NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	BLA 125276/S-149
Priority or Standard	Standard
Submit Date(s)	October 9, 2024
Received Date(s)	October 9, 2024
PDUFA Goal Date	August 9, 2025
Division/Office	DPACC/OII
Review Completion Date	August 5, 2025
Established/Proper Name	Tocilizumab
(Proposed) Trade Name	Actemra
Pharmacologic Class	Interleukin-6 antagonist monoclonal antibody
Applicant	Genentech, Inc.
Dosage form	Intravenous injection
Applicant proposed Dosing Regimen	Patients less than 30 kg weight: 12 mg per kg IV Patients at or above 30 kg weight: 8 mg per kg IV Administered by a 60-minute intravenous infusion
Applicant Proposed Indication(s)/Population(s)	To expand the approved COVID-19 population to pediatric patients: Hospitalized adult and pediatric patients aged 2 years and older with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Hospitalized adult and pediatric patients aged 2 years and older with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	840539006: Disease caused by severe acute respiratory syndrome coronavirus (disorder)
Recommended Dosing Regimen	Patients less than 30 kg weight: 12 mg per kg once Patients at or above 30 kg weight: 8 mg per kg once Administered by a 60-minute intravenous infusion

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Glossary

AC	Advisory committee
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAR T-cell	Chimeric antigen receptor T-cell
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Contract research organization
CRS	Cytokine release syndrome
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
DMC	Data monitoring committee
DPACC	Division of Pulmonary, Allergy, and Critical Care
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCTD	Electronic common technical document
ETASU	Elements to assure safe use
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good clinical practice
GRMP	Good review management practice
HHS	Health and Human Services
ICH	International Conference on Harmonization
ICU	Intensive care unit
Ig	Immunoglobulin
IL-6	Interleukin 6

IMV	Invasive mechanical ventilation
IND	Investigational New Drug
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NME	New molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing information
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PP	Per protocol
PPI	Patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGE	Special government employee
sJIA	Systemic juvenile idiopathic arthritis
SOC	Standard of care
TEAE	Treatment emergent adverse event
TCZ	Tocilizumab

1 Executive Summary

1.1. Product Introduction

Tocilizumab (TCZ) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 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.

TCZ binds 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.

The TCZ COVID-19 development program resulted in an Emergency Use Authorization (EUA) for adult and pediatric patients >2 years of age, and an approval for adult patients. EUA-99, issued June 24, 2021, authorized use of TCZ in hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal mechanical oxygenation (ECMO). TCZ was subsequently approved December 21, 2022, for a patient population of hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). TCZ authorization for pediatric patients 2 to 17 years of age continued under EUA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of TCZ for the hospitalized pediatric population with COVID-19 is supported by extrapolation of efficacy from previously approved adult and pediatric populations and through predicted pharmacokinetic data modeling and simulation for pediatric patients aged 2 years and older (Section 6.1.1); the Office of Clinical Pharmacology recommends approval for the proposed indication.

The safety of TCZ for pediatric patients ≥2 years of age hospitalized with COVID-19 requiring additional oxygen support is adequately demonstrated by the adult and pediatric safety data discussed in Section 8.1.4. The uncertainties present in the safety data are acceptable in the context of the benefit-risk assessment for this indication.

Based on the conclusions of substantial evidence of effectiveness and adequate demonstration of safety, the review team recommends approval of TCZ for pediatric patients ≥2 years of age hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) at doses of 12 mg/kg IV once for patients less than 30 kg weight or 8 mg/kg IV once for patients at or above 30 kg weight. With the approval of tocilizumab for the proposed COVID-19 indication, EUA-99 will be revoked.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Acknowledging residual uncertainties in the safety data, the available data support a favorable benefit-risk assessment and the approval of intravenous tocilizumab (TCZ) as a single dose at the doses noted above for pediatric patients ≥2 years of age hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The effectiveness of TCZ for this hospitalized pediatric population with COVID-19 is supported by extrapolation of efficacy from previously approved adult and pediatric populations through PK-exposure modeling.

The safety of TCZ for the proposed pediatric population comprises support from multiple sources of data from subjects with COVID-19 and other indications, in the context of a serious condition with unmet need in the pediatric population, and the single-dose use-case of hospitalized COVID-19. The conclusion of safety for pediatric subjects hospitalized for COVID-19 relies primarily on extrapolation from the established safety of chronic use of TCZ in systemic juvenile idiopathic arthritis (sJIA) among subjects 2 years of age and older, including 12-week, randomized, double-blind, controlled, trial data from study WA18221. Safety in the pediatric COVID-19 indication is also supported in part by the extrapolation of safety information from the adult COVID-19 indication, supplemented by available data from study WA43811 and the Applicant's EUA pharmacovigilance database that do not suggest new safety signals specific to the use of a single dose of TCZ in pediatric subjects hospitalized with COVID-19.

The review team acknowledges that the safety data from the adult safety database, study WA18221, study WA43811, and the Applicant's EUA pharmacovigilance database present some uncertainties when applied to the safety assessment of pediatric COVID-19. However, the following key points were considered to conclude that the safety of TCZ in pediatric patients hospitalized with COVID-19 who require supplemental oxygen support has been adequately demonstrated:

- The available COVID-19 data were collected during a public health emergency due to a pandemic viral infection in which vulnerability to disease, available treatments, and outcomes were evolving rapidly.
- In addition to chronic pediatric use in sJIA since its approval in April 2011 and use in other pediatric indications including polyarticular juvenile idiopathic arthritis (pJIA) and chimeric antigen receptor T-cell (CAR T-cell) associated cytokine release syndrome (CRS), single doses of TCZ for pediatric subjects with the hospitalized COVID-19 indication have been used clinically under Emergency Use Authorization since June 24, 2021.
- The public health emergency has expired, and the prevalence and severity of COVID-19 as a clinical entity has been significantly mitigated by the introduction of safe and effective vaccines and evolving immunity in the broader population of adults and children. In this context, collection of further prospective safety data on subject 2 years of age and older hospitalized with COVID-19 is infeasible unless the current COVID-19 milieu changes.

While the prevalence of hospitalized COVID-19 has decreased in pediatric subjects since the issuance of the EUA, the population of pediatric subjects who develop serious disease due to SARS-CoV-2 and are hospitalized with COVID-19 and require supplemental oxygen or mechanical respiratory support still represents a serious, life-threatening disease with an unmet need for safe and effective therapies. In this context, despite the uncertainties presented, the available safety data are sufficient to support a conclusion of safety for a single dose of intravenous TCZ within a benefit-risk framework that relies on treatment of a serious, life-threatening disease and an unmet need for safe and effective therapies for which further data collection is impractical.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The full spectrum of SARS-CoV-2 infection and COVID-19 is broad and spans a wide range of manifestations including asymptomatic infection, mild symptomatic illness with fever and headaches, pneumonia requiring hospitalization, and life-threatening respiratory failure with septic shock and multiple organ dysfunction syndrome. • Despite the introduction of safe and effective vaccines, additional therapeutic options, and evolution of the SARS-CoV-2 virus, children continue to be hospitalized with COVID-19, albeit with lower frequency compared to the height of the COVID-19 pandemic. • COVID-19 that requires hospitalization, systemic corticosteroids, and oxygen support (including supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO) represents a serious and life-threatening condition.	Pediatric patients hospitalized with severe COVID-19 represent a population with a serious and life-threatening condition.
Current Treatment Options	• Standard of care clinical management of pediatric patients ≥2 years of age hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, includes treatment with systemic corticosteroids and remdesivir. • Management of severe hospitalized COVID-19 in pediatric patients ≥2 years of age also includes the therapeutic option of tocilizumab under EUA since 2021 • Despite these therapeutic options, children hospitalized with COVID-19 still exhibit high morbidity and mortality	There is an unmet need for safe and effective therapies for the treatment of pediatric patients ≥2 years of age hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Tocilizumab has demonstrated efficacy in adults hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In pivotal studies, tocilizumab improved mortality, time to progression to mechanical ventilation or death, time from randomization to hospital discharge, and clinical status as assessed by a 7-point ordinal scale in the indicated population. • Primary evidence of the effectiveness in pediatric patients comes from efficacy extrapolation from adult patients with COVID-19 derived from PK-exposure modeling.	The PK-exposure modeling detailed in the submission provides substantial evidence of the effectiveness of tocilizumab for the proposed pediatric COVID-19 indication.
Risk and Risk Management	• Primary safety data from dedicated trials among the proposed pediatric COVID-19 population are significantly limited, due to the successful enrollment of only 2 subjects in study WA43811. • The safety of tocilizumab in adults hospitalized with COVID-19 and who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, was demonstrated using an adequate safety database derived from the EMPACTA, COVACTA, and REMDACTA clinical trials. These data are appropriate for extrapolation of safety to the pediatric population in the context of additional, high quality, supportive data from pediatric trials of tocilizumab utilized as the basis of a previous approval • The safety of tocilizumab in pediatric patients with systemic juvenile idiopathic arthritis was established on the basis of safety data from trial WA18211, a randomized, double-blind, placebo-controlled, 12-week trial of tocilizumab versus placebo among 112 tocilizumab-naïve	Available primary data from pediatric COVID-19 studies are not sufficient to justify a conclusion of safety for tocilizumab in the proposed pediatric indication alone. The adult COVID-19 safety database for tocilizumab provides supportive evidence for the safety of tocilizumab in the proposed pediatric population. The safety of tocilizumab was demonstrated in a separate pediatric population with high markers of systemic inflammation and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	subjects with systemic juvenile idiopathic arthritis, many of whom were receiving systemic corticosteroids and immunomodulators such as methotrexate. • The lack of adequate high-quality safety data in the pediatric COVID-19 population represents a significant source of uncertainty. However, the conclusion of safety is able to be supported in the particular context of this benefit-risk assessment for the pediatric COVID-19 population, based on the following factors: ○ The high unmet need for safe and effective therapies in pediatric patients who progress to this severity of COVID-19. ○ The limited available pediatric data collected from a novel pandemic viral infectious disease that represented a Public Health Emergency ○ Use of tocilizumab in the indicated population under an Emergency Use Authorization for over three years to date. ○ The consideration that additional data collection will likely be infeasible due to the introduction of safe and effective vaccines directed against SARS-CoV-2 and COVID-19, viral evolution with variants that have been associated with less severe outcomes, and increasing rates of immunity in the community. ○ The combination of high-quality adult safety data that allows for extrapolation of safety data to pediatric safety in COVID-19 as well as the availability of additional high-quality supportive pediatric safety data from a separate pediatric indication with a longer duration of chronic dosing as compared with a single dose for the treatment of COVID-19.	concomitant use of corticosteroids and longer, chronic dosing. Despite residual uncertainties, the totality of available data supports a conclusion of safety and a conclusion of a favorable benefit-risk evaluation for the use of tocilizumab in pediatric subjects ≥2 years of age hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.

1.4. Recommendation on Post-Marketing Requirement 4369-1

PREA Post-Marketing Requirement 4369-1 was issued with the approval of Supplement 138 of BLA 125276 on 21 Dec 2022. The PMR stated that the Applicant was to conduct a pharmacokinetic, pharmacodynamic, and safety study in pediatric patients hospitalized with COVID-19, with a study completion date of December 2024 and a final report submission timeline of June 2025.

The Applicant attempted to recruit subjects for the trial as designed and agreed upon. However, due to multiple factors (e.g., low recruitment, evolution of COVID-19 natural history, evolution of the COVID-19 prevention and treatment landscape), trial WA43811 was only able to recruit two pediatric subjects between protocol completion on 21 Oct 2021 and the end of trial on 27 Mar 2024. The last participant last visit was on 5 Dec 2022.

In October 2022 the Applicant proposed new PMR milestones based upon their difficulty recruiting for the trial. These included terminating the study and compiling a final report to support the use of TCZ in the COVID-19 pediatric population and other populations. The Applicant proposed to include the following data sources for TCZ safety and efficacy data in the final PMR report:

1) The PK-sIL-6R M&S study report supporting the TCZ dosing regimen for pediatric COVID-19 patients based on existing comprehensive PK, PD data from adult patients with COVID-19 and RA and pediatric patients with sJIA and polyarticular juvenile idiopathic arthritis (pJIA)
2) A review of COVID-19 pediatric data from the Roche Global Safety Database
3) A comprehensive summary for TCZ efficacy and safety in pediatric COIVD-19 patients from the published literature

FDA stated that the proposed approach appeared reasonable for submission, recommended submission of additional data on pediatric subjects with cytokine release syndrome (CRS), and agreed with a final report submission of deadline of January 2025.

Based on the Applicant's good-faith efforts and the contents of the submission, this reviewer recommends (and the Pediatric Review Committee agrees) that the PMR is considered to be fulfilled.

1.5. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

			Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**		
	☐	Clinical outcome assessment (COA) data, such as	
✔	☐	Patient reported outcome (PRO)	
	☐	Observer reported outcome (ObsRO)	
	☐	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify):	
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
X☐	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1. Analysis of Condition

On 04 Feb 2020, the U.S. Secretary of Health and Human Services (HHS) determined pursuant to section 564 of the federal Food, Drug, and Cosmetic Act that there was a significant potential for a public health emergency that had a significant potential to affect national security or the health and security of U.S. citizens living abroad and that involved a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China, in 2019 (2019-nCoV). The virus is now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the illness coronavirus disease 2019 (COVID-19).

On the basis of this determination, the U.S. Secretary of HHS declared that circumstances existed justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Food, Drug, and Cosmetic Act, subject to the terms of any authorization issued under that section. This Public Health Emergency for COVID-19 expired on 11 May 2023.

The full spectrum of SARS-CoV-2 infection and COVID-19 is broad and spans a wide range of manifestations including asymptomatic infection, mild symptomatic illness with fever and headaches, pneumonia requiring hospitalization, and life-threatening respiratory failure with septic shock and multiple organ dysfunction syndrome. At the time of this review and due to the introduction and uptake of safe and effective vaccines, evolving viral variants that may cause decreasing severity of disease, as well as development of immunity due to infection, the clinical characterization of SARS-CoV-2 and COVID-19 has evolved. At the time of this review, symptomatic COVID-19 most often presents clinically as a common, acute, infectious disease with upper respiratory symptoms caused by SARS-CoV-2. However, for those whose disease progresses in severity, severe COVID-19 is a serious and life-threatening condition characterized by pulmonary and systemic inflammatory responses, atypical pneumonia, and hypoxemia in serious cases.

Symptomatic COVID-19 includes symptoms of fever, headache, loss of smell or taste, cough, and other symptoms of respiratory infection. Severe COVID-19 is characterized by lower respiratory tract infection with SARS-CoV-2 leading to pulmonary inflammation and systemic inflammation, pneumonia, and hypoxemia with low peripheral oxygen saturations, or other markers of respiratory compromise such as respiratory rate >30 breaths per minute or PaO2/FiO2 <300 mm Hg. If COVID-19 continues to progress, both pulmonary and systemic inflammation worsen. Worsening pulmonary inflammation leads to the pathophysiology of acute respiratory distress syndrome (ARDS). This underlying pathophysiology leads to worsening symptoms of dyspnea and breathlessness, worsening hypoxemia, and critical illness requiring higher levels of supportive care including intensive care unit (ICU) admission. This critical severity of disease also often requires more aggressive forms of oxygen

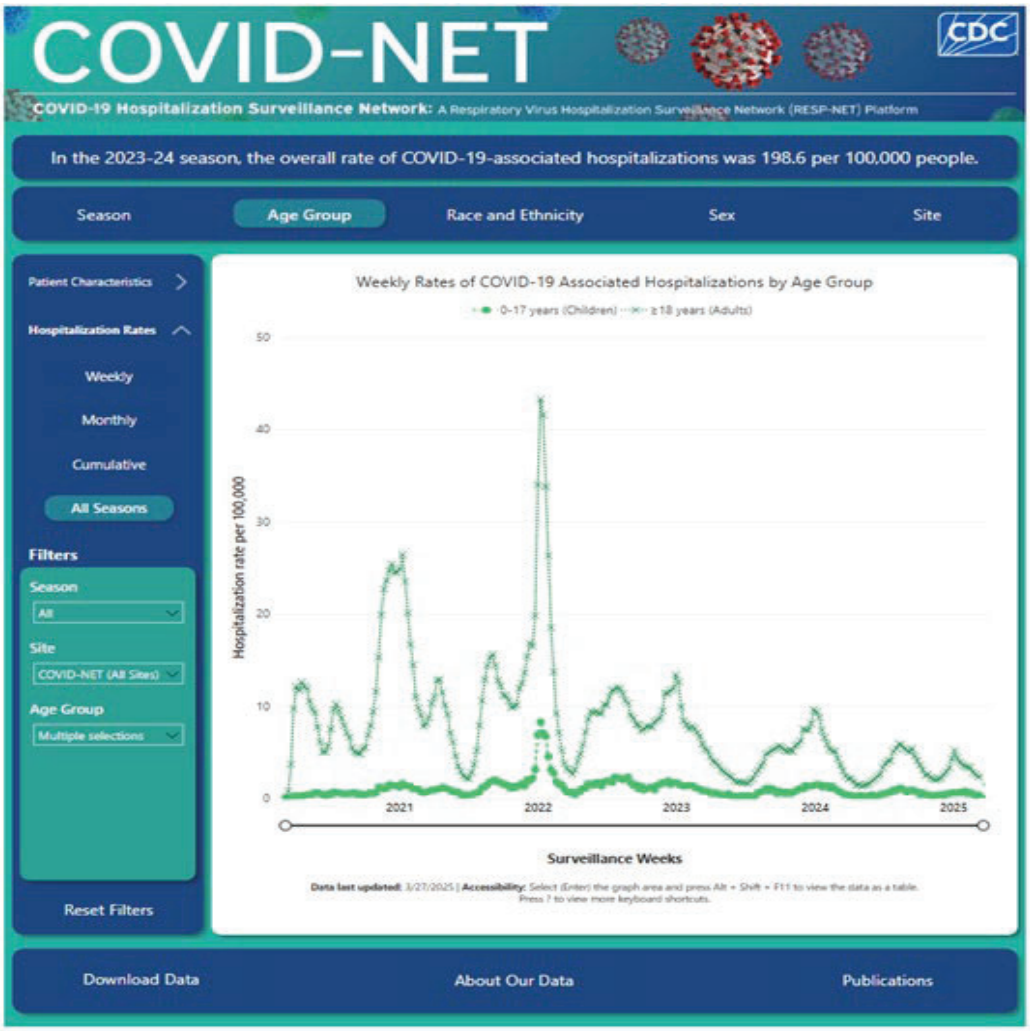
supplementation including delivery by high-flow nasal cannula or noninvasive ventilation. As systemic inflammation worsens, extrapulmonary manifestations of COVID-19 such as sepsis, shock, myocardial involvement, venous-thromboembolic events, and organ failure also increase in frequency, adding complexity to the patient's prognosis and clinical decision-making. If the disease continues to progress despite more aggressive measures, patients show pathophysiology consistent with moderate-to-severe ARDS requiring endotracheal intubation and invasive mechanical ventilation (IMV). Standard of care treatment of ARDS to improve mortality and oxygenation includes elements such as "lung protective ventilation" with low tidal volumes, patient proning among those with PaO2/FiO2 ratio <150 mm Hg, and a conservative fluid management strategy. ARDS physiology often also leads to additional complicating factors such as pulmonary hypertension and pulmonary shunting. This stage of disease may also be complicated with the extra-pulmonary manifestations of COVID-19 noted above. Extracorporeal membrane oxygenation (ECMO) may also be considered at this stage of disease, either as primary therapy to improve hypoxemic respiratory failure or as salvage therapy for those who are failing mechanical ventilation, although its benefit-risk ratio remains an area of controversy due to mixed results and uncertainties in prior clinical trials. In practice, the limited availability and high resource burden of ECMO has led to ECMO being used more frequently for select patients who have failed standard of care measures for ARDS.

The progression of COVID-19 is similar in pediatric patients, however the prevalence of serious, hospitalized COVID-19 in pediatric patients has consistently been substantially lower compared to the prevalence in adults. The US Centers for Disease Control and Prevention states that most children with SARS-CoV-2 infection experience asymptomatic or mild illness (https://www.cdc.gov/covid/hcp/clinical-care/for-pediatric-hcp.html). Select groups of pediatric patients may be at higher risk of severe illness requiring hospitalization, including subjects with comorbidities such as obesity, immune suppressive conditions, uncontrolled diabetes, cardiac disorders, lung disorders, and medically complex conditions. In addition, pediatric patients may be at risk of a post-viral inflammatory syndrome variously titled multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) occurring within several weeks following acute infection with SARS-CoV-2. While MIS-C often requires additional therapeutic decisions, IDSA reports that overall outcomes of children with MIS-C have been good with few fatalities reported (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

The prevalence of serious, hospitalized COVID-19 has sharply decreased in adults and pediatric patients since the height of the pandemic COVID-19 era due to the introduction of safe and effective vaccines, the evolution of viral variants, and growing combined immunity among the general population. However, for those adult and pediatric patients who still do progress to serious disease, the clinical syndrome of serious, hospitalized COVID-19 remains a condition with high morbidity and mortality. In this setting of severe and life-threatening illness of serious COVID-19, there remains an unmet need for safe and effective therapies for pediatric patients. A substantial number of adult and pediatric patients were hospitalized with COVID-19

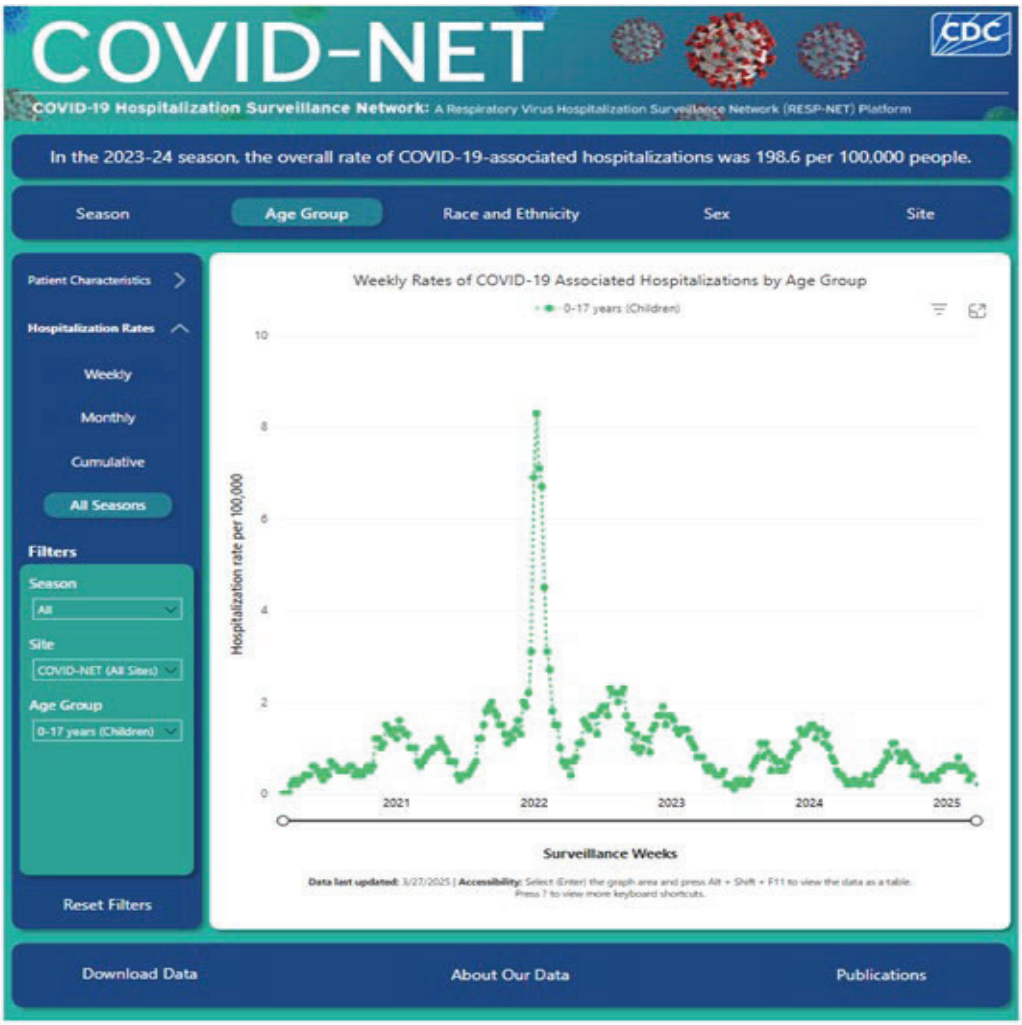
in the 2024 and 2025 calendar years to date despite the overall decrease in prevalence of serious disease since the peak of 2021, as documented in the Centers for Disease Control and Prevention COVID-NET COVID-19 Hospitalization Surveillance Network data. This resource provides data on COVID-19 hospitalizations over time in all patients and in pediatric patients alone, as summarized in Figure 1 and Figure 2, respectively, below. These data highlight the unmet need for additional safe and effective therapies among pediatric patients hospitalized with COVID-19.

Figure 1 CDC COVID-NET: Weekly Rates of COVID-19 Associated Hospitalizations per 100,000 People (Adult and Pediatric Patients)



Source: Screenshot from https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network, accessed 02 Apr 2025

Figure 2 CDC COVID-NET: Weekly Rates of COVID-19 Associated Hospitalizations per 100,000 People (Pediatric Patients)



Source: Screenshot from https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network, accessed 02 Apr 2025

2.2. Analysis of Current Treatment Options for Pediatric Patients

Treatment and prevention of serious COVID-19 in adults has been informed by large clinical trials supportive of the efficacy and safety of agents such as remdesivir, dexamethasone, baricitinib, TCZ, and SARS-CoV-2 vaccines, among others. While supportive care early in the pandemic was characterized by variable clinical decision-making regarding the timing of intubation, the use of agents with unproven efficacy, the role of anticoagulation, and other sources of uncertainty, increasing knowledge led to comprehensive and data-driven treatment guidelines (e.g., Alhazzani, et al, 2020[1]; Roche, et al, 2022[2]; COVID-19 Treatment Guidelines Panel, 2024[3]; Infectious Disease Society of America, 2024[4]). The currently approved and available products that form the basis of generally accepted standard of care for adults hospitalized with moderate-to-severe COVID-19 in the United States include systemic corticosteroids, remdesivir, and targeted anti-inflammatory agents such as JAK inhibitors (e.g., baricitinib) and IL-6 inhibition (e.g., TCZ).

Management of severe hospitalized COVID-19 in the pediatric population also includes standard of care treatment with systemic corticosteroids and remdesivir, however additional therapeutic agents utilized under EUA have yet to receive approval (see Table 1, below). Infectious Disease Society of America guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) acknowledge the lack of high-quality pediatric efficacy and safety data for COVID-19 therapies, but generally support the use of remdesivir and corticosteroids in pediatric subjects hospitalized with COVID-19, with additional suggestions for use of IL-6 blockade or JAK inhibitors in certain hospitalized patients. In addition, IDSA also provides guidance on immunomodulatory therapies as a mainstay of treatment for MIS-C.

[1] Alhazzani W, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19), Crit Care Med, 48(6):e440-e469, 2020.
[2] Roche N, et al. Update June 2022: management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline, Eur Respir J, 60(2), 2022.
[3] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Last update March 1, 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK570371/ and PMID: 34003615. Accessed 05/28/2025.
[4] Bhimraj A, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Disease Society of America. Last update February 12, 2025. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 05/28/2025.

Table 1 Summary of Treatment Armamentarium Relevant to Pediatric COVID-19

Product Name	COVID-19 Approval Date	Relevant Indication	Pediatric Status
FDA Approved Therapies in Adults			
COVID-19 Vaccines (e.g., Comirnaty, Pfizer-BioNTech COVID-19 Vaccine, Novavax, Spikevax, Moderna COVID-19 Vaccine)	First Vaccine EUA: 2020 First Vaccine Approval: 2021	For active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Approved populations include children. Authorized populations include children ≥6 months of age.
Remdesivir	EUA: 2020 Approval: 2020	For the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 kg) who are: - Hospitalized, or - Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.	Approved population includes children.
JAK Inhibitors (e.g., Baricitinib)	EUA: 2020 Approval: 2022	Baricitinib: For the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.	Not approved in children. Authorized in children ≥2 years of age
IL-6 Inhibitors (e.g., Tocilizumab)	EUA: 2021 Approval: 2022	Tocilizumab: For the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.	**Subject of this review**; revised EUA population included children ≥2 years of age
Other Therapies for COVID-19 in Adults			
Systemic Corticosteroids (e.g., dexamethasone)	N/A	Standard of care therapy for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.	Standard of care in children
C5a Inhibitors (e.g., Vilobelimab)	EUA 2023	For emergency use for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation	EUA does not include children

		(IMV), or extracorporeal membrane oxygenation (ECMO).	
IL-1 Receptor Antagonist (e.g., Anakinra)	EUA 2022	For the emergency use for the treatment of coronavirus disease 2019 (COVID-19) in certain hospitalized adult patients with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)	EUA does not include children

Source: Reviewer

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TCZ is an approved biologic product that is marketed in the United States as an IV and as a SC formulation (original BLA 125472, approved October 2013). TCZ was initially approved on 08 Jan 2010 for rheumatoid arthritis. Subsequent approvals and authorizations for TCZ are summarized below:

1. Supplements 7, 10, and 11, on 04 Jan 2011; Rheumatoid Arthritis: Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
2. Supplement 22, on 15 Apr 2011; Systemic Juvenile Idiopathic Arthritis: Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
3. Supplement 49, on 11 Oct 2012; Revision of Rheumatoid Arthritis Indication: Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatic Drugs (DMARDs).
4. Supplement 64, on 29 Apr 2013; Polyarticular Juvenile Idiopathic Arthritis: Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
5. Original BLA 125472, TCZ injection for subcutaneous use, on 21 Oct 2013: Label shared with BLA 125276
6. Supplement 112, on 22 May 2017; Giant Cell Arteritis: Adult patients with giant cell arteritis
7. Supplement 114, on 30 Aug 2017; Cytokine Release Syndrome: Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.
8. Supplement 131, on 04 Mar 2021; Systemic Sclerosis-Associated Interstitial Lung Disease: Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
9. EUA 099, on 24 Jun 2021; Coronavirus 2019 (COVID-19): 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 extracorporeal membrane oxygenation (ECMO)
10. Supplement 138, on 21 Dec 2022; Coronavirus 2019 (COVID-19): Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
    a. PREA PMR 4369-1 Issued: Conduct a pharmacokinetic, pharmacodynamic, and safety study in pediatric patients hospitalized with COVID-19.
        i. Pediatric studies were waived for pediatric patients 1 year of age and younger, as these studies would be impossible or highly impracticable

11. EUA 099 Revision, on 21 Dec 2022, Coronavirus 2019 (COVID-19): continue authorizing the emergency use of Actemra for the treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 148225 was opened in the Division of Antivirals on 18 Mar 2020 to investigate the use of IV TCZ as a treatment for COVID-19 in the setting of the evolving COVID-19 pandemic. Relevant events in the pediatric development of IV TCZ for this indication are summarized below:

1. Initial Pediatric Study Plan (iPSP), on 30 Jun 2020: Sponsor requested waiver of pediatric studies for pediatric subjects 0-1 years of age, and a deferral of pediatric studies for subjects 2-17 years of age for the COVID-19 indication until the results of study WA42380 were available.
2. Agreed iPSP, on 05 Jan 2021: Agreement reached for deferral of pediatric assessments for pediatric subjects 0 to 17 years of age until the efficacy and safety results of the adult COVID-19 studies of TCZ (i.e., cited studies REMDACTA, COVACTA, and MARIPOSA)
3. Pediatric Protocol, 28 Oct 2021: Initial submission of protocol WA43811, a single arm, open label, PK, PD, and safety study for subjects age 2-17 years of age.
4. PMR Revision under BLA 125276, on 14 Oct 2022: Revision of PMR 4369-1 to provide for a two-year extension for study completion of WA43811 and subsequent final report submission milestone dates.
5. Type D Meeting, on 19 Dec 2023: FDA and the Sponsor reached agreement on the available data contents of the submission to address the PMR, including:
    a. The PK-sIL-6R M&S study report supporting the TCZ dosing regimen for pediatric COVID-19 patients based on existing comprehensive PK, PD data from adult patients with COVID-19 and RA and pediatric patients with sJIA and pJIA.
    b. Available data from the two subjects enrolled in WA43811
    c. A review of COVID-19 pediatric data from the Roche Global Safety Database
    d. A comprehensive summary of TCZ efficacy and safety in pediatric COVID-19 patients from the published literature

    FDA noted that the adequacy of the data to support the safe and effective use of TCZ for the treatment of COVId-19 in hospitalized pediatric patients aged 2 years and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive mechanical ventilation, mechanical ventilation, or ECMO would be a review issue.
6. sBLA submission, on 09 Oct 2024

3.3. References to Other BLA Supplements

Note that BLA 125276 for ACTEMRA intravenous injection and BLA 125472 ACTEMRA subcutaneous injection share labeling. The regulatory decision-making and labeling changes encompassed by this review will be applied to BLA 125276 supplement 149 as well as BLA 125472 supplement 061.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The submission did not raise new review concerns that required OSI review.

4.2. Product Quality

The submission did not raise new review concerns that required Product Quality review.

4.3. Clinical Microbiology

The submission did not raise new review concerns that required Clinical Microbiology review.

4.4. Devices and Companion Diagnostic Issues

The submission did not include new device or companion diagnostics information that required review.

5 Nonclinical Pharmacology/Toxicology

5.1. Nonclinical Pharmacology/Toxicology Summary

No new nonclinical studies were submitted or required to support this efficacy supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 subclass directed against the human interleukin 6 receptor (IL-6R). Actemra (tocilizumab) was initially approved in the US on 08 Jan 2010 for the treatment of rheumatoid arthritis (RA) and has since been approved for the treatment of systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis, chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS), for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease, and for the treatment of COVID-19 in hospitalized adults with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The approval of COVID-19, Supplement-138, was associated with Post-Marketing Requirement (PMR) 4369-1 (required pediatric assessment under the Pediatric Research Equity Act (PREA)). This submission, Supplement-149, was to provide the final PMR report 4369-1 and expand the COVID-19 indication to pediatric patients.

The purpose of the clinical pharmacology review is to review the PMR report 4369-1 in support of the COVID-19 indication in pediatric patients from 2-18 years of age.

6.1.1. Recommendations

The Office of Clinical Pharmacology recommends approval of BLA125276/s149 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 2 Clinical pharmacology review issues and recommendations

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of the effectiveness in pediatric patients comes from efficacy extrapolation from adult patients with COVID-19
General dosing instructions	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.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No
Labeling	Overall, the proposed labeling recommendations are acceptable.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable

Abbreviations: IV, intravenous

6.1.2. Post-Marketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Tocilizumab is an IL-6 inhibitor. The PK of tocilizumab administered intravenously (IV) in patients with RA, pJIA, sJIA, CRS, and COVID-19 in adult patients is available in the approved label of ACTEMRA (BLA125276). The PK of IV tocilizumab in pediatric patients with COVID-19 is based on the PK data collected from clinical study WA43811.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

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.

Therapeutic Individualization

Not applicable.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The pharmacokinetics of intravenous administration of tocilizumab in pediatric COVID-19 patients was characterized in 2 pediatric patients treated with 12 mg/kg intravenously in Study WA43811. Table 3 below describes the key clinical pharmacology and pharmacokinetic characteristics of tocilizumab in pediatric patients with COVID-19.

Table 3 Key Clinical Pharmacology/Pharmacokinetic Characteristics of Tocilizumab in Patients With COVID-19

Key Pharmacology/Pharmacokinetics Characteristics	Summary of Tocilizumab in Pediatric Patients with COVID-19
Mechanism of action	Tocilizumab is IL-6 inhibitor
Pharmacodynamics	sIL-6R and IL-6 levels increased and CRP levels decreased over time post dose, consistent to those in adult patients with COVID-19
Pharmacokinetics	
PK exposure in COVID-19	Cmax (2 h): Patient (b) (6) 229 ug/mL; Patient (b) (6) 153 ug/mL

	Conc (day 7): Patient (b) (6) 62.7 ug/mL: Patient (b) (6) 9.8 ug/mL
DME in COVID-19 Pediatric Patients	
Volume of Distribution	Patient (b) (6) 2.27 L Patient 2.97 L
Clearance	Patient 0.0887 L/d Patient 0.133 L/d

Source: (b) (4)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, clinical pharmacology data provided supportive evidence of effectiveness.

The effectiveness of tocilizumab in pediatric patients with COVID-19 aged 2 years and older is supported by evidence from adequate and well-controlled studies of ACTEMRA in adults with COVID-19, pharmacokinetic and pharmacodynamic data in 2 pediatric patients with COVID-19 (WA43811), and simulated tocilizumab exposure in pediatric COVID-19 patients based on available tocilizumab pediatric PK data from other indications.

The PK exposure from the two pediatric patients with COVID-19 received tocilizumab 12 mg/kg IV in Study WA43811 were within the exposure range in adult patients with COVID-19 and in patients with pJIA, sJIA, RA and CRS (Table 4). The observed pediatric PK data in Study WA43811 is also consistent with the simulated data of tocilizumab exposure in pediatric COVID-19 patients (Figure 3), which supports the efficacy extrapolation from adult patients with COVID-19 to pediatric patients with COVID-19 (details presented in FDA EUA 99 Review in DARRTS on 24 Jun 2021).

Table 4 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	176

			(17–260)	(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	Adults[4]	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)
	Pediatrics[5]	12 mg/kg IV (Patient 1)	229	
		12 mg/kg IV (Patient 2)	153	

Data Source:
[1]Actemra (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)
[5]Concentration at 2 h post dose. Page 165, Bioanalytical Report, WA43811

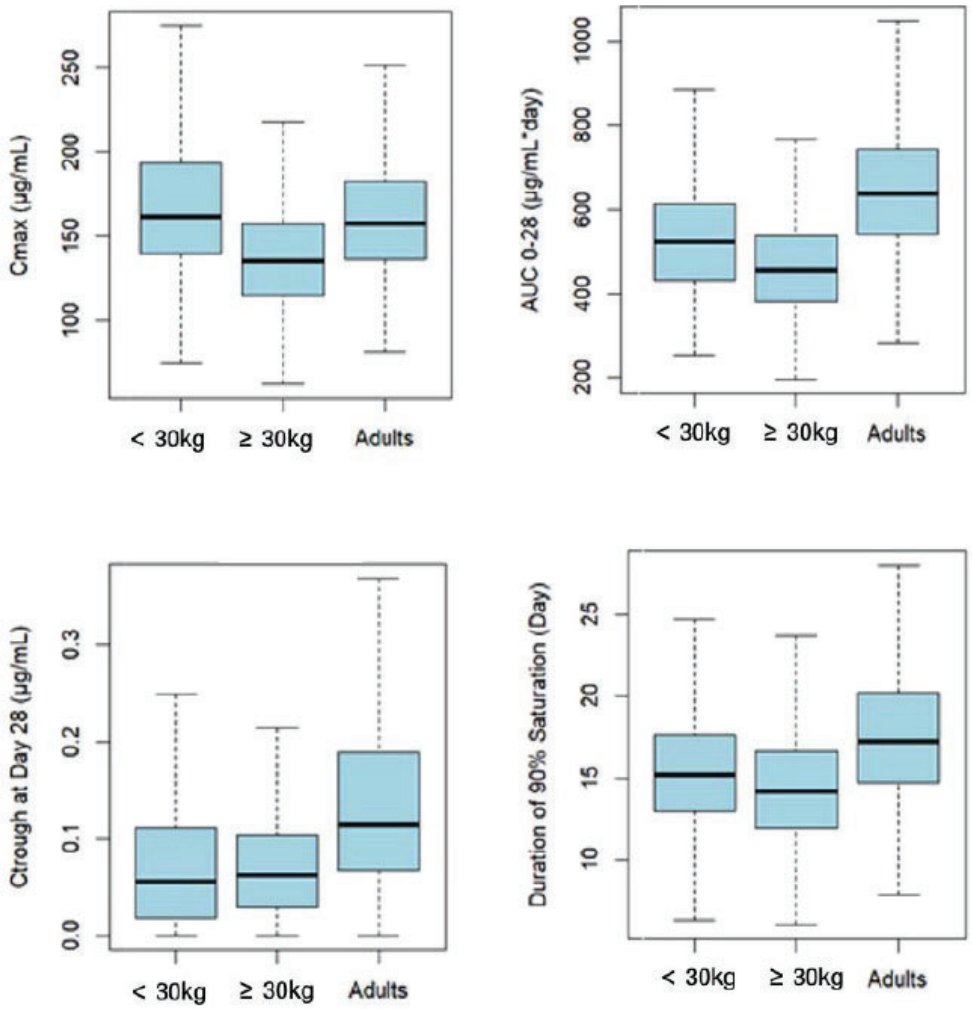
The response of sIL-6R, IL-6 and CRP exhibited the same trend in the two pediatric patients when compared with those in adult patients with COVID-19. Pre-dose serum sIL-6R concentrations in both participants were 69.3 and 33.5 ng/mL, respectively, and increased with time, with a maximum value reported on Day 21 (452 and 520 ng/mL, respectively). Serum concentration of IL-6 is missing at pre-dose for one participant and was 69.3 ng/mL for the other. Following the administration of TCZ, IL-6 concentrations increased steadily from Day 1 to Day 21 in both participants, reaching their maximal levels on Day 21 (97.5 and 125 ng/L, respectively). Serum concentrations of CRP were elevated in both participants at pre-dose (89.5 mg/L and 69.1 mg/L, respectively). CRP levels had decreased on Day 7, with concentrations reported at 1.6 mg/L and 0.6 mg/L, respectively. CRP levels remained below 2 mg/L in both participants until the end of their study participation. The duration of 90% of sIL-6R saturation was maintained for at least 3 weeks in both participants following the administration of TCZ IV 12mg/kg.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 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 is appropriate.

Tocilizumab has been approved in pediatric patients with pJIA, sJIA, CRS 2 years of age and above. Similar to the proposed dosing regimen in pediatric patients with COVID-19, for pediatric patients with pJIA, sJIA, CRS 2 years of age and above, the dose was higher for children less than 30 kg because of the higher weight-adjusted clearance in these children as compared to 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 as that in adult patients in the respective indications. In addition, 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 PK/PD 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 (details presented in FDA EUA 99 Review DARRTSed on June 24, 2021). Based on PK-sIL-6R modeling and simulation, the recommended dosing regimen for ACTEMRA is expected to result in comparable plasma exposures and PD response of tocilizumab in pediatric COVID-19 patients as observed in adults with COVID-19 (Figure 3). The simulated data is consistent with the observed data in Study WA43811, where the PK and PD of tocilizumab in the 2 pediatric patients with COVID-19 receiving tocilizumab 12 mg/kg IV were within those in adult patients with COVID-19 and in patients with pJIA, sJIA, RA and CRS (Table 4).

Figure 3 Comparison 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: FDA review for EUA000099 (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.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

Question on clinically relevant specifications (TBD)?

Not applicable.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Relevant Data Sources

Table 5 Relevant Data Sources Contributing to Pediatric Safety for the COVID-19 Indication

Subject Groups	Tocilizumab Pediatric Data (N)	Placebo Pediatric Data (N)	Tocilizumab Adult Data (N)	Placebo Adult Data (N)
Data in COVID-19-related Indications				
Subjects in controlled trials of TCZ for COVID-19	0	0	974	485
Subjects in single arm, uncontrolled trials of COVID-19 (WA43811)	2	N/A	N/A	N/A
Additional Data from Approved Pediatric Indications				
Subjects in R, DB, PC trials in sJIA of 12 weeks duration with additional open-label safety follow-up (WA18221)	75	37	N/A	N/A

7.2. Review Strategy

The Applicant submitted data from a population PK/exposure model to support the efficacy of TCZ in pediatric COVID-19 (see Section 6).

The Applicant submitted data from multiple sources to demonstrate the safety of TCZ for the pediatric COVID-19 indication, and the Division also reviewed extant data that formed the basis of previously approved pediatric indications for TCZ. The safety data deemed sufficient to inform the determination of the safety of TCZ for the pediatric COVID-19 indication proposed is derived from the adult and pediatric studies of TCZ noted in Table 5, above.

The most directly applicable and fit-for-purpose clinical trial data to support the safety of the proposed supplemental BLA for TCZ for a pediatric COVID-19 indication comprise data from a pediatric COVID-19 study, WA43811. However, that trial succeeded in enrolling only a total of two subjects, limiting its utility for decision-making regarding safety (Section 8.2.3). Consideration was given to the ability of the adult safety data used to inform the adult COVID-19 indication (Section 8.2.4) to support the safety in pediatric subjects, as well as to the applicability of data from previously approved pediatric indications (Section 8.2.5) in which TCZ was administered with repeat (chronic) dosing.

8 Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. WA43811 (Study 811)

8.1.1.1. Administrative Information

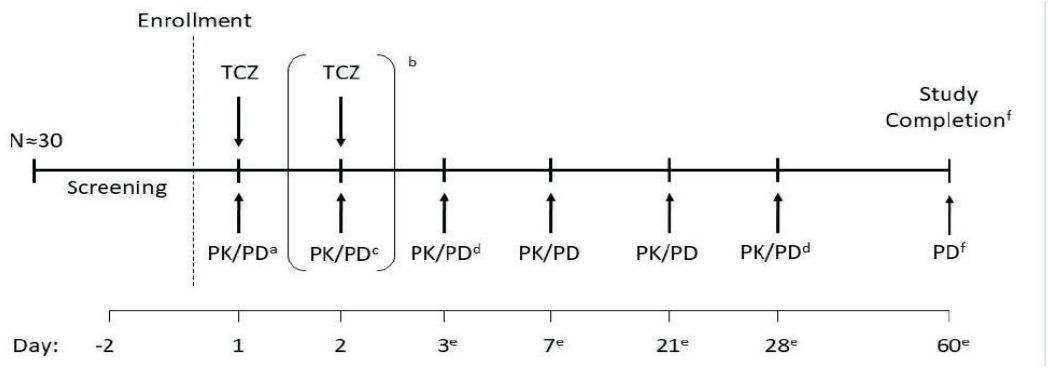
Study designation: WA43811, NCT05164133, EudraCT Number: 2021-005332-27, eponym: Gypsophila
Study title: A Phase 1b, single-arm, open-label study evaluating the pharmacokinetics, pharmacodynamics, and safety of tocilizumab in pediatric patients hospitalized with COVID-19.
Study dates: First subject enrolled (b) (6), last subject last visit (b) (6), study closure 27 Mar 2024
Study sites: 2 sites in the United States, 1 subject enrolled at each site
Study report date: Abbreviated clinical study report July 2024

8.1.1.2. Trial Design

Study WA43811 (Study 811) was a single-arm, uncontrolled, open-label study of TCZ to assess the pharmacokinetics, safety, and exploratory efficacy of TCZ 12 mg/kg IV once among up to 30 subjects less than 18 years of age with COVID-19 who were receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

The trial design is summarized in Figure 1, below. The study included a screening period of up to 3 days. Enrolled subjects were administered a single dose of TCZ on study Day 1, and an optional second dose 8 to 24 hours later if clinically indicated. Subjects were then followed clinically for a total of 60 days. PK and PD samples were acquired on study Day 1, 2, 3, 7, 21, and 28, with an additional PD sample collected at Day 60.

Figure 4 Study 811: Study Schema



PD = pharmacodynamic; PK = pharmacokinetic; TCZ = tocilizumab.
N = Number of participants.
a Both a predose and a postdose sample (within 15 minutes of completion of the infusion) was collected on Day 1.
b Optional second dose within 8–24 hours after the first dose, if clinically indicated.
c A postdose sample was collected within 15 minutes of completion of the infusion, if the optional second dose was administered.
d Not applicable for participants who weighed < 30 kg.
e If a participant received the optional second dose of TCZ on Day 2, subsequent days shifted to Day 4, Day 8, Day 22, and Day 29. The study completion visit was Day 60 (± 3 days).
f Upon study completion, a PD sample was collected. In case of early study discontinuation before Day 28, both a PK and PD sample was collected. In case of early study discontinuation after Day 28, only a PD sample was collected.
Source: Applicant submission.

8.1.1.3. Study Objectives

Primary Objectives

- To characterize the pharmacokinetics of TCZ through Day 28

Secondary Objectives

- To characterize the pharmacodynamics of TCZ through Day 60
- To evaluate the safety of TCZ through Day 60

Exploratory Objectives

- To explore the efficacy of TCZ through Day 60
- To assess proof of activity by assessment of pharmacodynamic biomarkers and other disease biomarkers, including, but not limited to, CRP that can increase the knowledge and understanding of disease biology.

8.1.1.4. Enrollment Criteria

Enrollment criteria for Study 811 identified a population of pediatric subjects hospitalized with moderate to severe, serious COVID-19 receiving corticosteroids and requiring supplemental oxygen or mechanical ventilation.

Inclusion

- Age less than 18 years at the time of signing Informed Consent or Assent
- Informed consent, as well as a signed assent form as determined by participant's age, site, and national standards.
- Hospitalized with COVID-19 with the following criteria:
    - Confirmed by PCR and evidenced by chest X-ray or CT scan
    - Received systemic corticosteroids
    - Oxygen saturation <93% on room air, or required supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO to maintain oxygen saturation >92% at screening and baseline
- WOCBP protections, comprising agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraception (for females) or a condom (for males), and agreement to refrain from donating eggs or sperm

Exclusion

- Gestational age <37 weeks
- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Comorbidities
    - Active tuberculosis infection
    - Uncontrolled active bacterial, fungal, viral, or other infection (besides COVID-19)
    - Diagnosis or suspected diagnosis of multisystem inflammatory syndrome in children
    - Received oral anti-rejection or immunomodulatory drugs within the past 3 months prior to enrollment
    - Moribund within the next 48 hours in the opinion of the investigator

8.1.1.5. Treatments Administered

Subjects received the following investigational product:

- IV TCZ 12 mg/kg for participants <30 kg) or 8 mg/kg for participants ≥30 kg up to two doses

Subjects continued to receive standard of care treatments for COVID-19 throughout the study.

8.1.1.6. Study Endpoints

The planned PK and safety endpoints for the study included the following assessments:

- Primary Endpoint: Serum concentrations of TCZ at specified timepoints and derived PK parameters (C_{max}, $AUC_{Days\ 0\text{-}28}$, $C_{Day\ 28}$, C_L, and volume of distribution)
- Secondary Endpoints:
    - Duration of 90% saturation of sIL-6R through Day 28
    - Serum concentrations of IL-6, sIL-6R, and CRP at specified timepoints
    - Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 grading scale
    - Incidence of serious adverse events
    - Change from baseline in targeted vital signs
    - Change from baseline in targeted clinical laboratory results
- Exploratory Endpoints:
    - Clinical improvement assessed using a 7-category ordinal scale
    - Duration of hospitalization (in days)
    - Duration of PICU or ICU stay (in days)
    - Mortality
    - Incidence of mechanical ventilation
    - Duration of supplemental oxygen

8.1.1.7. Safety Measures

Safety measures included data collection on adverse events, physical examinations, vital signs, electrocardiograms, clinical safety laboratory tests, and pregnancy testing (in applicable subjects). The schedules of safety activities are reproduced below as Table 6 and Table 7. The study also included additional safety measures that occurred after Day 28. For subjects discharged from the hospital, on Days 35, 45, and 60, the protocol called for study visits that included adverse event assessments, vital signs, and safety laboratory assessments. Subjects hospitalized after Day 28 received daily adverse event assessments, and weekly data collection of safety laboratory assessments and vital signs.

The safety measures put in place were appropriate for an assessment of the safety and PK of the investigational product in the context of pediatric subjects hospitalized for COVID-19. The definition of adverse events and serious adverse events were consistent with federal regulation.

Table 6 Study 811 - Schedule of Activities from Screening to Day 2

	Screening [a, b]	Treatment		
Study Day	−2 to 0	Day 1 [c]		Day 2
Time after Initial Treatment (Assessment Window)		Baseline 0 Predose	15 Minutes after End of TCZ Infusion	
Informed consent or assent	x			
Review of inclusion and exclusion criteria	x	x [d]		
Demographics	x			
Medical history	x			
Complete physical examination [e]	x			
Weight [f]	x			
COVID-19 diagnosis [g]	x			
Chest X-ray or CT scan [h]	x			
Single ECG	x			
Pregnancy test [i]	x			
Vital signs, SpO_2, FiO_2, and oxygen flow rate [j]	x	x		
Oxygen support type [k]	x	x		x
Ordinal scoring [l]		x		x
Adverse events [m]	x [l]	x [l]	x	x
Concomitant medications [n]	x	x	x	x
Hematology [o]	x	x		
Chemistry panel [p]	x	x		
TCZ administration [q]		x		Optional [r]

COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; eCRF = electronic Case Report Form; FiO_2 = fraction of inspired oxygen; IxRS = interactive voice or web-based response system; PD = pharmacodynamic; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = peripheral capillary oxygen saturation; TCZ = tocilizumab.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations (including physical examination) performed prior to obtaining informed consent and within 24 hours before screening may be used; such tests do not need to be repeated for screening. Individuals who do not meet the criteria for participation in this study may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion, as described in Section 5.4.

[b] Informed consent must be documented before any study-specific screening procedure is performed. The screening and baseline visit may be performed on the same day, provided that the participant meets all of the study eligibility criteria as outlined in Section 5.1 and Section 5.2 prior to enrollment. If the screening and baseline visits occur on the same day, assessments do not need to be repeated.

[c] Day 1 is defined as the day on which the infusion of the first dose of study drug is started. If possible, predose baseline assessments should be performed on the same date.

[d] After eligibility criteria have been reviewed again at baseline, enrollment must be confirmed in the IxRS.

[e] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified after enrollment should be reported as adverse events (see Section 8.3.8).

[f] If it is not feasible to weigh bed-bound participants, historical body weight may be used.

[g] COVID-19 test (SARS-CoV-2 PCR) to confirm diagnosis should be collected within 7 days prior to enrollment.

[h] Chest X-ray or CT scan should be performed within 7 days prior to enrollment.

[i] Female participants of childbearing potential, including those who have had a tubal ligation, will have a urine or serum pregnancy test at screening. If a urine pregnancy test is positive, it must be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[j] On Day 1, all vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature) and oxygen saturation (SpO_2), must be recorded prior to administration of TCZ for establishing the baseline. For participants requiring supplemental oxygen, the oxygen flow rate (in liters per minute [L/min]) and/or FiO_2 should also be recorded. Approximately 15 minutes after the infusion, vital signs must again be measured in order to detect any potential signs of an anaphylactic or serious hypersensitivity reaction (results of this assessment do not have to be recorded in the eCRF). Refer to Section 8.2.2 for detailed information on vital signs measurements.

[k] Changes in supplemental oxygen support type should be assessed daily at the time of ordinal scale score determination.

[l] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1, then daily every morning (between 8:00 a.m. and 12:00 p.m.) for participants who remain hospitalized. See Section 8.1.1 for additional details.

[m] After informed consent and assent (if applicable) have been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 60 days after the first dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Appendix 2).

[n] Include any medication (e.g., prescription drugs, over-the-counter drugs, vitamins, or herbal supplements) or vaccine used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. COVID-19 vaccinations should be recorded also if received more than 7 days prior to initiation of study treatment.

[o] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

[p] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, urate, LDH, ferritin, CRP, and procalcitonin.

[q] Study drug should be administered after collection of all samples for predose pharmacokinetics, pharmacodynamics and exploratory biomarker analyses (refer to Table 5 for details). The initial study drug infusion should be given within 4 hours of confirming enrollment (see footnote d).

[r] If signs or symptoms do not improve (e.g., a sustained fever, an increased supplemental oxygen requirement), one additional infusion of TCZ can be given 8–24 hours after the first TCZ infusion (see Section 6.1). Approximately 15 minutes after infusion, vital signs must be measured in order to detect any potential signs of an anaphylactic/serious hypersensitivity reaction, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

Source: Applicant submission

Table 7 Study 811 - Schedule of Activities on Days 3 to 28

Study Day	Days 3–28 [a]																								Early Discontinuation [b]
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Vital signs, SpO_2, FiO_2, and oxygen flow rate [c]	x				x							x							x							x	x
Oxygen support type [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [h]	x				x							x							x							x	x
Chemistry panel [i]	x				x							x							x							x	x
Central laboratory																											
Blood samples for PK and PD	See Table 5.																										

COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; PD = pharmacodynamic; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation.

[a] If participants are discharged from hospital prior to Day 28, follow-up visits should be conducted on Days 7, 14, 21, and 28 (± 1 day). The follow-up visit on Day 14 may be conducted as a telephone visit. Vital signs, SpO_2, FiO_2, oxygen flow rate, and laboratory testing will not be required for telephone visits. Participants should return to the site for the Day 7, 21, and 28 visits in order to collect the PK and PD samples (see Table 5 for further details). Although PK and PD sample collection on Day 28 is not applicable for participants who weigh <30 kg, they should still come to the site, if possible.

[b] For participants who discontinue from the study early. Participants who discontinue from study treatment should continue in the study and complete all assessments through Day 60.

[c] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature) and oxygen saturation (SpO_2) should be recorded at or around the time of ordinal scale score determination, if feasible. For participants requiring supplemental oxygen, the oxygen flow rate (in liters per minute [L/min]) and/or FiO_2 should also be recorded. Following hospital discharge, these parameters should be recorded at each return visit to the clinic. Refer to Section 8.2.2 for detailed information on vital signs measurements. Vital signs, oxygen saturation, oxygen flow rate (in liters per minute [L/min]) and/or FiO_2 will not be recorded if follow-up visits are conducted by telephone.

[d] Changes in the type of supplemental oxygen support should be assessed daily at the time of ordinal scale score determination. For participants discharged with supplemental oxygen, the type of support should be assessed during follow-up visits if and when home oxygen use was stopped.

[e] Assessment of clinical status using the ordinal scale should be recorded daily every morning (between 8:00 a.m. and 12:00 p.m.) for participants who remain hospitalized. The ordinal scale score will not be recorded after hospital discharge, except in the case of re-hospitalization. See Section 8.1.1 for additional details.

[f] All adverse events will be reported until 60 days after the first dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Appendix 2).

[g] Include any medication (e.g., prescription drugs, over-the-counter drugs, vitamins, or herbal supplements) or vaccine used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion or discontinuation visit. COVID-19 vaccinations should be recorded also if received more than 7 days prior to initiation of study treatment.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[i] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, urate, LDH, ferritin, CRP, and procalcitonin. Chemistry laboratory assessments will not be performed if follow-up visits are conducted by telephone.

Source: Applicant submission

8.1.1.8. Statistical Analysis Plan

A statistical analysis plan was provided for the protocol. However, as only two subjects were enrolled, no formal statistical analyses were conducted.

8.1.1.9. Protocol Amendments

There were no amendments to the protocol.

8.1.2. **Study Results**

Compliance with Good Clinical Practices

The Applicant attests to the following:

- The protocol, informed consent, and other relevant documents were reviewed and approved by an Institutional Review Board or Independent Ethics Committee prior to initiation.

- The study was conducted in accordance with the consensus ethical principles including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable ICH GCP guidelines, and applicable laws and regulations.

Patient Disposition

Two subjects were enrolled in the study at two centers in the United States. Subject (b) (6) completed the study, and Subject (b) (6) discontinued the study at Day 58 due to withdrawal by the subject.

Protocol Violations/Deviations

There were no protocol deviations reported during the study period.

Demographic Characteristics

The demographics of the two enrolled subjects are presented below (Table 8).

Table 8 Study 811: Demographic Characteristics

Demographic Parameters	**TCZ Treatment Group** (N= 2)	
	Subject (b) (6)	Subject (b) (6)
Sex	(b) (6)	
Age (years)		
Age Group		
BMI (kg/m^2)		Not Listed
Race	Not reported	Unknown
Ethnicity	Not stated	(b) (6)
Region	United States	United States

Source: Adapted from Applicant submission

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9 Study 811: Baseline Disease Characteristics

Baseline Disease Parameters	**TCZ Treatment Group** (N= 2)	
	Subject (b) (6)	Subject (b) (6)
Medical History	Asthma, scoliosis, chromosome 1p36 deletion, developmental delay, epilepsy, gastroesophageal reflux disease, hypothyroidism, septo-optic dysplasia	Autistic disorder, speech delay
Baseline Ordinal Scale	4; oxygen supplementation mask (high flow mask)	4; oxygen supplementation mask (high flow mask)
Days from First COVID-19 Symptoms	3	7
Days from COVID-19 Diagnosis	2	5
COVID-19 Medications	Remdesivir, dexamethasone	dexamethasone
sIL-6R ng/L	33500	69300
IL-6 ng/L	N/A	1.82
Ferritin (pmol/L)	244.92	N/A
CRP (mg/L)	89.5	69.1

Source: Adapted from Applicant submission

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The review revealed no clinically relevant concerns with treatment compliance, concomitant medications, and rescue medication use within the context of the limitations discussed above.

Efficacy Results – Primary Endpoint

PK parameters for the primary endpoints were calculated for each subject enrolled (see Section 6). No formal statistical analyses were conducted because only 2 subjects were enrolled.

Data Quality and Integrity

The review revealed no clinically relevant concerns with data quality and integrity within the context of the limitations discussed above.

Efficacy Results – Secondary and other relevant endpoints

PK parameters for the secondary biomarker endpoints and safety endpoints were calculated for the two subjects enrolled and are incorporated into the Clinical Pharmacology review (see Section 6, above). Data from the secondary efficacy endpoints were provided in the submission (see Table 10, below). Summary statistics were not calculated in the setting of only 2 subjects enrolled. Safety endpoint data are presented in the Section 8.2, below.

Table 10 Study 811: Efficacy Results

Efficacy Parameter	Subject (b)(6) Result	Subject (b)(6) Result
Exploratory Endpoints		
Improvement on 7-point Ordinal Scale	Discharged or "ready to discharge" on Day 7	Discharged or "ready to discharge" after Day 3
Duration of Hospitalization (days, including pre-enrollment)	8	3
Duration of PICU or ICU Stay (days, including pre-enrollment)	5	2
Mortality	Alive at final recorded timepoint	Alive at final recorded timepoint
Incidence of Mechanical Ventilation	None	None
Duration of Supplemental Oxygen	3 days	2 days

Source: Adapted from Applicant submission

Dose/Dose Response, Durability of Response, Persistence of Effect

The limitations of the study did not allow for assessments of dose/dose response, durability of response, or persistence of effect.

8.1.3. Assessment of Efficacy Across Trials

The small sample size limits the ability of Study 811 to provide a reliable assessment of efficacy in pediatric subjects for the COVID-19 indication. No efficacy conclusions can be drawn based on the results of the submitted trial data alone. The most relevant data for efficacy are provided by extrapolation from adult exposure data (see Section 6).

8.1.4. Integrated Assessment of Effectiveness

Substantial evidence of effectiveness for TCZ in the proposed pediatric population is supported by evidence from adequate and well-controlled studies of TCZ in adults with COVID-19 and predicted PK modeling and simulation for pediatric patients aged 2 years and older with COVID-19 (see Section 6).

8.2. Review of Safety

8.2.1. Safety Review Approach

The most directly relevant and applicable clinical trial database for TCZ in pediatric COVID-19 comprises data from 2 subjects in Study 811 (see above). However, in terms of overall exposure outside of the COVID-19 indication proposed, TCZ has been approved for other pediatric indications since 2011.

Due to the limited data from Study 811, safety data were also submitted from multiple data sources and indications to support the safety of TCZ for the proposed indication, as detailed in Table 5, above. The safety assessment of TCZ for pediatric COVID-19 relies in part on the applicability of data from the adult COVID-19 trials of TCZ, and TCZ data from non-COVID-19 indications. The International Council on Harmonization guideline E11A on pediatric extrapolation[5] (Version 21, August 2024) was used as a guide to determine the applicability of data from these other populations to the pediatric COVID-19 indication. The totality of safety data can be broadly divided into the following categories for the purposes of this review and a determination of safety, which are discussed in further detail below:

- Safety data from pediatric COVID-19 studies of TCZ
- Safety data from adult COVID-19 studies of TCZ, intended for extrapolation of safety
- Safety data from TCZ studies in approved pediatric indications (non-COVID-19)
- TCZ pharmacovigilance data, post-marketing data, and literature support

While each of these sources of data have limitations, the totality of data are adequate to support a conclusion of safety for TCZ in the proposed indication in the context of a serious, life-threatening disease with unmet need, in which additional data collection is not feasible (see Section 1.3).

8.2.2. Review of the Safety Database

Overall Exposure

The exposure of 2 subjects to TCZ in the newly submitted study WA43811 does not provide adequate exposure to assess safety in a pediatric population when viewed in isolation. However, TCZ has been approved for pediatric indication since 2011. As a result, supportive data with adequate pediatric exposure in patients 2 years of age and older were leveraged to provide the safety assessment for the pediatric COVID-19 indication. Specifically, the pediatric safety data from the previous approvals of TCZ for systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and cytokine release syndrome indications were reviewed for applicability to the proposed pediatric population.

[5] available at: https://database.ich.org/sites/default/files/ICH_E11A_Guideline_Step4_2024_0821.pdf

Adequacy of the safety database:

TCZ has been approved for pediatric indications since 2011. While the submitted safety database for Study 811 is not adequate to characterize the safety of TCZ in the pediatric COVID-19 indication alone, supportive data adequately characterizing the safety of TCZ in pediatric patients is provided by the exposure data reviewed for the systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and cytokine release syndrome indications, acknowledging uncertainties in applying data across conditions. The primary supportive data for this determination is the high-quality, 12-week, randomized, double-blind, placebo-controlled data among TCZ-naïve pediatric subjects provided by trial WA18221 (see Section 8.2.5.1, below). Additional reassurance is provided by the adult COVID-19 safety database through extrapolation, as discussed in 8.2.4. When considered together, the totality of data reviewed is determined to be adequate in the setting of the benefit-risk evaluation and unique context of the hospitalized pediatric COVID-19 indication.

8.2.3. Safety Data from Pediatric COVID-19 Trials (Study 811)

8.2.3.1. Adequacy of Applicant's Clinical Safety Assessments

General Assessment

The Applicant presented data from the two subjects enrolled in Study 811. Review information is provided for these data below. While these data from Study 811 are directly relevant to the assessment of safety in pediatric patients with COVID-19 in terms of adequacy, duration, and content of protocol-mandated assessments and analysis, the sample size of 2 total subjects enrolled is not sufficient alone to support the safety in pediatric patients for the proposed indication.

Issues Regarding Data Integrity and Submission Quality

There were no issues regarding data integrity or submission quality that affect the clinical assessment of safety for this application.

Categorization of Adverse Events

Adverse events were categorized using the MedDRA thesaurus. The NCI CTCAE version 5.0 was used for adverse event severity.

Routine Clinical Tests

Routine clinical testing for the study included vital signs, physical exams, and laboratory testing including chemistry and hematology.

8.2.3.2. Safety Results

Deaths

There were no deaths during the study.

Serious Adverse Events

One subject had one SAE of device dislocation during the study.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations due to adverse effects during the study.

Significant Adverse Events and Treatment Emergent Adverse Events

One subject experienced two adverse events during the study. The first AE, device dislocation, was categorized as a SAE. The second AE, neutropenia, was categorized as Grade 1 in severity.

Laboratory Findings

Investigators reported neutropenia in one subject, as discussed above.

Vital Signs

There were no clinically relevant trends in vital signs during the study.

Immunogenicity

The small sample size precludes any conclusions based on the immunogenicity safety data.

8.2.3.3. Safety Analyses by Demographic Subgroups

The small sample size of Study 811 precludes any clinically meaningful analysis of subgroups.

8.2.4. Extrapolation of Adult Safety Data in COVID-19 to Pediatric Safety in COVID-19

TCZ was approved as BLA 125276, supplement 138, on 21 Dec 2022 for the treatment of hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The primary evidence of efficacy

was derived from the open-label RECOVERY trial[6] (NCT04381936, PMID: 33933206), with supportive evidence from the COVACTA[7] (NCT04320615, PMID: 35475258), EMPACTA[8] (NCT04372186, PMID: 33332779), and REMDACTA[9] (NCT04409262, PMID: 34609549) trials. The safety database utilized for a determination of safety included the randomized, double-blind, placebo-controlled trials COVACTA, EMPACTA, and REMDACTA. The reader is referred to the product label under BLA 125276 and to the review by Dr. Robert H. Lim (dated 21 Dec 2022).

Guidance from ICH E11A provides the following questions that should be considered when considering pediatric extrapolation. These questions and their applicability to the current submission are discussed below.

1. **What is the age-range of the target pediatric population to be studied as part of the safety extrapolation?**

The age-range of the target pediatric population to be studied is ≥2 to 18 years of age.

2. **What amount/quality of safety data are available from the reference population?**

The primary safety database from the adult reference population comprises data from three randomized, double-blind, placebo-controlled trials of TCZ in adults with COVID-19, with eponyms REMDACTA, COVACTA, and EMPACTA. These randomized trials evaluated a total of 974 subjects who received TCZ versus 485 who received placebo. The quality, content, and duration of the collected safety data from these three studies were considered adequate to support the safety assessment for approval in adults.

While not part of the basis for a safety determination in adults with COVID-19, further supplemental safety data supporting the safety of TCZ for adult subjects hospitalized with COVID-19 are provided by multiple additional trials available in the scientific literature that examined TCZ in the adult COVID-19 indication but did not form the basis of a determination of safety for the approval, including the RECOVERY trial.

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[6] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206

[7] Rosas IO, et al. Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). EClinicalMedicine. 2022 May;47:101409. doi: 10.1016/j.eclinm.2022.101409. Epub 2022 Apr 21. PMID: 35475258

[8] Salama C, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jan 7;384(1):20-30. doi: 10.1056/NEJMoa2030340. Epub 2020 Dec 17. PMID: 33332779

[9] Rosas IO, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med. 2021 Nov;47(11):1258-1270. doi: 10.1007/s00134-021-06507-x. Epub 2021 Oct 5. PMID: 34609549

3. Are there known on- or off-target effects of the investigational drug relevant to pediatric safety?

Previous pediatric approvals have noted that IL-6 inhibition could potentially have effects on immune and skeletal system development, and effects on rare outcomes such as malignancy are not well characterized, which would be relevant to pediatric use. These long-term potential risks of TCZ continue to be evaluated through studies associated with PMR 2678-2 (See pJIA review under BLA125276 on 02 May 2025 from Emily Gotschlich). The required study has undergone multiple revisions, and final clinical study reports are not available to quantify and characterize these risks at the time of this review. While the long-term safety of use of TCZ is unknown (e.g., in sJIA/pJIA patients), these potential effects on immune and skeletal system development are likely less relevant in the setting of the single dose use-case for the COVID-19 indication.

More broadly, the safety profile of TCZ includes the following known risks described in product labeling:

- Warnings and precautions: serious infections including fatal infections (bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens), gastrointestinal perforation, hepatotoxicity resulting in liver transplant or death, guidance on laboratory monitoring due to the risk of neutropenia and thrombocytopenia, immunosuppression with notes regarding increased risk of malignancies with immunosuppressants, hypersensitivity reactions including anaphylaxis and drug reaction with eosinophilia and systemic symptoms (DRESS) including fatal events, warnings regarding the use of TCZ in demyelinating disorders, and avoidance of live vaccine administration
- Common adverse reactions with an incidence of at least 5% include upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, and injection site reactions
- Indication-specific adverse event profiles from the pooled adult safety population of the EMPACTA, COVACTA, and REMDACTA trials as part of the TCZ COVID-19 development program include the following additional terms that occurred in at least 3% of the TCZ-treated patients and more commonly than in the pooled placebo arm:
    - Hepatic transaminases increased
    - Constipation
    - Urinary Tract Infection
    - Hypertension
    - Hypokalemia
    - Anxiety
    - Diarrhea
    - Insomnia
    - Nausea

(b) (4)

The duration of therapy with TCZ is again relevant in considering these adverse events and adverse reactions since the Applicant proposes a single-dose for the pediatric COVID-19 indication. In this setting, the adult data from the COVID-19 indication may be the most relevant to support pediatric safety.

However, the relationship between duration of TCZ use and the serious adverse reactions noted above is not characterized in the approved labeling for any indication. Because the relationship between duration of use and adverse events is unclear, the rare events noted in the adult development programs for various indications may still be relevant to pediatric single dose use for COVID-19 (e.g., serious and fatal infections, immunosuppression in the setting of concomitant corticosteroid therapy). In addition, patterns of neutropenia, thrombocytopenia, and liver enzyme elevations occurred in the adult COVID-19 program despite only limited, episodic use for this indication.

4. **Are data needed to account for age-specific short- and longer-term adverse effects in the target pediatric population, which may not have been identified in studies in the reference population?**

While the noted increased risk of malignancy with immunosuppression is an important concern in pediatric subjects, it is not expected that the short duration of use of TCZ for COVID-19 would be sufficient to increase the risk of malignancy in a clinically meaningful way. The Applicant is in the process of collecting data regarding long-term safety including immunologic and skeletal development through a previous PMR, as discussed above. The other known risks and adverse reactions to TCZ in the adult populations do not raise concern for longer-term adverse effects that would require additional studies in the target pediatric population.

5. **How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?**

The duration of treatment in the adult COVID-19 population is expected to be similar to the proposed pediatric COVID-19 population. The available pediatric data from 2 pediatric subjects with COVID-19 do not allow for a direct estimate of treatment effect size. However, the Applicant has provided an estimate of treatment effect size that relies on model-based PK/exposure simulation and extrapolation. This estimated effect size is proposed to be similar to the adult effect size, in part because the model relies heavily on adult data.

6. **How do the expected drug exposures in the reference and target pediatric populations compare? Does the exposure needed to target a specific PD effect or clinical response predict a specific toxicity in the target pediatric population?**

The Applicant proposes doses of 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. Both dosing strategies have been previously approved in pediatric patients for other indications, including those for chronic use.

Drug exposures are expected to be comparable to the adult reference population in clinical use. Clinical pharmacology review of the data (see Section 6.3.2, above) notes that PK exposure from the two pediatric patients with COVID-19 received TCZ 12 mg/kg IV in Study WA43811 were within the exposure range in adult patients with COVID-19 and in patients with pJIA, sJIA, RA and CRS.

This reviewer leveraged previous analyses from the Applicant and the review team for the pJIA indication, summarized in Dr. Nikolay Nikolov's primary clinical review (See Section 7.5.1 of primary review under BLA125276 on 25 Mar 2013) to obtain information on the relationship between PK-exposure and toxicity. These analyses assessed adverse events rates by TCZ exposure quartiles, incorporating data from the 8 mg/kg and 10 mg/kg doses in subjects <30 kg for chronic administration. Dr. Nikolov concluded that the analyses do not indicate a clear TCZ PK exposure dependence for clinical safety events in patients with pJIA to a duration of 16 weeks. While these analyses utilized a 10 mg/kg dose that differed from those proposed for COVID-19, the single-use exposure proposed for the pediatric COVID-19 indication is considerably shorter than the 16-week timeframe evaluated, which provides some reassurance regarding any exposure-toxicity relationship.

7. **What information is already known from non-clinical sources that can be leveraged to the target population?**

There are no additional nonclinical safety data that allay the concerns for adverse events raised in the adult TCZ COVID-19 development program and other TCZ development programs.

8. **Are there other differences between the reference and target population that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population, excipients in the formulation for the reference population)?**

Standard of care medical therapies for adult COVID-19 are similar to those utilized in pediatric COVID-19. These include corticosteroids, supplemental oxygen, remdesivir, and supportive care.

Pediatric COVID-19 is characterized by some differences from the reference adult population. First, publicly available data (e.g., CDC data, available at: https://www.cdc.gov/covid/risk-factors/index.html) and studies suggest multiple comorbidities that can be associated with worse clinical outcomes in adult COVID-19, including diabetes, cancer, hypertension, chronic kidney disease, obesity, chronic lung disease, immunocompromise, chronic liver disease, HIV, and cardiovascular disease. While many of these comorbidities may be present in pediatric subjects, they may be present in a lower proportion of children, and children are less likely to present with multiple comorbidities.

One additional feature of the pediatric COVID-19 spectrum of disease is that pediatric patients may be at risk of MIS-C or PIMS-TS occurring within several weeks following acute infection with SARS-CoV-2, which is not present in the reference population of adults. MIS-C/PIMS-TS represents an area of uncertainty for the pediatric use of TCZ, since the submitted materials do not contain data that are able to characterize the effect of TCZ – if any – on MIS-C/PIMS-TS. This is not intended to imply a specific risk for MIS-C/PIMS-TS due to TCZ use, indeed, limited case reports and an open-label substudy from the RECOVERY trial (NCT04381936) advocate for the use of TCZ to manage this condition. However, the occurrence of MIS-C/PIMS-TS represents a fundamental difference in the clinical presentation of COVID-19 between pediatric patients and adults that is not adequately addressed by the available data and is not encompassed as part of the intended indication.

Conclusions on Extrapolation of Adult COVID-19 Safety Data to Pediatric COVID-19

Based on the totality of the data, it is reasonable to extrapolate adult safety data from COVID-19 to the pediatric indication as part of a broader decision for safety including supportive data from the pediatric pJIA indication (discussed below) and the limited available data from Study 811 and the Applicant's pharmacovigilance database submitted from children with COVID-19. The decision to accept extrapolation of adult safety for this benefit-risk evaluation relies primarily on the narrow and unique set of particular conditions present for this disease and the context of the available data. This decision relies on the judgment that, for patients hospitalized and requiring supplemental oxygen or higher levels of care, their COVID-19 represents a serious and life-threatening condition with high unmet need for therapies in pediatric patients who progress to this severity of disease. Importantly, this decision relies on the context of the data coming from a novel pandemic viral infectious disease that represented a Public Health Emergency with use of TCZ under an Emergency Use Authorization for over four years to date. The decision also incorporates the consideration that additional data collection is infeasible due to the introduction of safe and effective vaccines directed against SARS-CoV-2 and COVID-19, viral evolution with variants that have been associated with less severe outcomes, and increasing rates of immunity in the community. Finally, this decision to extrapolate adult safety data to pediatric safety in COVID-19 is importantly supported by the availability of high-quality supportive pediatric safety data from a separate pediatric indication with a longer duration of chronic dosing (see below).

8.2.5. Safety Data from Approved Pediatric Indications (non-COVID-19)

8.2.5.1. Safety Data Supporting the Systemic Juvenile Idiopathic Arthritis (sJIA) Indication

Sources of Safety Data

Trial WA18221 formed the primary safety database for BLA 125276, Supplement 22, to provide the basis of approval of TCZ for the sJIA indication. Additional randomized safety data were submitted for the sJIA application from trial MRA316JP, supplemented by non-randomized safety data from studies MRA011JP, MRA317JP, MRA324JP, but did not form the basis for

approval. The safety data in the sJIA development program were reviewed thoroughly in the primary clinical review by Dr. Kathleen Coyle (page 571 of 808), the Cross-Discipline Team Leader Review by Dr. Sarah (Okada) Yim (page 505 of 808), and the Summary Review of Regulatory Action memo by Dr. Badrul Chowdhury (page 499 of 808), available as part of the action package submitted for BLA 125276, supplement 22, on 01 Aug 2012 by Mary Grace Lubao. The study design and relevant safety results for trial WA18221 are summarized below.

The Summary Review of Regulatory Action memo for this supplement relates the following regarding the safety of TCZ for subjects 2 years and older with sJIA:

- The safety profile of Actemra in patients with rheumatoid arthritis has already been established. The safety data with Actemra in patients with sJIA comes from the single study WA18221 ... Given the limited population and the known safety information from other populations, the safety database in patients with sJIA is acceptable.
- Actemra has safety concerns, including serious infections, gastrointestinal perforation, and changes in blood counts and liver function tests. The clinical program submitted to support this new indication was limited in size due to the patient population, but no unique safety signal was identified.
- Currently, there is no approved treatment for the treatment of sJIA. Given the submitted efficacy data, unmet need, and the known safety findings, the overall risk benefit profile in patients with sJIA is acceptable.

Trial WA18221

Trial WA18221 (NCT00642460, literature reference PMID: 23252525) was a three-part, 2:1 randomized, double-blind, placebo-controlled study with escape treatment with TCZ and open-label extension among 112 pediatric subjects with sJIA with an inadequate response to NSAIDS and corticosteroids, with or without concomitant methotrexate treatment. The randomized portion of the trial included TCZ "escape criteria" for subjects with clinical worsening to begin TCZ or increase TCZ dose. Notably, 101 (90%) of enrolled subjects utilized oral glucocorticoids (max dose of 0.5 mg/kg prednisone equivalent or 30 mg per day, whichever was lowest) at baseline and during the study, and 78 (70%) of these subjects also received concomitant methotrexate at baseline and during the study for their sJIA. The three parts of the study had the following characteristics:

- Part 1: a 2:1 R, DB, PC, 12-week study of TCZ IV 8 mg/kg Q2Wk (or 12 mg/kg for subjects <30 kg) versus placebo in 112 pediatric subjects 2 to 17 years of age with sJIA
- Part 2: a 92-week, single-arm, open-label extension study of TCZ in pediatric subjects 2 to 18 years of age continuing from Part 1
- Part 3: a 3-year, single arm, open-label extension study of TCZ in pediatric subjects 2 to 18 years of age continuing from Part 2

The relevant portion of the study for purposes of review of the COVID-19 indication is the randomized study data to Week 12 (Part 1).

Trial WA18221: Study Population

Available data regarding the study population for Part 1 are summarized in Table 11, below.

Table 11 sJIA Study WA18221 (ITT Population): Baseline Demographic and Clinical Disease Characteristics

Demographic or Clinical Disease Parameters	Randomized Treatment	
	PBO N = 37	Any TCZ N = 75
Sex		
Male	20 (54%)	36 (48%)
Female	17 (46%)	39 (52%)
Age (years)		
Mean (SD)	9 (4)	10 (5)
Weight (kg)		
Mean (SD)	32 (17)	35 (21)
Height (cm)		
Mean (SD)	121 (20)	126 (24)
Race*		
American Indian/Alaska	2 (5%)	0
Black	0	1 (1%)
White	32 (86%)	67 (89%)
Other	3 (8%)	7 (9%)
Ethnicity		
Hispanic	12 (32%)	20 (27%)
Non-Hispanic	25 (66%)	55 (73%)
Region*		
North America	8 (22%)	16 (21%)
Europe	18 (49%)	43 (57%)
South America	10 (27%)	12 (16%)
Rest of World	1 (3%)	4 (5%)
Duration of Disease (years)		
Mean (SD)	5 (4.5)	5 (4)
Background oral corticosteroid dose, baseline and through the study (mg/kg/day)		
Mean (SD)	0.27 (0.17)	0.29 (0.18)
Subjects with ≥0.3 mg/kg/day	18 (49%)	37 (49%)
Background methotrexate dose, baseline and through the study		
YES	26 (70%)	52 (69%)
Prior use of a biologic Agent		
YES	29 (78%)	63 (84%)

Source: Reproduced and adapted from primary clinical review of Dr. Kathleen Coyle (referenced above), based on data adapted from WA18221 Clinical Study Report.
*Categorization represents items included in source material.

Trial WA18221: Deaths to Week 12

There were no deaths during the randomized treatment period.

Trial WA18221: Serious Adverse Events to Week 12

Serious adverse event data in Study WA18221 are summarized in Table 12, below.

Table 12 sJIA Study WA18221 (Randomized Safety Population to Week 12): Serious Adverse Events

Serious Adverse Event	Treatment	
	PBO N = 35 N (%)	**Any TCZ N = 75 N (%)**
Any SAE	0	3 (4)
Infection and Infestations	0	2 (3)
Arthritis Bacterial	0	1 (1)
Varicella	0	1 (1)
Skin and Subcutaneous Tissue Disorders	0	1 (1)
Angioedema	0	1 (1)
Urticaria	0	1 (1)

Source: Adapted from WA18221 Clinical Study Report. (resource: \\CDSESUB1\evsprod\BLA125276\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\systemic-jia\5351-stud-rep-contr\study-wa18221\wa18221.pdf)

Trial WA18221: Treatment-Emergent Adverse Events to Week 12

Summary data regarding adverse events detailed in the review by Dr. Coyle are summarized in Table 13, below.

Table 13 sJIA Study WA18221 (Randomized Safety Population to Week 12): Common Adverse Events

Adverse Event	Treatment	
	PBO N = 35 N (%)	**Any TCZ N = 75 N (%)**
Upper Respiratory Tract Infection	4 (11)	10 (13)
Nasopharyngitis	1 (3)	8 (11)
Headache	3 (8)	7 (9)
Diarrhea	1 (3)	5 (7)
Urticaria	0	3 (4)
Vomiting	0	3 (4)
Neutropenia	1 (3)	3 (4)
Oropharyngeal Pain	1 (3)	3 (4)
Arthropod Bite	0	3 (4)
Back Pain	0	3 (4)
Viral Gastroenteritis	0	3 (4)
Cough	1 (3)	2 (3)
Dizziness	1 (3)	2 (3)
Hematuria	1 (3)	2 (3)
Abdominal Pain	0	2 (3)
Dysmenorrhea	0	2 (3)
Gastrointestinal Disorder	0	2 (3)
Pharyngitis	2 (5)	2 (3)

Source: Reproduced and adapted from primary clinical review of Dr. Kathleen Coyle (referenced above), based on data adapted from WA18221 Clinical Study Report.

Additional relevant data categorizations were provided in the Clinical Study Report and are adapted in Table 14, below.

Table 14 sJIA Study WA18221 (Randomized Safety Population to Week 12): Adverse Events by Selected System Organ Class Groupings

Adverse Event	Treatment	
	PBO N = 35 N (%)	**Any TCZ N = 75 N (%)**
Any AE	23 (62)	66 (88)
Any Infection AE	11 (30)	34 (45.3)
Any Gastrointestinal Disorder AE	2 (5)	14 (19)
Any Skin and Subcutaneous Disorder AE	2 (5)	12 (16)
Any Musculoskeletal and Connective Tissue Disorder AE	5 (14)*	9 (12)
Blood and Lymphatic System Disorders AE	2 (5)	6 (8)
Investigations AE	0	6 (8)**

Source: Adapted from WA18221 Clinical Study Report. (resource: \\CDSESUB1\evsprod\BLA125276\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\systemic-jia\5351-stud-rep-contr\study-wa18221\wa18221.pdf)
*Note that these events were labeled as preferred term "juvenile arthritis"
**Note that these events were attributed primarily to AST, ALT, and/or bilirubin total laboratory value increases

Trial MRA316JP

MRA316JP (NCT00144599, literature reference PMID: 18358927) was a R, DB, PC, 12-week withdrawal study of ongoing treatment with TCZ (N = 20) versus withdrawal to placebo (N = 23) after 6 weeks of open-label TCZ treatment, among a selected responder population of 43 subjects with sJIA age 2 to 19 years of age from the 56 total enrolled pediatric subjects.

While these data provide some limited support to characterize the safety of TCZ in pediatric populations, the initial open-label administration of TCZ to all subjects in the study limits the interpretation of the safety data from the randomized, double-blind, placebo-controlled, TCZ-withdrawal portion of the study for purposes of informing a determination of safety in another condition such as COVID-19.

Comparability of Tocilizumab Use-Case and Condition

SJIA is an idiopathic condition characterized by systemic inflammation, symptoms and biomarkers of systemic inflammation (e.g., fevers, leukocytosis, elevated erythrocyte sedimentation rate, hyperferritinemia), and multiorgan involvement (e.g., joints, lymphadenopathy, hepatosplenomegaly, uveitis). The clinical course of sJIA can include severe inflammatory complications such as macrophage activation syndrome and death. TCZ use in sJIA occurs not uncommonly in the presence of severe active inflammatory manifestations of the disease, and TCZ can be administered as add-on therapy to other immunosuppressive drugs, such as systemic corticosteroids and/or methotrexate.

While the underlying acute infectious cause of COVID-19 and chronic idiopathic inflammatory cause of sJIA exhibit important differences, both conditions include broadly dysregulated inflammation and dysregulated release of multiple cytokines leading to systemic inflammation and multiorgan manifestations. Both conditions may often involve the use of multiple immunosuppressive drugs in the setting where TCZ use is considered as an appropriate treatment option.

Approved Labeling of Tocilizumab for sJIA

TCZ is approved for the treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis. Pediatric dosing for intravenous TCZ includes approved doses of 8 mg/kg (or 12 mg/kg for patients less than 30 kg), and dosing is not changed by the presence or absence of underlying corticosteroid treatment.

In addition to the Warnings and Precautions shared across TCZ indications, relevant portions of labeled clinical trials experience with TCZ in sJIA include the following:

- Infections: In the 12-week controlled phase, the rate of all infections in the ACTEMRA-IV group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the 12-week controlled phase, the rate of serious infections in the ACTEMRA-IV group was 11.5 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.
- Macrophage activation syndrome: In the 12-week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment
- Infusion reactions: In the 12-week controlled phase, 4% of ACTEMRA-IV and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment. Within 24 hours after infusion, 16% of patients in the ACTEMRA-IV treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA-IV group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia, and headache. One of these events, urticaria, was considered serious.
- Neutropenia: During routine monitoring in the 12-week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the ACTEMRA-IV group, and in no patients in the placebo group.
- Thrombocytopenia: During routine monitoring in the 12-week controlled phase, 1% of patients in the ACTEMRA-IV group and 3% in the placebo group had a decrease in platelet count to no more than 100,000 per mm^3.
- Elevated Liver Enzymes: During routine laboratory monitoring in the 12-week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA-IV group and in 0% of placebo patients.
- Lipids: During routine laboratory monitoring in the 12-week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA-IV

group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA-IV group and 0% of the placebo group.

Duration of Treatment

The R, DB, PC safety data from WA18211 considered for this review included TCZ administration for a total of 12 weeks in previously TCZ-naïve pediatric patients.

Conclusions on the Applicability of Systemic Juvenile Idiopathic Arthritis Safety Data to the Pediatric COVID-19 Indication

Results from Part 1 of Study WA18221 represent high quality, randomized, double-blind, placebo-controlled, safety data from 112 TCZ-naïve pediatric subjects with systemic disease and concomitant corticosteroid use from a serious condition characterized by multisystem inflammation. When considering the applicability of data provided by the R, DB, PC, 12-week trial WA18221 utilized for the determination of safety of TCZ for the sJIA indication, the chronic duration of administration for sJIA raises confidence in the safety of the acute single-dose use of TCZ at equivalent doses that is proposed for the COVID-19 indication. Given these conditions, it is reasonable to utilize these data to support the safety of TCZ for the pediatric COVID-19 indication proposed, in conjunction with partial extrapolation of safety data from the adult COVID-19 program. As noted above, this decision relies on the context of the data coming from a novel pandemic viral infectious disease that represented a Public Health Emergency, use of TCZ under an Emergency Use Authorization, the consideration that additional data collection is infeasible, and a combination of high-quality R, DB, PC data from the adult COVID-19 indication and the pediatric sJIA of sufficient duration to inform the decision.

8.2.5.2. Safety Data Supporting the Polyarticular Juvenile Idiopathic Arthritis (pJIA) Approval

Sources of Safety Data

Trial WA19977 formed the primary safety database for BLA 125276, Supplement 64, to provide the basis of approval of TCZ for the pJIA indication. Additional safety data were submitted for the pJIA application from non-randomized studies MRA318JP and MRA319JP, but these studies did not form the basis for approval. The safety data in the pJIA development program were reviewed thoroughly in the primary clinical review by Dr. Nikolay Nikolov (page 507 of 870), the Cross-Discipline Team Leader Review by Dr. Sarah (Okada) Yim (page 481 of 870), and the Summary Review of Regulatory Action memo by Dr. Badrul Chowdhury (page 474 of 870), available as part of the action package submitted for BLA 125276, supplement 64, on 07 May 2013 by Mary Grace Lubao. The study design and relevant safety results for trial WA19977 are summarized below.

The Summary Review of Regulatory Action relates the following regarding the safety of TCZ for subjects 2 years and older with pJIA:

- The safety profile of Actemra in patients with rheumatoid arthritis has already been established. The safety data with Actemra in patients with pJIA comes from the single study WA19977. Given the limited population and the known safety information from other populations, the safety database in patients with pJIA is acceptable for approval. However, long term safety of use of Actemra in pJIA patients is unknown and a post-marketing safety study will be required to evaluate risks such as malignancies, serious infections, gastrointestinal perforations, and effect on skeletal growth and development. Actemra will be the first IL-6 targeting product for pJIA. IL-6 has known effects on immune and skeletal system development, and existing safety data for Actemra in pediatric patients are limited.

Trial WA19977

Study WA19977 (NCT00988221, literature reference PMID: 24834925) was a R, DB, PC, 24-week withdrawal study of ongoing treatment with TCZ (N = 82) versus withdrawal to placebo (N = 84) after 16 weeks of non-randomized TCZ treatment, among a selected responder population of 166 (of the 188 subjects enrolled) subjects with pJIA ages 2 to 17 years old with inadequate response or intolerance to methotrexate, followed by an additional 64 weeks of open label treatment. 148 (89%) of these subjects received concomitant methotrexate at baseline and during the study.

The run-in and withdrawal study design of MRA318JP implies that no portion of this study represents randomized, double-blind, placebo-controlled data from TCZ-naïve subjects. Because of this design, the data from MRA318JP are not directly applicable to characterizing the safety of TCZ in the proposed COVID-19 pediatric population, since the majority of pediatric subjects with COVID-19 would be unlikely to have previous TCZ exposure. However, study MRA318JP still provides supplemental safety data from the randomized withdrawal portion of the study as well as additional exposure data.

In addition, and pertinent to the questions of exposure dependence in laboratory abnormalities and AEs as well as the applicability of TCZ safety data across populations, Dr. Nikolov's primary clinical review included analyses of dose-dependency of adverse events among 10 mg/kg and 8 mg/kg dose groups in patients with a body weight less than 30 kg. Additional analyses included PK exposure dependence of common adverse events in the System Organ Class categories of "All Body Systems", "Infections and Infestations", and "Gastrointestinal Disorders" across quartiles of PK exposure (see Table 15, below). Dr. Nikolov's review concludes that the analyses conducted as part of the pJIA safety review do not indicate a clear TCZ PK exposure-dependence of clinical safety in patients with pJIA based on 16-week data across PK exposure quartiles. In addition, Dr. Nikolov's review included analyses of the exposure-adjusted event rates across indications of pJIA, adult rheumatoid arthritis, and sJIA as a method of comparing AE rates across adult and pediatric indications (see Table 16, below). Dr. Nikolay concluded two things from these data. First, that the rates of the AEs and SAEs were highest in the sJIA program, consistent with the generally much sicker population of sJIA, which is at a higher

baseline risk of developing toxicities compared with the rest of the subsets of juvenile idiopathic arthritides or the adult RA population. Second, that the safety profile of the pJIA program is consistent with the overall safety profile of TCZ in adult RA patients. These conclusions suggest data-driven support for the extrapolation of TCZ safety from adult to pediatric populations in related conditions, with appropriate consideration of the underlying clinical condition.

Table 15 Tocilizumab pJIA Review: Study WA19977: Common AE Rates by System Organ Class and Preferred Term by PK Exposure Quartiles to Week 16 [AUC4wks, Cmax, and Cwk15]

Body System Preferred Terms	AUC_{4wks}			
	Q1 N=45 n [P100-PY]	Q2 N=44 n [P100-PY]	Q3 N=44 n [P100-PY]	Q4 N=44 n [P100-PY]
All Body Systems	74 [499.8]	73 [511.3]	117 [879.5]	79 [493.0]
Infections and infestation	27 [182.4]	31 [217.1]	36 [270.6]	18 [112.3]
Gastrointestinal disorders	11 [74.3]	11 [77]	20 [150.3]	17 [106.1]
	C_{max}			
	Q1	Q2	Q3	Q4
All Body Systems	78 [528.2]	81 [591.4]	93 [692.2]	91 [551.1]
Infections and Infestation	34 [230.2]	23 [167.9]	31 [230.7]	24 [145.3]
Gastrointestinal disorders	10 [67.7]	19 [138.7]	15 [111.7]	15 [90.8]
	C_{wk16}			
	Q1	Q2	Q3	Q4
All Body Systems	88 [633.5]	68 [517.0]	97 [701.3]	81 [511.3]
Infections and Infestation	33 [237.5]	21 [159.7]	30 [216.9]	21 [132.6]
Gastrointestinal disorders	10 [72.0]	10 [76.0]	19 [137.4]	19 [119.9]

Source: Table 56 of the Primary Clinical Review of BLA125276, Supplement 64, by Dr. Nikolay Nikolov (adapted from Applicant's WA19977 clinical study report, Table 28) available on page 604 of 870 of the action package submitted for BLA 125276, supplement 64, on 07 May 2013 by Mary Grace Lubao.

Table 16 Tocilizumab pJIA Review: Comparison of Overall Safety in pJIA, Adult Rheumatoid Arthritis, and sJIA Development Programs

Comparison of Overall Safety in pJIA Adult RA, and sJIA Development Programs			
	pJIA	Adult RA	sJIA*
N	188	4009	112
Exposure, PY	184	14993	202
Number of patients/events (rate per 100-PY)			
All AEs	159/885 (480)	3799/45198 (301)	111/1660 (822)
Infections and infestation	*115/302 (164)*	*3077/14112 (94)*	*102/570 (282)*
Gastrointestinal disorders	*60/131 (71)*	*2072/5467 (37)*	*67/145 (72)*
Deaths	0	85 (0.6)	3 (1.5)
SAEs	17/23 (13)	1255/2194 (15)	35/47 (23)
Serious infections	*9/9 (5)*	*507/668 (5)*	*20/22 (11)*
AEs leading to withdrawal	6/6 (3)	749/754 (5)	6/6 (3)
Neutrophils decrease, n (%)			
CTC Grade 3	8 (4%)	212 (5%)	26 (23%)
CTC Grade 4	-	33 (<1%)	2 (2%)
Platelets decrease, n (%)			
CTC Grade 3	1 (<1%)	18 (<1%)	1 (1%)
CTC Grade 4	1 (<1%)	14 (<1%)	-
ST elevation, n (%)			
CTC Grade 3	3 (2%)	35 (<1%)	3 (3%)
CTC Grade 4	-	3 (<1%)	1 (1%)
ALT elevation, n (%)			
CTC Grade 3	3 (2%)	129 (3%)	9 (8%)
CTC Grade 4	-	6 (<1%)	1 (1%)
Total bilirubin elevation, n (%)			
CTC Grade 3	1 (<1%)	2 (<1%)	-
CTC Grade 4	-	1 (<1%)	-
Source: Summary of Clinical Safety, Adapted from Tables 24. and 25 and 120-day safety update *the clinical data cut-off for the sJIA program is as of May 31, 2011, the two-year data from the ongoing study WA18221			

Source: Table 59 of the Primary Clinical Review of BLA125276, Supplement 64, by Dr. Nikolay Nikolov, available on page 607 of 870 of the action package submitted for BLA 125276, supplement 64, on 07 May 2013 by Mary Grace Lubao

Study MRA318JP

MRA318JP (NCT00144664) was a single treatment arm, open-label 12-week study of TCZ in 19 subjects 2 to 19 years of age with PJIA, as well as MRA319JP, the long-term extension of this study. As with Study MRA316JP, above, these data provide only limited support to characterize the safety of TCZ and do not contribute substantially to the determination of safety for the pediatric COVID-19 population.

Comparability of Tocilizumab Use-Case and Condition

In contrast to sJIA (above), pJIA is characterized by more limited inflammation, with lower levels of inflammatory biomarkers, and target-organ involvement generally limited to 4 or fewer joints. The clinical course of pJIA, when compared to sJIA, is less likely to include severe inflammatory complications. TCZ use in pJIA occurs as add-on therapy to other immunosuppressive drugs, such as methotrexate.

When compared with sJIA, the overall clinical condition of patients with pJIA shares fewer similarities to patients hospitalized with COVID-19 requiring additional oxygen support, mostly due to the lower severity and lack of systemic inflammatory response. Broadly, however, both

conditions may often involve the use of multiple immunosuppressive drugs in the setting where TCZ use is considered as an appropriate treatment option.

Approved Labeling of Tocilizumab for pJIA
TCZ is approved for the treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Pediatric dosing for intravenous TCZ is 8 mg/kg (or 10 mg/kg for patients less than 30 kg) with or without methotrexate.

While additional specific safety labeling of TCZ for the polyarticular juvenile idiopathic arthritis indication is provided in the labeling, the design of the pJIA trials discussed above limit the applicability of these safety data to the COVID-19 indication.

Duration of Treatment
Despite its R, DB, PC, design elements, the trial design of study WA19977 meant that these subjects were not TCZ-naïve, limiting the applicability of the noted safety events to the pediatric COVID-19 indication.

Conclusions on the Applicability of pJIA Safety Data to the Pediatric COVID-19 Indication
In the opinion of this reviewer, the safety data submitted for the pJIA indication incorporate significant uncertainties when considering their applicability to the COVID-19 indication. The available randomized pJIA safety data from WA19977 were double-blinded and placebo-controlled, however the subjects included had all previously received TCZ for 16 weeks and exhibited acceptable tolerability. Because of these limitations, the available pJIA safety data do not represent the quality of safety data that would directly inform safety conclusions for TCZ in the COVID-19 indication. However, acknowledging the uncertainties in applying data across different indications, available data from the pJIA development program and review do provide supportive data and analyses that inform the validity of the extrapolation of adult safety data in adults to related pediatric conditions as well as supporting a lack of PK exposure-dependence of adverse events among pediatric patients receiving TCZ.

8.2.5.3. Safety Data Supporting the Cytokine Release Syndrome (CRS) Approval

Safety Data for the CRS Indication
Safety data for the CRS indication are discussed in the Appendix (Section 17.4.1).

Conclusions on the Applicability of Cytokine Release Syndrome Safety Data to the Pediatric COVID-19 Indication
In the opinion of this reviewer, the safety data submitted for the CRS indication incorporate significant uncertainties when considering their applicability to the COVID-19 indication. Specifically, the available CRS data were not collected in dedicated interventional trials to evaluate the efficacy or safety of TCZ, but rather derived from secondary analyses of CAR T-cell trials. The review notes that no studies considered in the review incorporated TCZ-specific AE

collection. In addition, the designs of the considered studies limit the application of relatedness criteria and application of an AE to a single agent due to the multiple interventions that subjects received. Because of these limitations, the available CRS data do not represent the standard of high-quality data from well-controlled trials that would provide justification for applying or extrapolating the safety conclusions from CRS to a further determination of safety for TCZ for the COVID-19 indication.

8.2.5.4. Conclusions on the Application of Tocilizumab Pediatric Safety Data from Approved Indications to COVID-19

When considering whether TCZ safety data from other indications could be applicable to the pediatric COVID-19 indication, this review team concluded that the data from Study WA18221 in sJIA are relevant to support the safety of TCZ for the proposed pediatric COVID-19 indication, while data from the pJIA studies only provides additional supportive evidence. Data from Part 1 of Study WA18221 in sJIA represent high quality, randomized, double blind, placebo-controlled, safety data from 112 TCZ-naïve pediatric subjects with systemic disease and concomitant corticosteroid use from a serious condition characterized by multisystem inflammation. Adequate safety was demonstrated for chronic administration of TCZ in the sJIA indication, which raises confidence in the safety of the single dose use of TCZ at similar doses proposed for the pediatric COVID-19 indication. Given these conditions, it is reasonable to utilize these data as clinically meaningful evidence of the pediatric safety of TCZ to inform the safety assessment for TCZ for the proposed pediatric COVID-19 indication, in conjunction with and supporting the extrapolation of safety data from the adult COVID-19 program. The pJIA data provide supplemental support for particular questions such as the validity of safety data extrapolation with TCZ use from an adult to a pediatric population in a related condition, as well as the lack of clear PK exposure-dependence of adverse events.

As noted above, use of the safety data from approved indications relies on the unique context of these data gathered for an indication of a novel pandemic viral infectious disease that represented a Public Health Emergency, use of TCZ under an Emergency Use Authorization, the consideration that additional data collection will be infeasible, and a combination of high-quality R, DB, PC data from the adult COVID-19 indication and the pediatric sJIA of sufficient duration to inform the decision.

8.2.6. Safety in the Post-market Setting for COVID-19, CRS, and ARDS

Safety Concerns Identified Through Post-market Experience

Data from literature searches and pharmacovigilance data were submitted as part of this application, and – where relevant – are discussed above and in the Appendices.

8.2.7. Integrated Assessment of Safety

While the prevalence of hospitalized COVID-19 has decreased in pediatric subjects since the height of the COVID-19 pandemic and the issuance of EUA 099 for the use of TCZ, the population of pediatric patients who develop serious disease due to SARS-CoV-2 and are hospitalized with COVID-19 and require supplemental oxygen or mechanical respiratory support still represents a serious, life-threatening disease with an unmet need for safe and effective therapies. In this context, despite the uncertainties presented, the available safety data are sufficient to support a conclusion of safety for a single dose of intravenous TCZ within a benefit-risk framework that relies on treatment of a serious, life-threatening disease and an unmet need for safe and effective therapies.

This decision is informed by extrapolation of safety from the adequate adult safety database (Section 8.2.4), the availability of high quality pediatric safety data from an indication with systemic inflammation despite systemic corticosteroids and immunomodulators (i.e., sJIA, Section 8.2.5.1), the limited use proposed for the COVID-19 indication, and the long history of TCZ use in approved pediatric populations such as sJIA in addition to over 4 years of use in pediatric patients hospitalized with COVID-19 under EUA. The decision to accept these data as evidence of safety for the benefit-risk evaluation of TCZ in pediatric COVID-19 is dependent upon on the narrow set of particular conditions present for this disease and the context of the available data, as discussed above.

8.3. Conclusions and Recommendations

The safety of TCZ for pediatric patients ≥2 years of age hospitalized with COVID-19 requiring additional oxygen support is adequately demonstrated by the adult and pediatric safety data discussed in Section 8.1.4. The uncertainties present in the safety data are acceptable in the context of the benefit-risk assessment for this indication.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for the current application.

10 Pediatrics

The proposed indication encompasses pediatric subjects. The reader is referred to the review, above, for more details. The reader is also referred to the PMR/PMC section (Section 13) for additional information on ongoing relevant PMRs and PMCs for the safety of TCZ in pediatric patients.

In addition, this review clarifies the scope of pediatric waivers for BLA 125276 as part of its action on Supplement 149 (as well as BLA 125472, Supplement 061). The proposed indication for Supplement 149 reviewed above will add 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 extracorporeal membrane oxygenation (ECMO) to the previously approved adult indication. The current waiver of PREA-mandated studies under BLA 125276 was granted with the approval of Supplement 138 for COVID-19 in adults. Per the approval letter for Supplement 138, the granted waiver encompasses pediatric subjects less than 1 year of age, because studies in this patient population would be impossible or highly impracticable.

Extending Waiver of Pediatric Studies to Encompass 0 to Less Than 2 Years of Age
Based on our review of the available evidence in Supplement 149, the Division plans to extend the COVID-19 indication to 2 years of age and older. The current waiver of pediatric studies only provides a waiver for subjects less than 1 year of age. Therefore, the Division proposed (and the Pediatric Review Committee agreed) to revise the waiver for pediatric studies to also encompass patients 1 to < 2 years of age in the approval letter for the current supplement, for the same reason that studies in this age group would be impossible or highly impracticable. The text below documents the regulatory history and conveys the rationale behind the amendment of the pediatric waiver age. This amendment covers the “gap” that currently exists for assessment of pediatric patients 1 to < 2 years of age for the COVID-19 indication.

Regulatory History of Pediatric Waivers and Relevant PMRs
Genentech submitted their Initial Pediatric Study Plan (iPSP) on 30 Jun 2020. In this iPSP, the Applicant requested a waiver of pediatric studies for pediatric subjects 0-1 years of age, and a deferral of pediatric studies for subjects 2-17 years of age for the COVID-19 indication until the results of study WA42380 were available. The Agreed iPSP under IND 148225 from 05 Jan 2021 included a requested deferral of all proposed pediatric assessments for patients 0−17 years of age to enable safety and efficacy data to be obtained from the adult studies of TCZ in the

treatment of COVID-19 pneumonia, including the ongoing REMDACTA (WA42511) study. No drug-specific waivers of pediatric assessments were requested at this time.

Tocilizumab was authorized on 24 Jun 2021 through Emergency Use Authorization 099 for the treatment of COVID-19 in hospitalized adult 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).

A pediatric protocol for study WA43811 was submitted 29 Oct 2021. This initial submission of protocol WA43811 proposed a single arm, open label, PK, PD, and safety study for 30 pediatric subjects 2 to 17 years of age. The study was allowed to proceed.

PMR 4369-1 was included as part of the approval action for tocilizumab in the adult COVID-19 indication on 21 Dec 2022 (see action package from BLA 125276, Supplement 138). PMR 4369-1 stated "Conduct a pharmacokinetic, pharmacodynamic, and safety study in pediatric patients hospitalized with COVID-19", without criteria for the age range of the study. A waiver was granted for pediatric patients <1 year of age because studies would be impossible or highly impracticable. The existing EUA 099 was revised on 21 Dec 2022 (due to the adult approval action) to continue authorizing the emergency use of Actemra for the treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

The Applicant proposed a PMR milestone revision on 14 Oct 2022 under BLA 125276, eCTD 0867, SDN 1569. The Applicant noted that enrollment in WA43811 was extremely slow, with only 2 subjects enrolled since first site activation in February 2022. The Applicant proposed that the milestone dates for Study Completion and Final Report Submission for PMR 4369-1 and its ongoing associated study WA43811 be extended by two years due to slow recruitment, with new goals dates of December 2024 and June 2025, respectively.

In their meeting package from 07 Nov 2023, the Applicant noted ongoing enrollment challenges in study WA43811 and proposed a revised data package for consideration by the Division as a means for fulfillment of PMR 4369-1. The meeting package included the proposed indication of "Treatment of COVID-19 in hospitalized 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."

In a DPMH Consult Request document from 16 Nov 2023 under IND 148225, the consulting DPACC team stated the following, "At the time of the adult indication approval, a PMR was issued (PMR 4369-1) to conduct a PK/PD and safety study in pediatric patients hospitalized with COVID-19 ages 2 years and older receiving systemic steroids and on supplemental oxygen, non-invasive MV, iMV, or ECMO (n=30). At that time, the EUA was reissued for pediatric patients." However, this stated age range was erroneous, as it was not part of the PMR wording.

In a Written Response provided 19 Dec 2023 under IND 148225, the Division stated (verbatim) "Ultimately, the adequacy to support the safe and effective use of tocilizumab for the treatment of COVID-19 in hospitalized pediatric patients aged 2 years and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive mechanical ventilation, mechanical ventilation, or ECMO will be a review issue."

The ongoing review of submitted materials under BLA 125276 Supplement 149 includes limited data from study WA43811 in the COVID-19 indication, which recruited subjects using age criteria of 2 to 17 years of age (inclusive). The review also includes supportive safety data from study WA18221 in the systemic juvenile idiopathic arthritis indication, which recruited subjects between 2 and 17 years of age (inclusive). This reviewer also notes that no pediatric approval for tocilizumab includes subjects less than 2 years of age to date.

Based on the available safety information, an approval action in subjects younger than 2 years of age would not be justified. However, the current waiver of pediatric studies only encompasses pediatric subject less than 1 year of age. In considering a revision of the waiver, this reviewer notes the slow enrollment that prevented the full enrollment of study WA43811, attributed to the changing landscape of COVID-19.

An amended PREA waiver has been submitted through a PREA PeRC Template submitted under BLA 125276 on 30 Jun 2025 by Phuong Nina Ton, RPM to reflect the proposed regulatory decisions.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The supplemental application proposed to expand the indication for Coronavirus Disease 2019 (COVID-19) by inclusion of a new population, pediatric patients aged 2 years and older. The change in the indication affected the following sections of the Prescribing Information (PI): 1 INDICATIONS AND USAGE, 2 DOSAGE AND ADMINISTRATION, 8 USE IN SPECIFIC POPULATIONS, and 12 CLINICAL PHARMACOLOGY with minor changes in 6 ADVERSE REACTIONS and 14 CLINICAL STUDIES. The changes are the following:

1.7 Coronavirus Disease 2019 (COVID-19)

ACTEMRA® (tocilizumab) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult and pediatric patients aged 2 years and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

2.8 Recommended Dosage for Coronavirus Disease 2019 (COVID-19)

Administer ACTEMRA by intravenous infusion only.

The recommended dosage of ACTEMRA for treatment of patients with COVID-19 given as a single 60-minute intravenous infusion is:

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

8.4 Pediatric Use

COVID-19 – Intravenous Use

The safety and effectiveness of ACTEMRA have been established for the treatment of pediatric patients aged 2 years and older with COVID-19. Use of ACTEMRA in these age groups is supported by evidence from adequate and well-controlled studies of ACTEMRA in adults with COVID-19 *[See Adverse Reactions (6.11) and Clinical Studies (14.11)]*, predicted pharmacokinetic data modeling and simulation for pediatric patients aged 2 years and older with COVID-19 *[See Clinical Pharmacology (12.3)],* safety data from a randomized, double-blind, placebo-controlled study of ACTEMRA in pediatric patients aged 2 years and older with systemic juvenile idiopathic arthritis, and additional uncontrolled pharmacovigilance data in pediatric patients aged 2 years and older with COVID-19 who received ACTEMRA under Emergency Use Authorization.

12.3 Pharmacokinetics

The recommended dosage for pediatric patients aged 2 years and older with COVID-19 was based on the PK-sIL-6R modeling and simulation and the information was added to this subsection under the *COVID-19 -Intravenous Administration* heading with the following language:

COVID-19 -Intravenous Administration

Based on PK-sIL-6R modeling and simulation, the recommended dosing regimen for ACTEMRA is expected to result in comparable plasma exposures of tocilizumab in pediatric COVID-19 patients aged 2 years and older with COVID-19 as observed in adults with COVID-19 *[see Use in Specific Populations (8.4)].*

The Applicant has also submitted a labeling supplement to align the labels under BLA 125472/S-061.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required for this supplement.

13 Post-marketing Requirements and Commitment

No new or additional PMRs or PMCs are indicated based on the review of the current submission.

Human Carcinogenicity or Tumor Development

No additional data related to human carcinogenicity or tumor development were submitted for review. This reviewer notes the ongoing status of PMR 2678-2, noted below, that includes long-term assessments of carcinogenicity in pediatric subjects.

Human Reproduction and Pregnancy

Assessments of use of TCZ in pregnancy were conducted under the following fulfilled PMR:

- **PMR 2596-2:** Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes.

Pediatrics and Assessment of Effects on Growth

Ongoing or submitted assessments of long-term use of TCZ including pediatric patients are proceeding under the following PMRs:

- **PMR 2678-2:** A long-term safety study in pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of pediatric pJIA patients treated with other biologics as standard of care. Patients should be followed for 5 years.
- **PMR 3262-1:** Further characterize the safety of tocilizumab in the treatment of patients with chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome including the collection of data on the timing of tocilizumab administration relative to the nature and onset of adverse events. Submit the final data report and data set.

14 Division Director (Clinical) Comments

Genentech (The Applicant) has submitted a supplemental Biologics Licensing Application (sBLA 125276/S-149) for tocilizumab (TCZ, Actemra), a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody. The proposed indication is to expand the approved COVID-19 population to include pediatric patients aged 2 years and older hospitalized with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The proposed dosing regimen is a single dose of 12 mg/kg in patients < 30 kg and 8 mg/kg in patients ≥ 30 kg.

The review team has concluded that the safety and effectiveness of TCZ have been established for the treatment of pediatric patients aged 2 years and older with COVID-19, and I agree with their conclusion. Use of TCZ in this age group is supported by evidence from adequate and well-controlled studies of TCZ in adults with COVID-19, predicted pharmacokinetic data modeling and simulation for pediatric patients aged 2 years and older with COVID-19, safety data from a randomized, double-blind, placebo-controlled study of TCZ in pediatric patients aged 2 years and older with systemic juvenile idiopathic arthritis, and additional uncontrolled pharmacovigilance data in pediatric patients aged 2 years and older with COVID-19 who received ACTEMRA under Emergency Use Authorization.

The safety assessment relies on multiple sources of data, as outlined above. The conclusions of this safety review rely on the unique context of these data which were gathered for an indication of a novel pandemic viral infectious disease that represented a public health emergency, use of TCZ under an Emergency Use Authorization, a combination of high-quality data from the adult COVID-19 indication and chronic dosing of TCZ of sufficient duration in other approved pediatric indications (e.g. sJIA), and the consideration that additional data collection will be infeasible.

Benefit Risk Assessment and Regulatory Action
The review team has concluded that the submitted efficacy and safety data support the use of tocilizumab in treating pediatric patients aged 2 years and older hospitalized with COVID-19, and I agree with their conclusions. While the prevalence of hospitalized COVID-19 has decreased in pediatric subjects since the height of the COVID-19 pandemic, the population of pediatric patients who are hospitalized with COVID-19 and require supplemental oxygen or mechanical respiratory support still represent an unmet need for safe and effective therapies. In this context, the benefit-risk assessment for TCZ for the proposed indication is favorable.

The Division and the Applicant have reached agreement on final labeling language. The action for this application will be **Approval**. As a part of this approval, the PREA waiver will be updated to also include patients 1-2 years of age, such that the final waiver will be in patients < 2 years of age and EUA 99 will be revoked.

15 Appendices

15.1. References

Relevant references were provided as in-line citations.

15.2. Financial Disclosure

No new covered clinical studies, as defined in 21 CFR Part 54 (c), were submitted as part of the review of this BLA efficacy supplement. Since study WA43811 enrolled a total of 2 subjects and was not relied upon for a determination of efficacy, it was not considered a covered study under the regulation cited above.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. In Vivo Study

Study designation: WA43811
Study title: A Phase 1b, single-arm, open-label study evaluating the pharmacokinetics, pharmacodynamics, and safety of tocilizumab in pediatric patients hospitalized with COVID-19.
Study design: Study WA43811 was designed as a single-arm, uncontrolled, open-label study of tocilizumab to assess the pharmacokinetics, safety, and exploratory efficacy of tocilizumab 12 mg/kg IV once among up to 30 subjects less than 18 years of age with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The study included a screening period of up to 3 days. Enrolled subjects were administered a single dose of TCZ on study Day 1, and an optional second dose 8 to 24 hours later if clinically indicated. Subjects were then followed clinically for a total of 60 days. PK and PD samples were acquired on study Day 1, 2, 3, 7, 21, and 28, with an additional PD sample collected at Day 60.

Objectives:

Primary

- To characterize the pharmacokinetics of TCZ through Day 28

Secondary

- To characterize the pharmacodynamics of TCZ through Day 60
- To evaluate the safety of TCZ through Day 60

Exploratory

- To explore the efficacy of TCZ through Day 60
- To assess proof of activity by assessment of pharmacodynamic biomarkers and other disease biomarkers, including, but not limited to, CRP that can increase the knowledge and understanding of disease biology

Bioanalytical Method

A valid bioanalytical method was developed and used in analyzing the PK data.

Number of Subjects

- Planned: 30 pediatric participants to be enrolled from birth to less than 18 years old who were hospitalized with COVID-19, confirmed by positive PCR test, and who were receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation
- Enrolled: 2 pediatric participants

  One participant was (b) (6) and (b) (6) Both the participants were (b) (6) years of age. (b) (6) participant in the study was (b) (6) while (b) (6) participant's ethnicity was not stated.

Results

PK

Following the administration of one single dose of TCZ IV 12 mg/kg, TCZ concentration was maximal within 2 hours of TCZ injection in both participants and decreased steadily thereafter.

Table 17 Individual PK Concentrations

	Visit	Nominal Time (hr)	Actual Time (hr)	Drug Concentration (ug/mL)
Tocilizumab + SOC (N=2)				
(b) (6) / 12 mg/kg				
	Day 1 - Pre-Dose	-1	-1.08	BLQ
	Day 1	2	1.82	229
	Day 7	144	112.3	62.7
	Day 21	480	455.6	8.56
(b) (6), 12 mg/kg				
	Day 1 - Pre-Dose	-1	-1.27	BLQ
	Day 1	2	1.97	153
	Day 7	144	167.13	9.8
	Day 21	480	475.93	62

BLQ set to LLOQ/2 with LLOQ=0.1 ug/mL
Program: /_Projects/RO4877533_COVID-19_30441/NCA/WA43811/_WA43811_NCA/Step 3/NCA_TLGs/programs/l_pkconc.R
Output: /_Projects/RO4877533_COVID-19_30441/NCA/WA43811/_WA43811_NCA/Step 3/NCA_TLGs/output/l_pkconc_RO

Source: Listing of PK Data in 16.2.5 Compliance and Drug Concentration Data

PD

Serum concentrations for soluble interleukin 6 receptor (sIL-6R) and interleukin 6 both increased following the administration of TCZ, with a maximum observed on Day 21 in the 2 participants.

Table 18 Individual sIL-6R and IL-6 Concentrations

	Visit	Nominal Time (hr)	Actual Time (hr)	sIL-6R (ng/mL)	IL6 (ng/L)
Tocilizumab + SOC (N=2)					
(b) (6) / 12 mg/kg					
	Day 1 - Pre-Dose	-1	-1.08	33.5	
	Day 1	2	1.82	34.6	23
	Day 7	144	112.3	279	75
	Day 21	480	455.6	452	97.5
(b) (6) / 12 mg/kg					
	Day 1 - Pre-Dose	-1	-1.27	69.3	1.82
	Day 1	2	1.97	68.3	20.5
	Day 7	144	167.13	407	35.5
	Day 21	480	475.93	520	125

sIL-6R: soluble InterLeukin 6 Receptor
IL6: Interleukin 6
Program: /_Projects/RO4877533_COVID-19_30441/NCA/WA43811/_WA43811_NCA/Step 6/NCA_TLGs/programs/l_pkconc.R
Output: /_Projects/RO4877533_COVID-19_30441/NCA/WA43811/_WA43811_NCA/Step 6/NCA_TLGs/output/l_pdconc_RO

Source: Listing of PD Data in 16.2.5 Compliance and Drug Concentration Data

Conclusion
No statistical conclusion can be drawn from the study due to limited number of subjects (n=2). However, the PKPD data from the two subjects were within the range of that in adult patients with COVID and other pediatric patient population (See Table 4).

15.3.2. Pharmacometrics

A population PKPD model characterizing the PK of tocilizumab and the exposure of sIL-6r in subjects with COVID-19 from Study WA42380 and Study CA42481 was developed and reviewed in BLA125276/s-138 (see cross disciplinary team review in DARRTS on 21 Dec 2022). In this submission, based on the final PKPD model, simulations were performed on the tocilizumab and sIL-6R concentrations following the proposed dosing regimens–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 in pediatric patients with COVID-19. The results of the simulation have been used to update the labeling of tocilizumab in pediatric patients with COVID-19.

The simulation results showed that the PK and PD parameters were comparable between pediatrics (12 mg/kg TCZ IV for BW < 30 kg or 8 mg/kg TCZ IV for BW ≥ 30 kg) with COVID-19 pneumonia and adults (8 mg/kg TCZ IV) (Figure 1). Shown below are the model predictions used to inform the labeling:

- Based on PK-sIL-6R modeling and simulation, the recommended dosing regimen for ACTEMRA is expected to result in comparable plasma exposures of tocilizumab in pediatric COVID-19 patients as observed in adults with COVID-19.

- For one dose of 8 mg/kg tocilizumab IV in pediatric patients with a BW≥30kg, the estimated median (range) C_{max} and C_{day28} of tocilizumab were 135 (63.5-312) mcg/mL

and 0.0804 (below the quantification limit (BQL) -5.05) mcg/mL, respectively. For one dose of 12 mg/kg tocilizumab IV in pediatric patients (above 2 years of age) with a BW<30 kg, the estimated median (range) C_{max} and C_{day28} of tocilizumab was 163 (75.4-396) mcg/mL and 0.0814 (BQL-11.6) mcg/mL, respectively.

15.4. Additional Submitted Sources of Data

15.4.1. Tocilizumab Literature Search and Pediatric Pharmacovigilance Data in the COVID-19 Indication

The Applicant submitted a review of pharmacovigilance safety database findings as well as a literature search for TCZ use in the pediatric COVID-19 indication. These data were reviewed as part of the safety review for the pediatric COVID-19 indication.

COVID-19 Pediatric Pharmacovigilance Data

The pharmacovigilance data submitted included 258 cases of global, off-label, marketing data of TCZ use corresponding to the indication of COVID-19 or related terms from spontaneous reporting, literature reporting, clinical trial sources, and including subjects treated under EUA in the United States. The timeframe of cases examined was cumulative until 30 Apr 2024. The Applicant asserts that the majority of these cases correspond to the COVID-19 indication statement proposed, including the requirement for supplemental oxygen and concomitant corticosteroids.

Regarding the sources of pharmacovigilance data, the Applicant states the following:
The company safety database records information on the following:

- *Reports from interventional clinical trials: all cases with SAEs or some designate non-serious AEs, where tocilizumab is considered "suspect"*
- *Reports from unsolicited sources: including all serious and non-serious cases arising from spontaneous reports, scientific literature, Internet and digital media and other sources (e.g., newspapers and lay media)*
- *Reports from solicited sources: including all serious and non-serious cases arising from organized data collections systems, including non-interventional studies, market research and patient support programs*

The Applicant provided data on the characteristics of the examined pharmacovigilance cases (Table 19 and Table 20, below).

Table 19 COVID-19 Pharmacovigilance Data: Data Source Characteristics of Cases Involving the Use of Tocilizumab for COVID-19

Parameter	Number of Cases (%)
Total Cases	258 (100)

Reporter Type	Healthcare Professional	257 (99.6)
Data Source	Literature - Non-interventional Study or Program	153 (59.3)
	Literature - Spontaneous	90 (34.9)
	Spontaneous	11 (4.3)
	Clinical Study, Non-interventional study/program	4 (1.6)
Country	United States of America	100 (38.7)
	Rest of World	158 (61.3)

Source: Adapted from Applicant-submitted materials

Table 20 COVID-19 Pharmacovigilance Data: Demographic and Clinical Characteristics of Cases Involving the Use of Tocilizumab for COVID-19

Parameter		Number of Cases (%)
Total Cases		**258 (100)**
Sex	Female	90 (34.9)
	Male	126 (48.8)
	Not Reported	42 (16.3)
Age Range (Years)	< 2	28 (10.9)
	≥ 2 to <13	121 (46.9)
	≤ 13 to <18	109 (42.2)
Indication	COVID-19	212 (82.2)
	Multisystem inflammatory syndrome in children	27 (10.5)
	COVID-19 pneumonia	23 (8.9)
	Coronavirus infection	11 (4.3)
	Cytokine storm	9 (3.5)
	Suspected COVID-19	8 (3.1)
	Encephalopathy	5 (1.9)
	Cytokine release syndrome	3 (1.2)
	Multiple organ dysfunction syndrome	3 (1.2)
	Encephalitis	2 (0.8)
	Pneumonia	2 (0.8)
	SARS-CoV-2 test positive	2 (0.8)
	Multisystem inflammatory syndrome	2 (0.8)
	Acute respiratory distress syndrome	1 (0.4)
	Inflammation	1 (0.4)
	Inflammatory marker increased	1 (0.4)
	Acute respiratory failure	1 (0.4)
	Respiratory failure	1 (0.4)
	Hemophagocytic lymphohistiocytosis	1 (0.4)
	Pneumonia viral	1 (0.4)
	Post-acute COVID-19 syndrome	1 (0.4)
	Pulmonary alveolar hemorrhage	1 (0.4)
	Thrombotic microangiopathy	1 (0.4)

Source: Adapted from Applicant-submitted materials. Note that the cumulative total in the Indication column can exceed 100% because 59 cases listed multiple indications.

Pharmacovigilance Adverse Event Data

The Applicant's submission notes 258 patients identified by Genentech through their global pharmacovigilance database, reporting a total of 607 AEs. Of these 258 cases, 237 patients provided data in which no clinical adverse event was reported; these cases comprised 540 of 607 AEs with terms such as "off-label use", "no adverse event", "intentional product use issue"

and similar terms. The remaining 21 cases reported 67 AEs. 59 of 607 AEs (9.7%) were reported as serious.

5 of the 21 AE cases reported AEs with fatal outcome. 3 of the 21 AE cases reported AEs that were already part of TCZ approved labeling. The remaining 18 of these 21 AE cases reported AEs that were not previously labeled for TCZ. Through additional information, 5 of these 21 AE cases were excluded from further review due to negative latency in 4 cases (i.e., the adverse event began prior to TCZ use) and a claim of counterfeit TCZ use in 1 case. After these exclusions, 13 cases reported 54 AEs mapped to preferred term listings. While the potential selection bias of reported cases inherent in the pharmacovigilance data must again be acknowledged, each listed AE was reported in no more than 0.5% of the reported pharmacovigilance population of 258 cases. In the majority of these cases, reported AEs had potential alternative explanations (e.g., COVID-19 and critical illness) that limit the accurate attribution of AEs to TCZ use specifically.

Conclusions on the Applicability of Pharmacovigilance Safety Data to the Pediatric COVID-19 Indication

When compared to pre-specified clinical trial safety data, the submitted pharmacovigilance data are limited in interpretability by the lack of controls, unclear follow-up time, potential selection bias in case selection and reporting of AEs, and the lack of required safety data collection on structured data elements (e.g., clinical safety laboratories, vital signs, AEs). However, despite these limitations, the pharmacovigilance data do provide additional safety data for consideration as part of the totality of TCZ safety data relevant to the pediatric COVID-19 indication. As part of the totality of safety data reviewed, these pharmacovigilance data do not present signals for new adverse events that would limit the use of tocilizumab for the proposed indication, or that would be sufficiently supported to be included in product labeling.

15.4.2. Cytokine Release Syndrome

Sources of Safety Data Utilized for Approval

The multidisciplinary review for BLA 125276 Supplement 114, submitted as "Division Director Review" by Dr. Natasha Kormanik (available starting on page 422 of 530 as part of the action package submitted for BLA 125276, supplement 114, on 06 Sep 2017 by Ashley Wallace) provides review of the data utilized as the basis of approval for TCZ for the cytokine release syndrome indication. These data comprised a pooled dataset (designated CTL019) of selected patients from five CAR T-Cell therapy trials. The pediatric subjects were identified from trials CCTL019B2202 and CCTL019B2205J, both addressing CAR T-cell efficacy and safety in the setting of B-cell acute lymphocytic leukemia (ALL) with protocol criteria for TCZ use in cases of CRS. No separate trials with TCZ as the primary investigational agent or intervention were undertaken or considered for this indication.

The review details 25 subjects in the age grouping of age 2 years to <12 years of age and 17 subjects in the age grouping of 12 years to <18 years of age. Subjects received a median of one

dose of TCZ with a range of one to four doses. No adverse reactions related to TCZ were reported, although the review notes that no studies considered in the review incorporated TCZ-specific AE collection.

The quality of the safety data utilized to approve TCZ for the CRS indication and inform the approved labeling was deemed sufficient for regulatory decision-making in the context of the unmet medical need for treatments for CRS. The review's benefit-risk assessment notes that the adverse reaction profile of TCZ is established in multiple populations and also notes that there were no adverse reactions attributed to TCZ in the pediatric trials of CAR T-cell therapy evaluated for this action. The review acknowledges that these CAR T-cell clinical trials did not collect safety data prospectively for TCZ specifically and that "there remains some concern" regarding the safety of TCZ in pediatric CRS. Finally, the review referenced the pediatric safety data from the sJIA and pJIA indications, and it further noted that prospectively collected data in CRS would be useful to confirm the conclusion of safety.

Comparability of Tocilizumab Use-Case and Condition

The Applicant's submission of non-COVID-19 safety information relies on data for the use of TCZ for the treatment of cytokine release syndrome (CRS). CRS is an on-target effect of chimeric antigen receptor (CAR) T-cell therapy that occurs in 13-48% of subjects. The symptoms of CRS include tachycardia, fever, hypotension, capillary leak, nausea, and potential progression to multi-organ dysfunction. These symptoms are attributed to the release of inflammatory cytokines – and especially of high levels of interleukin 6 – by immune effector cells and target cells.

The positioning of CRS as a condition that is similar to COVID-19 is a source of uncertainty due to multiple significant differences between the disease characteristics and pathogenesis of CRS in the pediatric CAR T-cell population and the pediatric COVID-19 population proposed. The most notable differences include the presence of malignancy and the use of CAR T-cell background therapy among those evaluated for the approved CRS indication. CRS is an inflammatory condition associated almost exclusively (within the framework of the approved indication) with therapy for an oncologic condition, in which IL-6 is heavily implicated as a driver of the inflammatory syndrome. In CRS, the dosage of CAR T-cell therapy can be modified, and the expected course is dependent on underlying condition, tumor burden, and additional factors. In contrast, COVID-19 is an acute infectious condition caused by the SARS-CoV2 virus that may result in broadly dysregulated cytokine release in the setting of serious illness, as well as ARDS, whose clinical course is determined by multiple host- and pathogen-related factors. Similarities between CRS and COVID-19 include escalating severity that can necessitate critical care in some cases. In addition, the clinical and pulmonary management of capillary leak due to CRS can be similar to ARDS in terms of management decisions for respiratory failure, although the underlying pathology may differ.

Approved Labeling of Tocilizumab for Cytokine Release Syndrome

TCZ is approved for adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome under BLA125276 supplement 114. This approval references the data sources noted above. Pediatric dosing for TCZ is 8 mg/kg (or 12 mg/kg for patients less than 30 kg) with or without high-dose corticosteroids.

In the context of the limitation noted above, the safety labeling for the CRS indication notes that no adverse reactions related to TCZ were reported.

Duration of Treatment

Treatment with TCZ comprised one to four doses in the reviewed studies.

Additional Data Sources

The Applicant submitted the results of a literature review for TCZ use in CRS and a review of the Applicant's pharmacovigilance safety database for the CRS indication. Due to limitations in the quality of the data, these data did not influence the regulatory decision-making for the pediatric COVID-19 indication. The literature review data sources are discussed below.

In addition to safety data utilized for the TCZ CRS approval, the Applicant submitted case reports and similar journal articles that describe 41 patients who received TCZ for cytokine release syndrome. In the opinion of this reviewer, the quality of the additional CRS data provided by the Applicant is not sufficient for regulatory decision-making for the COVID-19 indication. In addition to the retrospective and uncontrolled study design, the cited papers do not consistently provide the dose of TCZ, concomitant medications that might confound the safety evaluation. Perhaps most importantly, the referenced literature does not provide detailed listings of adverse events on the enrolled patients to allow for conclusions related to safety.

The Applicant presents additional data from studies of TCZ in cytokine release syndrome through four referenced articles.

1. Raj R, Uppuluri R, VS V. Tocilizumab Use in Children with Cytokine Release Syndrome. Indian Pediatrics. 2021;58:186-7. PMID: 33632957

This small pediatric case series published in 2021 details the clinical scenarios of three children who received TCZ for presumed cytokine release syndrome due to different causes. It is unclear whether this article is peer-reviewed. The cases described comprised the following:

- A 15-month-old female who received a stem cell transplant for severe combined immune deficiency and subsequently developed elevated liver enzymes, respiratory distress, and a highly elevated ferritin suggestive of cytokine release syndrome. The child was treated with one dose of TCZ 4 mg/kg. The case series reports serial drop of serum ferritin within 48 hours.

- An 8-year-old male diagnosed with Hodgkin's Lymphoma with elevated liver enzymes, pancytopenia, and a highly elevated ferritin suggestive of cytokine release syndrome was treated with one dose of TCZ (dose not provided). The case series reports a drop of serum ferritin within 72 hours.
- A 12-year-old male with hepatitis A infection with elevated liver enzymes, respiratory distress, and hypotension suggestive of cytokine release syndrome was treated with one dose of TCZ 4 mg/kg. The case series reports recovery of normal blood counts with tapering steroids and cyclosporin. The neutropenic phase of TCZ treatment was complicated by candidal sepsis.

The ability of this case series to support the safety of TCZ in pediatric patients with COVID-19 is limited. It does not provide adequate information to confirm the diagnosis of cytokine release syndrome in the patients described. The dose of TCZ is only provided for two of the three children. It provides few details on safety associated with TCZ use other than one noted case of candidal sepsis.

2. Maude S, Teachey D, Rheingold S, et al. Durable remissions after monotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children and young adults with relapsed/refractory all. In Haematologica 2016;101(5):183-184.

This citation references an abstract at the European Hematology Association in 2016 which is not accessible through PubMed. It presents limited results of 59 children and young adult patients who underwent chimeric antigen receptor-modified T cells therapy for relapsed/ refractory acute lymphoblastic leukemia. The only noted statement in the abstract regarding TCZ reads "Severe CRS requiring hemodynamic or respiratory support occurred in 27%, was associated with high disease burden, and was reversed with the anti-IL6R agent tocilizumab". No additional details regarding TCZ dose, safety, or markers of efficacy is available in this reference.

This reviewer did discover an associated peer-reviewed article (PMID 25317870) discussing these data, stating that nine subjects were treated with TCZ for severe cytokine release syndrome. Six of these subjects received glucocorticoids and four of these subjects received a second dose of TCZ.

The ability of this abstract and article to support the safety of TCZ in pediatric patients with COVID-19 is limited. The dose of TCZ is not provided. It provides no specific safety details or listings associated with TCZ use.

3. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. New England Journal of Medicine. 2013;368(16):1509-18.

This case series describes the use of chimeric antigen receptor-modified T-cells with specificity for CD19 in two pediatric subjects with relapsed and refractory pre-B-cell acute lymphoblastic

leukemia. One subject (a 10-year-old female) received etanercept and TCZ for severe cytokine release syndrome. While some safety details are provided, the relationship to TCZ use is not detailed, and the attribution of any safety event to TCZ use is confounded by the presence of etanercept.

The ability of this abstract to support the safety of TCZ in pediatric patients with COVID-19 is limited. The dose of TCZ is not provided. It provides no specific safety details or listings associated with TCZ use.

4. Awasthi R, Lee, C., Bittencourt H, Rives S, et al. Pharmacokinetics and pharmacodynamics of tocilizumab for the management of cytokine release syndrome (CRS) in pediatric and young-adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) treated with chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel (CTL019). Presented at: the 2018 ASPHO Conference; May 2-5, 2018; Pittsburgh, PA. Poster 709.

This citation references an abstract at the American Society of Pediatric Hematology/Oncology in 2018. This abstract cites results from the ELIANA trial (NCT02435849) of tisagenlecleucel anti-CD19 chimeric antigen receptor modified T-cell therapy, which recruited 75 subjects with relapsed/refractory B-cell acute lymphoblastic leukemia. The abstract describes the PK/PD of TCZ in CRS management. The abstract reports that 28 of 58 subjects with cytokine release syndrome in the study received the first dose of TCZ at a median of 5 days after the onset of cytokine release syndrome.

The ability of this abstract to support the safety of TCZ in pediatric patients with COVID-19 is limited. The dose of TCZ is not provided. It provides no specific safety details or listings associated with TCZ use.

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