ in pediatric patients is based on predictions of TCZ PK and sIL6R dynamics in pediatric COVID−19 pneumonia patients using the integrated population PK-sIL6R model combining data from adult patients with RA and pediatric patients with sJIA and pJIA, and supplemented with data from adult patients with moderate to severe COVID-19 pneumonia. PopPK-sIL6R simulations (performed at ordinal scale 3 to 6) showed comparable TCZ exposure and duration of 90% sIL6R saturation in pediatric patients aged ≥ 2 years dosed with 12 mg/kg TCZ IV for body weight (BW) < 30 kg and 8 mg/kg TCZ IV for BW≥ 30 kg, as compared to adult patients with hospitalized COVID-19 pneumonia administered with 8 mg/kg TCZ IV and overlapping TCZ exposure to pediatric patients with other diseases (Figure 5 and Table 17).

Reviewer comments: In this simulation, the adult body weight of 90 kg was used because it is the average adult body weight in the two trials used for the population

PK model in COVID-19. This is acceptable. The simulation showed that the exposure as well as the PD response as presented as duration of 90% saturation in pediatric patients given the proposed dosing regimen is in the range of that in adults and overlapping TCZ exposure to pediatric patients with other diseases, and thus provided support from the PKPD perspective for the pediatric dosing.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR ACTEMRA® (tocilizumab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use ACTEMRA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous use
Original EUA Authorized Date: 06/2021

---------- EUA FOR ACTEMRA (tocilizumab)----------
The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of ACTEMRA for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). However, ACTEMRA is not FDA-approved for this use.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage of ACTEMRA is a single 60-minute intravenous infusion as follows:

Patients less than 30 kg weight	12 mg/kg
Patients at or above 30 kg weight	8 mg/kg

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

Maximum dosage in COVID-19 patients is 800 mg per infusion.

Preparation and Administration
- For patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)

----------CONTRAINDICATIONS----------
ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious Infections – do not administer ACTEMRA during any other concurrent active infection (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity – ACTEMRA treatment is not recommended in patients with elevated ALT or AST above 10 times the upper limit of the reference range. (5.3)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, and liver function tests. (5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – avoid use with ACTEMRA. (5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension and nausea (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to ACTEMRA (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Genentech at us_drug.safety@gene.com or call 1-888-835-2555 (6.2).

----------DRUG INTERACTIONS----------
Interactions with CYP450 Substrates: Caution should be exercised when co-administering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. (7)

----------USE IN SPECIFIC POPULATIONS---
- Pregnancy: ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. (8.1)
- Lactation: Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19. (8.2)
- Pediatric Use: ACTEMRA is not authorized or approved for emergency use for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients less than 2 years of age. (8.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of ACTEMRA® (tocilizumab) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. However, ACTEMRA is not FDA-approved for this use.

ACTEMRA is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of ACTEMRA under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is an FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition;
- The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s); and
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There is no adequate, approved and available alternative to ACTEMRA for treatment of adults and pediatric patients (2 years of age and older) hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. For information on clinical studies of ACTEMRA and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for COVID-19

The recommended dosage for emergency use of ACTEMRA authorized under this EUA given as a single 60-minute intravenous infusion is:

Recommended Intravenous Dosage for COVID-19	
Patients less than 30 kg weight	12 mg/kg
Patients at or above 30 kg weight	8 mg/kg

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

Maximum Dosage in COVID-19 patients is 800 mg per infusion.

ACTEMRA subcutaneous administration is not authorized for the treatment of COVID-19 patients.

No dose adjustment is required in elderly patients >65 years of age or in patients with mild or moderate renal impairment.

2.2 Preparation and Administration Instructions for Intravenous Infusion

ACTEMRA for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Use a sterile needle and syringe to prepare ACTEMRA.
- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.

– Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle (0.4 mL/kg and 0.6 mL/kg for 8 mg/kg and 12 mg/kg dosages, respectively)

– Step 2. Withdraw the amount of ACTEMRA for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

  - The fully diluted ACTEMRA solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) or room temperature for up to 24 hours and should be protected from light.
  - The fully diluted ACTEMRA solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
  - ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
  - Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
  - The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.

- ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates or discolorations are noted, the product should not be used.
- Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

3 DOSAGE FORMS AND STRENGTHS

Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

In COVID-19 patients, ACTEMRA should not be administered if patients have any other concurrent active infection, including localized infection.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis).

The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients with chronic or recurrent infection, or who have a history of a serious or an opportunistic infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient; initiate appropriate antimicrobial therapy, and closely monitor the patient.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials for chronic indications, primarily as complications of diverticulitis, in patients treated with ACTEMRA. Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation.

5.3 Hepatotoxicity

Patients hospitalized with COVID-19 may have elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19.

During randomized, controlled studies, treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. Serious cases of hepatic injury have been observed in patients taking intravenous or subcutaneous ACTEMRA chronically. In this setting, the time to onset for cases ranged from months to years after treatment initiation with ACTEMRA.

The decision to administer ACTEMRA should balance the potential benefit against the risks of acute treatment with ACTEMRA. ACTEMRA is not recommended in COVID-19 patients with elevated ALT or AST above 10 times the upper limit of the reference range. When ACTEMRA is used for treatment of COVID-19, ALT and AST should be monitored according to current standard clinical practice.

5.4 Laboratory Parameters

In randomized, controlled trials, patients receiving ACTEMRA had higher rates of neutropenia, thrombocytopenia, and elevations of ALT or AST.

ACTEMRA is not recommended in COVID-19 patients with an absolute neutrophil count (ANC) less than 1000 per mm^3, platelet count below 50,000 per mm^3, or ALT or AST above 10 times the upper limit of the reference range *[see Warnings and Precautions (5.3)]*. Monitor ALT, AST, neutrophils and platelet counts according to current standard clinical practice.

5.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA. These events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

5.6 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in rheumatoid arthritis clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.7 Active Hepatic Disease and Hepatic Impairment

ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

5.8 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA.

Refer to Section 5 **Warnings and Precautions** of the FDA-approved Prescribing Information for additional safety information on risks associated with chronic use of ACTEMRA.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in the Fact Sheet:

- Serious Infections *[see Warnings and Precautions (5.1)]*

6.1 Adverse Reactions from Clinical Studies

The adverse reaction rates observed in the clinical studies of ACTEMRA used to support this EUA cannot be directly compared to rates in the clinical studies of ACTEMRA for rheumatoid arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome and may not reflect the rates observed in clinical practice.

The safety evaluation of ACTEMRA in COVID-19 was based on 4 clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and 3 randomized, double-blind, placebo controlled trials (EMPACTA, COVACTA, and REMDACTA). Safety data from RECOVERY is not provided here as collection of adverse event data was limited. In EMPACTA, COVACTA, and REMDACTA, a total of 974 patients were exposed to ACTEMRA. Patients in EMPACTA, COVACTA, and REMDACTA received a single, 60-minute infusion of intravenous ACTEMRA 8 mg/kg (maximum dose of 800 mg). If clinical signs or symptoms worsened or did not improve, one additional dose of ACTEMRA 8 mg/kg could be administered between 8–24 hours after the initial dose.

<u>EMPACTA</u>

EMPACTA (NCT04372186) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in hospitalized adult patients with COVID-19 pneumonia. The safety analysis was based on 250 patients in the ACTEMRA arm and 127 patients in the placebo arm.

During the study, there were 29 (12%) deaths in the ACTEMRA arm and 15 (12%) in the placebo arm. Serious adverse events occurred in 38 (15%) patients in the ACTEMRA arm and 25 (20%) in the placebo arm. Serious infections occurred in 13 (5%) patients in the ACTEMRA arm and 9 (7%) in the placebo arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA arm and more commonly than observed in the placebo arm are summarized in **Table 1**.

Table 1. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA Arm and More Commonly than Observed in the Placebo Arm Through Day 60[a]

Preferred Term	ACTEMRA N = 250 n (%)	PLACEBO N = 127 n (%)
Constipation	16 (6%)	4 (3%)
Anxiety	15 (6%)	4 (3%)
Headache	8 (3%)	3 (2%)

[a] Patients are counted once for each category regardless of the number of reactions

COVACTA

COVACTA (NCT04320615) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in adult patients hospitalized with COVID-19 pneumonia. The safety analysis was based on 295 patients in the ACTEMRA arm and 143 patients in the placebo arm.

During the study, there were 72 (24%) deaths in the ACTEMRA arm and 36 (25%) in the placebo arm. Serious adverse events occurred in 116 (39%) patients in the ACTEMRA arm and 64 (45%) in the placebo arm. Serious infections occurred in 71 (24%) patients in the ACTEMRA arm and 42 (29%) in the placebo arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA arm and more commonly than observed in the placebo arm are summarized in **Table 2**.

Table 2. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA Arm and More Commonly than Observed in the Placebo Arm Through Day 60[a]

Preferred Term	ACTEMRA N = 295 n (%)	PLACEBO N = 143 n (%)
Urinary tract infection	24 (8%)	5 (3%)
Acute kidney injury	21 (7%)	7 (5%)
Hypertension	21 (7%)	3 (2%)
Diarrhea	18 (6%)	3 (2%)
Delirium	14 (5%)	3 (2%)
Insomnia	12 (4%)	5 (3%)
Thrombocytopenia	11 (4%)	2 (1%)
Alanine aminotransferase increased	10 (3%)	2 (1%)
Deep vein thrombosis	10 (3%)	3 (2%)

[a] Patients are counted once for each category regardless of the number of reactions

REMDACTA

REMDACTA (NCT04409262) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of intravenous ACTEMRA in

combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalized patients with COVID-19 pneumonia; only adult patients enrolled. The safety analysis was based on 429 patients in the ACTEMRA + RDV arm and 213 patients in the placebo + RDV arm.

During the study, there were 98 (23%) deaths in the ACTEMRA + RDV arm and 55 (26%) deaths in the placebo +RDV arm. Serious adverse events occurred in 141 (33%) patients in the ACTEMRA + RDV arm and 76 (36%) in the placebo + RDV arm. Serious infections occurred in 97 (23%) patients in the ACTEMRA + RDV arm and 59 (28%) in the placebo + RDV arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA + RDV arm and more commonly than observed in the placebo + RDV arm are summarized in **Table 3**.

Table 3. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA + RDV Arm and More Commonly than Observed in the Placebo + RDV Arm Through Day 60[a]

Preferred Term	ACTEMRA + RDV N = 429 n (%)	PLACEBO + RDV N = 213 n (%)
Constipation	54 (13%)	25 (12%)
Pneumonia	33 (8%)	10 (5%)
Septic shock	24 (6%)	10 (5%)
Hypokalemia	23 (5%)	6 (3%)
Hyperglycemia	22 (5%)	9 (4%)
Insomnia	21 (5%)	7 (3%)
Nausea	19 (4%)	7 (3%)
Anxiety	14 (3%)	4 (2%)
Hypoglycemia	14 (3%)	2 (1%)
Thrombocytopenia	14 (3%)	2 (1%)
Pain	13 (3%)	2 (1%)

[a] Patients are counted once for each category regardless of the number of reactions
RDV=remdesivir

The most common adverse reactions (≥3%) reported in ACTEMRA-treated patients and at least 1% more commonly than in the placebo arm from the pooled safety-evaluable population from the Phase 3, randomized, double-blind, studies EMPACTA, COVACTA, and REMDACTA were constipation, anxiety, diarrhea, insomnia, hypertension, and nausea.

Refer to Section 6 **Adverse Reactions** of the FDA-approved Prescribing Information for additional information on adverse reactions associated with chronic use of ACTEMRA.

6.2 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to ACTEMRA within 7 calendar days from the onset of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "ACTEMRA use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Genentech US Drug Safety
Fax: 1-650-238-6067 or 1-650-225-4630
E-mail: us_drug.safety@gene.com or call Genentech at 1-888-835-2555 to report adverse events.

The prescribing health care provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with ACTEMRA.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

7.1 Interactions with CYP450 Substrates

Inhibition of IL-6 may lead to increased metabolism of drugs that are CYP450 substrates. Caution should be exercised when co-administering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. The effect of ACTEMRA on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Refer to Section 7.2 **Drug Interactions** of the FDA-approved Prescribing Information for ACTEMRA for further details.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary
The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Refer to Section 8.1 **Pregnancy** of the FDA-approved Prescribing Information for additional information on risks and data associated with chronic use of ACTEMRA.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

The FDA has granted an EUA for the emergency use of ACTEMRA for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Pediatric use is supported by evidence justifying emergency use of ACTEMRA for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, as well as safety and dosing information of ACTEMRA in pediatric patients for other uses. However, ACTEMRA is not approved for this use *[see Dosage and Administration (2), Clinical Studies (14)]*.

ACTEMRA is not authorized or approved for the emergency use for patients younger than 2 years of age.

8.5 Geriatric Use

In EMPACTA, COVACTA, and REMDACTA combined, 375/973 (39%) patients in the ACTEMRA arm and 170/482 (35%) in the placebo arm were 65 years of age or older. No overall differences in safety or effectiveness of ACTEMRA were observed between patients 65 years of age and older and those less than 65 years of age in these studies.

In RECOVERY, 691/2022 (34%) patients allocated to ACTEMRA and 739/2094 (35%) patients allocated to usual care alone were 70 years of age or older. No overall differences in effectiveness of ACTEMRA were observed between patients 70 years of age and older and those less than 70 years of age in this study.

11 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to pale yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.5. Each single-dose vial, formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation.

12.2 Pharmacodynamics

Refer to Section 12.2 **Pharmacodynamics** of the FDA-approved Prescribing Information for additional information on pharmacodynamics data associated with chronic use of ACTEMRA.

12.3 Pharmacokinetics

The pharmacokinetics of tocilizumab in COVID-19 adult patients was estimated by a population pharmacokinetic analysis of a dataset composed of 380 adult patients treated with 8 mg/kg intravenously.
For one dose of 8 mg/kg intravenous tocilizumab, the estimated median (range) Cmax and Cday28 of tocilizumab were 151 (77.5-319) mcg/mL and 0.229 (0.00119-19.4) mcg/mL, respectively.
For two doses of 8 mg/kg intravenous tocilizumab separated by 8 hours, the estimated median (range) Cmax of tocilizumab was 290 (152-604) mcg/mL.

Distribution

In COVID-19 adult patients treated with one or two infusions of 8 mg/kg intravenously separated by 8 hours, the estimated central volume of distribution was 4.52 L, and the estimated peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Elimination

In COVID-19 adult patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of intravenous 8 mg/kg. The average linear clearance in the population pharmacokinetic analysis was estimated to be 17.6 mL per hour in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL per hour in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL per hour in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL per hour in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support).

Specific Populations

In COVID-19 adult patients, exposure following body-weight-based intravenous dosing (8 mg/kg tocilizumab up to 100 kg body weight with a maximum dose of 800 mg tocilizumab) was dependent on body weight and disease severity. Within a specified OS category, compared to patients with a mean body weight of 80 kg, exposure was 20% lower in patients weighing less than 60 kg. Exposure in patients weighing more than 100 kg was in the same range as exposure in patients with a mean body weight of 80 kg. For an 80 kg patient, exposure decreases as disease severity increases; for each category increase on the OS, exposure decreases consistently by 13%.

Refer to Section 12.3 **Pharmacokinetics** of the FDA-approved Prescribing Information for additional information on pharmacokinetics associated with chronic use of ACTEMRA.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hospitalized Patients with COVID-19

The clinical evaluation of ACTEMRA in hospitalized COVID-19 patients was based on 4 clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and 3 randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA).

RECOVERY

RECOVERY (NCT04381936) was a large, randomized, controlled, open-label, multi-center platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19 pneumonia. All eligible patients received usual care and underwent an initial (main) randomization. Eligible patients for the trial had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization to receive either intravenous ACTEMRA or usual care alone.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomized, with 2022 patients in the ACTEMRA + usual care arm and 2094 patients in the usual care alone arm.The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White (76%). At baseline, 14% of patients required invasive mechanical ventilation, 41% of patients required non-invasive ventilation or high-flow oxygen, and 45% of patients required low flow oxygen; 82% of patients were reported to be receiving systemic corticosteroids.

The primary outcome was time to death through Day 28. The hazard ratio comparing the ACTEMRA + usual care arm to the usual care alone arm was 0.85 (95% CI: 0.76 to 0.94), a statistically significant result ($p = 0.0028$). The probabilities of dying by Day 28 were estimated to be 30.7% and 34.9% in the ACTEMRA and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis. The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).

The median time to hospital discharge was 19 days in the ACTEMRA + usual care arm and >28 days in the usual care arm (hazard ratio [95% CI] = 1.22 [1.12 to 1.33]).

Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the ACTEMRA + usual care arm and 42% (754/1800) in the usual care alone arm (risk ratio [95% CI] = 0.84, [0.77 to 0.92]).

EMPACTA

EMPACTA (NCT04372186) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in hospitalized, non-ventilated adult patients with COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) result, had pneumonia confirmed by radiography, and had SpO2 < 94% on ambient air. Patients were randomized at a 2:1 ratio to receive one infusion of either 8 mg/kg ACTEMRA, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 389 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication, grouped as randomized (249 in the ACTEMRA arm; 128 in the placebo arm). In the mITT population (n=377)

at randomization, median age was 57 years (range 20-95); 59.2% of patients were male, 56.0% were of Hispanic or Latino ethnicity, 52.8% were White, 20.4% were American Indian/Alaska Native, 15.1% were Black/African American and 1.6% were Asian. At baseline, 35 (9.3%) patients were not on supplemental oxygen, 242 (64.2%) patients required low flow oxygen and 100 (26.5%) patients required high-flow oxygen. The median time from symptom onset was 8.0 days. At baseline, across treatment arms, 72.7% patients reported systemic corticosteroids use and 47.7% received remdesivir.

The primary efficacy endpoint was the cumulative proportion of patients who required mechanical ventilation or died by Day 28 estimated by the Kaplan-Meier method. For patients who received ACTEMRA, there was an observed improvement in the time to progression to mechanical ventilation or death compared to patients who received placebo (log-rank p value = 0.0360; HR [95% CI] = 0.56 [0.33 to 0.97]). The cumulative proportion of patients who required mechanical ventilation or died by Day 28 was 12.0% (95% CI, 8.52% to 16.86%) in the ACTEMRA arm and 19.3% (95% CI, 13.34% to 27.36%) in the placebo arm.

The median time to hospital discharge or “ready for discharge” (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) through Day 28 was 6.0 days in the ACTEMRA arm and 7.5 days in the placebo arm (HR [95% CI]=1.16 [0.91 to 1.48]).

Mortality at Day 28 was 10.4% in the ACTEMRA arm versus 8.6% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 2.0% [95% CI, -5.2% to 7.8%]).

COVACTA

COVACTA (NCT04320615) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in adult patients hospitalized with severe COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive RT-PCR result, had pneumonia confirmed by radiography, and had oxygen saturation of 93% or lower on ambient air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less. Patients were randomized at a 2:1 ratio to receive one infusion of either 8mg/kg ACTEMRA, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 452 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication, grouped as randomized (294 in the ACTEMRA arm; 144 in the placebo arm). For the overall mITT population (n=438) at randomization, median age was 62 years (range 22-96); 69.9% of patients were male, 32.2% were of Hispanic or Latino ethnicity, 57.5% were White, 15.1% were Black/African American and 8.7% were Asian. At baseline, 3.4% of patients were not on supplemental oxygen, 27.9% were on low flow oxygen, 30.4% were on non-invasive ventilation or high flow oxygen, and 38.4% were on invasive mechanical ventilation. The median time from symptom onset was 11.0 days. At baseline, across treatment arms, 22.4% patients reported systemic corticosteroids use and 5.7% received remdesivir.

The primary efficacy endpoint was clinical status on Day 28 assessed on a 7-category ordinal scale consisting of the following categories:

1. Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen);
2. Non–ICU hospital ward (or “ready for hospital ward”), not requiring supplemental oxygen;
3. Non–ICU hospital ward (or “ready for hospital ward”), requiring supplemental oxygen;
4. ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen;
5. ICU, requiring intubation and mechanical ventilation;
6. ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy);
7. Death

There were no statistically significant differences observed in the distributions of clinical status on the 7-category ordinal scale at Day 28 when comparing the ACTEMRA arm to the placebo arm.

The median time to hospital discharge or “ready for discharge” was 20 days in the ACTEMRA arm and 28 days in the placebo arm (HR=1.35 [95% CI, 1.02 to 1.79]).

Mortality at Day 28 was 19.7% in the ACTEMRA arm versus 19.4% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 0.3% [95% CI, -7.6 to 8.2]).

REMDACTA

REMDACTA (NCT04409262) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of intravenous ACTEMRA in combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalized patients with severe COVID-19 pneumonia. Eligible patients were at least 12 years of age with confirmed SARS-CoV-2 infection, including a positive polymerase chain reaction (PCR) and pneumonia confirmed by radiography, and required supplemental oxygen > 6 L/min to maintain SpO2 >93%. Patients were randomized at a 2:1 ratio to receive blinded treatment of either ACTEMRA + RDV or a matching placebo + RDV. Study treatment was given in combination with standard of care. Patients assigned to the ACTEMRA + RDV arm received one infusion of ACTEMRA 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo + RDV arm received one infusion of placebo. For both arms, if clinical signs or symptoms worsened or did not improve one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 649 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of all patients who received any amount of ACTEMRA/placebo, grouped as randomized (430 in the ACTEMRA + RDV arm; 210 in the placebo + RDV arm). For the overall mITT population (n=640) at randomization, median age was 60 years (range 20-93); 63.3% of patients were male, 51.6% were Hispanic or Latino ethnicity, 67.0% were White, 10.9% were Black/African American and 3.4% were Asian. At baseline, 6.6% were on low flow oxygen, 79.8% were on non-invasive ventilation or high flow oxygen, and 13.6% were on invasive mechanical ventilation. The median time from symptom onset was 8 days. At baseline, the majority of patients had received corticosteroids (84.2% across treatment arms).

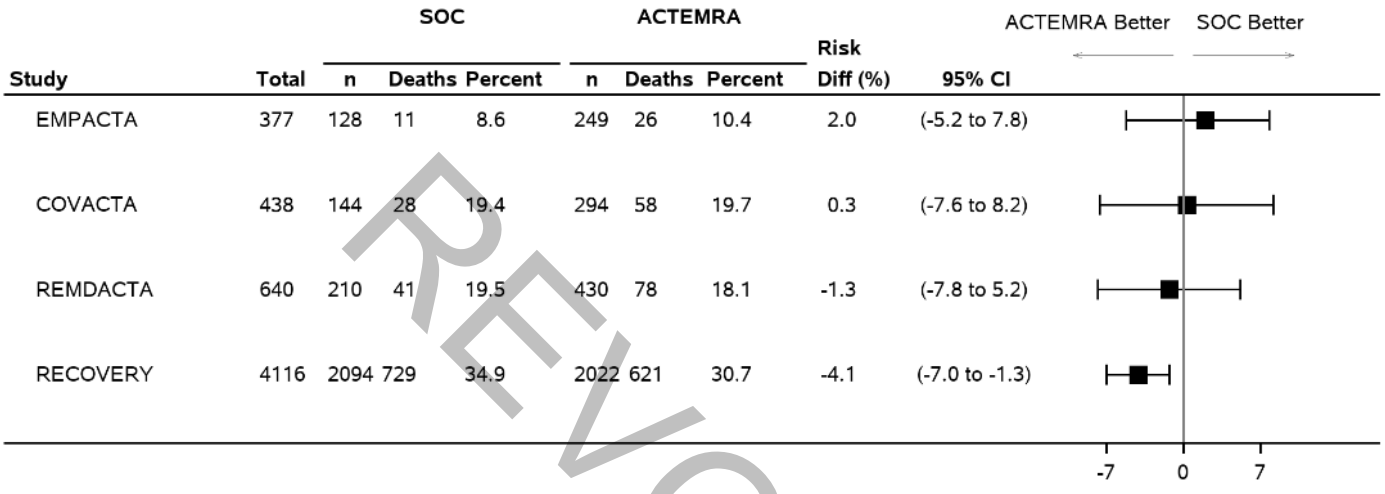
The primary efficacy endpoint was time from randomization to hospital discharge or “ready for discharge” up to Day 28. There were no statistically significant differences observed between treatment arms with respect to time to hospital discharge or “ready for discharge” through Day 28 (HR 0.965 [95% CI: 0.78 to 1.19]) or time to mechanical ventilation or death through Day 28 (HR 0.980 [95% CI: 0.72 to 1.34]).

Mortality at Day 28 was 18.1% in the ACTEMRA + RDV arm versus 19.5% in the placebo + RDV arm (weighted difference [ACTEMRA arm - placebo arm]: -1.3% [95% CI, -7.8% to 5.2%]).

Mortality Across Trials

Mortality outcomes were assessed at Day 28 across all 4 trials. These data, expressed as risk differences comparing ACTEMRA to placebo or standard of care treatment alone, are summarized in **Figure 1**.

Figure 1. Risk Differences Through Day 28 for EMPACTA, COVACTA, REMDACTA and RECOVERY



EMPACTA, COVACTA, and REMDACTA risk differences and 95% CIs were calculated as weighted differences using the Cochran-Mantel-Haenszel test stratified by study-specific stratification factors at randomization.
RECOVERY risk difference and 95% CI were estimated using the Kaplan-Meier approach.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ACTEMRA injection is a preservative-free, sterile clear, colorless to pale yellow solution. Under this EUA, ACTEMRA is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Storage and Handling

Do not use beyond expiration date on the container or package. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials from light by storage in the original package until time of use.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS" (https://www.gene.com/download/pdf/actemra_eua_patient_fact_sheet.pdf) and provide them with a copy of this Fact Sheet prior to administration of ACTEMRA. However, if providing this information will delay the administration of ACTEMRA to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after ACTEMRA administration.

18 MANUFACTURER INFORMATION

Manufactured by Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

To access the most recent ACTEMRA COVID-19 Fact Sheets and authorization letter, visit https://www.actemrahcp.com/covid-19.

Fact Sheet for Patients, Parents and Caregivers
Emergency Use Authorization (EUA) of ACTEMRA® (tocilizumab) for Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you or your child with ACTEMRA for the treatment of coronavirus disease 2019 (COVID-19). Taking ACTEMRA may benefit certain people in the hospital with COVID-19 who are receiving corticosteroids and require supplemental oxygen, or a machine that helps with their breathing (ventilator) or a machine that adds oxygen to the blood outside the body (extracorporeal membrane oxygenation or ECMO). This Fact Sheet contains information to help you understand the risks and benefits of taking ACTEMRA you or your child have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make ACTEMRA available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). ACTEMRA is not FDA-approved for this use. Read this Fact Sheet for information about ACTEMRA. Talk to your or your child's healthcare provider about your options or if you have any questions. It is your choice for you or your child to take ACTEMRA or stop it at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. You or your child can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your or your child's other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your or your child's other medical conditions to become worse.

What is ACTEMRA?
ACTEMRA is a FDA-approved prescription medicine that is used to treat adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well, to treat adults with giant cell arteritis (GCA), for slowing the rate of decline in lung function in adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD), and to treat people aged 2 years and older with polyarticular juvenile idiopathic arthritis, systemic

juvenile idiopathic arthritis, and chimeric antigen receptor (CAR) T-cell induced severe or life-threatening Cytokine Release Syndrome (CRS). ACTEMRA is not FDA- approved to treat COVID-19. ACTEMRA is not authorized for subcutaneous use in people with COVID-19.

There is limited information known about the safety or effectiveness of using ACTEMRA to treat people in the hospital with COVID-19. Available results from clinical trials in adults indicate that treatment with ACTEMRA may decrease the risk of dying in hospitalized patients with COVID-19 who are receiving corticosteroids and who require supplemental oxygen, or a ventilator or ECMO. The safety and effectiveness of ACTEMRA have not been studied in children hospitalized with COVID-19.

The FDA has authorized the emergency use of ACTEMRA for the treatment of COVID-19 in hospitalized adults and children (2 years of age and older) who are receiving corticosteroids and who require supplemental oxygen, or a ventilator or ECMO under an EUA. For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

What should I tell my or my child's healthcare provider before I or my child take ACTEMRA?
Tell your or your child's healthcare provider if you or your child:

- Have an infection other than COVID-19
- Have liver problems
- Have any stomach-area pain or have had diverticulitis or ulcers in your stomach or intestines
- Have any allergies, including to any of the ingredients in ACTEMRA
- Have or had a condition that affects your nervous system, such as multiple sclerosis
- Have recently received or are scheduled to receive a vaccine
- Plan to have surgery or a medical procedure
- Are pregnant or plan to become pregnant
- Are breast-feeding a child or plan to breastfeed
- Have any serious illnesses
- Are taking any medications (prescription, over-the-counter, vitamins, or herbal products)

How will I receive ACTEMRA?
ACTEMRA is given to you or your child through a vein (intravenous or IV) 1 time as a single dose. If you or your child do not improve after receiving one dose of ACTEMRA, a second dose may be given at least 8 hours after the first dose.

Who should generally not take ACTEMRA?
Do not take ACTEMRA if:
You or your child are allergic to tocilizumab, the active ingredient in ACTEMRA, or any of the ingredients in ACTEMRA. For a complete list of ingredients in ACTEMRA, refer to the Medication Guide for ACTEMRA® (tocilizumab) at https://www.gene.com/download/pdf/actemra_medguide.pdf.

What are the important possible side effects of ACTEMRA?
The most important side effects of ACTEMRA are:

Serious infections: ACTEMRA is a medicine that affects your or your child's immune system. ACTEMRA can lower the ability of your or your child's immune system to fight infections other than COVID-19.

ACTEMRA can make you or your child more likely to get infections or worsen any infection that you or your child have, other than COVID-19.

Tears (perforation) of the stomach or intestines: Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

Liver problems (hepatotoxicity): Some people taking ACTEMRA have experienced serious life-threatening liver problems, which required a liver transplant or led to death.

Changes in certain laboratory test results: Your or your child's healthcare provider should do blood tests before you or your child start receiving ACTEMRA. You or your child should not receive ACTEMRA if your or your child's neutrophil (white blood cells that help the body fight off bacterial infections) or platelet (blood cells that help with blood clotting and stop bleeding) counts are too low or your or your child's liver function tests are too high.

Allergic reactions: Tell your or your child's healthcare provider right away if you or your child have symptoms such as rash, swelling of your lips, tongue, or throat, or hives (raised red patches of skin that are often very itchy). This may mean you or your child are having an allergic reaction.

Nervous system problems: While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

For more information see the Medication Guide for ACTEMRA® (tocilizumab), at https://www.gene.com/download/pdf/actemra_medguide.pdf.

What other treatment choices are there?
Like ACTEMRA, FDA may allow for the emergency use of other medicines to treat people in the hospital with COVID-19. Go to https://www.covid19treatmentguidelines.nih.gov/ for information on the emergency use of other medicines that are not approved by FDA to treat people in the hospital with COVID-19. Please consult your or your child's healthcare provider on which medicine or combination of medicines might be right for you or your child. Your or

your child's healthcare provider may talk with you about clinical trials you or your child may be eligible for.

It is your choice for you or your child to be treated or not to be treated with ACTEMRA. Should you decide not to receive it or for your child to not receive it, it will not change your or your child's standard medical care.

What if I am pregnant or breastfeeding?
There is limited experience giving ACTEMRA to pregnant women or breastfeeding mothers. ACTEMRA may harm your unborn baby. It is unknown if ACTEMRA passes into your breast milk. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

Pregnancy exposure registry
Genentech has a registry for pregnant women who take ACTEMRA. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking ACTEMRA, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

How do I report side effects or adverse events with ACTEMRA?
Contact your or your child's healthcare provider if you or your child have any side effects that bother you or do not go away. Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to Genentech, Inc. by calling 1-888-835-2555.

How can I learn more about COVID-19?
- Ask your or your child's healthcare provider
- Visit https://www.cdc.gov/COVID19
- Contact your local or state public health department

What is an Emergency Use Authorization?
The United States FDA has made ACTEMRA available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

ACTEMRA as a treatment for COVID-19 has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. All of these

criteria must be met to allow for the medicine to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for ACTEMRA is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless terminated or revoked (after which the products may no longer be used under the EUA).

This Fact Sheet may be updated as new data become available. The most recent version of this Fact Sheet is available at https://www.gene.com/download/pdf/actemra_eua_patient_fact_sheet.pdf for download.

Genentech, Inc.
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Revised: 06/2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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06/24/2021 03:17:53 PM

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06/24/2021 03:26:58 PM

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06/24/2021 03:34:15 PM

EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFLAMMATION AND IMMUNOLOGY
DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE
ADDENDUM

EUA:	99
Product:	Tocilizumab
Sponsor:	Hoffmann-La Roche Ltd
Intended Population:	Hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

This addendum references the EUA summary review for tocilizumab for the treatment of COVID-19, dated June 24, 2021.

On page 4 of the summary EUA review Section III, Proposed Use and Dosing of the Product Under the EUA, in the 1st sentence under the sub-bullet for rationale for dosing regimen, the terms “double-blind” and “placebo-“ should be removed given that RECOVERY was an open-label trial with the comparator arm reflecting usual care alone.

On page 10 of the summary EUA review Section VIII, Human Clinical Efficacy, in the 3rd sentence of the 4th paragraph, the secondary endpoints are listed, and “duration of hospital stay” should be replaced with “time to hospital discharge.”

On page 14 of the summary EUA review Section VIII, Human Clinical Efficacy, the term “time to” should be removed from the subheading “Time to Mechanical Ventilation (MV) or Death” because the analysis was based on cumulative incidence. Additionally, in the 2nd sentence of the paragraph that follows, the term “hazard” should be replaced with “risk” and “time to” should be removed.

On page 17 of the summary EUA review Section VIII, Human Clinical Efficacy, the last sentence in the “Mortality” subsection should instead state that “However, 13.1% of patients did not have Day 60 mortality collected during the study.”

On page 24 of the summary EUA review Section VIII, Human Clinical Efficacy, the last sentence in the “Mortality” subsection should instead state that “However, 8.8% of patients did not have Day 60 mortality collected during the study.”

On page 26 of the summary EUA review Section VIII, Human Clinical Efficacy, Figure 2 should include a footnote stating that the risk differences presented in the figure are based on Kaplan-Meier estimates of mortality.

On page 28 of the summary EUA review Section VIII, Human Clinical Efficacy, subsection Integrated Analysis of Efficacy, the end of the 2nd sentence of the 2nd paragraph on the page should be amended to read as "…patients on non-invasive and invasive mechanical ventilation…"

On pages 34, 37, and 39 of the summary EUA review Section IX, Human Clinical Safety, the sentences referring to "Hy's Law" should be amended to refer to "laboratory criteria for potential Hy's Law."

None of these corrections alter the conclusion of the review or alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients, Providers, and Caregivers.

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/s/

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07/12/2021 02:51:13 PM

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