PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB IN PEDIATRIC PATIENTS HOSPITALIZED WITH COVID-19**
PROTOCOL NUMBER:	WA43811
VERSION NUMBER:	1
TEST COMPOUND:	Tocilizumab (RO4877533)
STUDY PHASE:	Phase Ib
EUDRACT NUMBER:	2021-005332-27
IND NUMBER:	148225
NCT NUMBER:	To be determined
MEDICAL MONITOR	Min Bao, M.D.
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
21-Oct-2021 23:51:27	Company Signatory	Tsai, Larry (tsail5)

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB IN PEDIATRIC PATIENTS HOSPITALIZED WITH COVID-19**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the contract research organization.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE Ib, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB IN PEDIATRIC PATIENTS HOSPITALIZED WITH COVID-19**

Study Rationale

Although an increasing number of treatment options for coronavirus disease 2019 (COVID-19) are becoming available in adults, and vaccines are able to effectively prevent severe acute respiratory syndrome corona virus-2 infection and reduce the risk of hospitalization in adults, there are very limited treatment options developed for children and no vaccine has been approved in children less than 12 years old as of the time of study design. Thus, there is an urgent medical need for effective therapies in children with COVID-19, especially those who are hospitalized and who require supplemental oxygen.

Tocilizumab (TCZ) has demonstrated a favorable benefit/risk profile in adults hospitalized with COVID-19 and has an established efficacy and safety profile in approved pediatric indications, making it a potentially effective treatment option for COVID-19 in hospitalized pediatric patients. The purpose of this Phase Ib study is to assess the pharmacokinetics, pharmacodynamics, safety, and exploratory efficacy of TCZ in pediatric patients from birth to less than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Objectives and Endpoints

This study will evaluate the pharmacokinetics, pharmacodynamics, safety and exploratory efficacy of TCZ in pediatric participants hospitalized with COVID-19. Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of TCZ through Day 28	• Serum concentrations of TCZ at specified timepoints and derived PK parameters (C_{max}, $AUC_{Days\ 0\text{-}28}$, $C_{Day\ 28}$, CL, and volume of distribution)
Secondary Objectives	**Corresponding Endpoints**
• To characterize the pharmacodynamics of TCZ through Day 60	• Duration of 90% saturation of sIL-6R through Day 28 • Concentrations of IL-6, sIL-6R, and CRP at specified timepoints
• To evaluate the safety of TCZ through Day 60	• 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 test results

$AUC_{Days\ 0\text{-}28}$ = area under the concentration–time curve up to Day 28; CL = total clearance of drug; $C_{Day\ 28}$ = serum concentration on Day 28; C_{max} = maximal serum concentration; CRP = C-reactive protein; IL-6 = interleukin 6; PK = pharmacokinetic; sIL-6R = soluble interleukin-6 receptor; TCZ = tocilizumab.

Overall Design

This is a Phase Ib, single-arm, open-label study to assess the pharmacokinetics, pharmacodynamics, safety, and exploratory efficacy of TCZ for the treatment of pediatric patients from birth to less than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The main scope of the study is to characterize the pharmacokinetics of the dosing regimens proposed in the pediatric patient population.

At least 30 pediatric participants will be enrolled from birth to less than 18 years old who are hospitalized with COVID-19, confirmed by positive PCR and a chest X-ray or computed tomography scan, and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Overall, at least 10 participants in each body weight category (< 30 kg, ≥ 30 kg) will be enrolled in the study.

Following a screening period of maximum 3 days, participants will receive a single dose of open-label TCZ on Day 1 (with the option of a second dose 8–24 hours later if clinically indicated), and subsequently followed-up for a total of 60 days after first dose of study drug. Participants who are still hospitalized after Day 60 should be followed until hospital discharge.

An interim analysis to confirm the dosing regimens will be performed when at least 5 participants in each body weight category (< 30 kg, ≥ 30 kg) are enrolled and have completed the study assessments to Day 28. The interim analysis will be considered successful if the duration of 90% saturation of soluble interleukin 6 receptor (sIL-6R) in at least 90% of the pediatric participants included in the interim analysis is greater or equal to the 5th percentile of the distribution of the duration of 90% saturation of sIL-6R observed in adult patients with COVID-19 pneumonia of similar disease severity. If the interim analysis is not successful, then the study will be put on temporary hold while alternative dosing regimens will be assessed.

Participants < 2 years old may only be enrolled once the interim analysis is concluded.

As this is a single-arm, open-label study, no independent Data Monitoring Committee will be used. However, an Internal Monitoring Committee (IMC) consisting of Sponsor representatives who are not part of the study team and Scientific Oversight Committee (SOC) including external experts will be established. The IMC and SOC will periodically review safety data after certain patient numbers have been enrolled or other study milestones have been reached. Details on responsibilities and operating principles of the IMC and SOC will be described in a charter.

A study schema is provided in Section 1.2 (see Figure 1). The schedules of activities and a sample collection schedule are provided in Section 1.3 (see Table 1–Table 5).

Number of Participants

At least 30 pediatric participants will be enrolled from birth to less than 18 years old who are hospitalized with COVID-19, confirmed by positive PCR test, and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. At least 10 participants weighing less than 30 kg and at least 10 participants weighing 30 kg or more will be enrolled. Participants < 2 years old may be enrolled after the interim analysis is concluded.

Study Treatment

The investigational medicinal product for this study is IV TCZ.

TCZ will be administered as a single IV infusion. Participants with a body weight ≥ 30 kg will receive TCZ at a dose of 8 mg/kg, and participants with a body weight < 30 kg will receive TCZ at a dose of 12 mg/kg. Infusion times and volumes will be adjusted based on patient age.

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 infusion. The second dose of TCZ must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of TCZ.

All participants will also receive standard of care per local practice for the treatment of COVID-19.

Duration of Participation

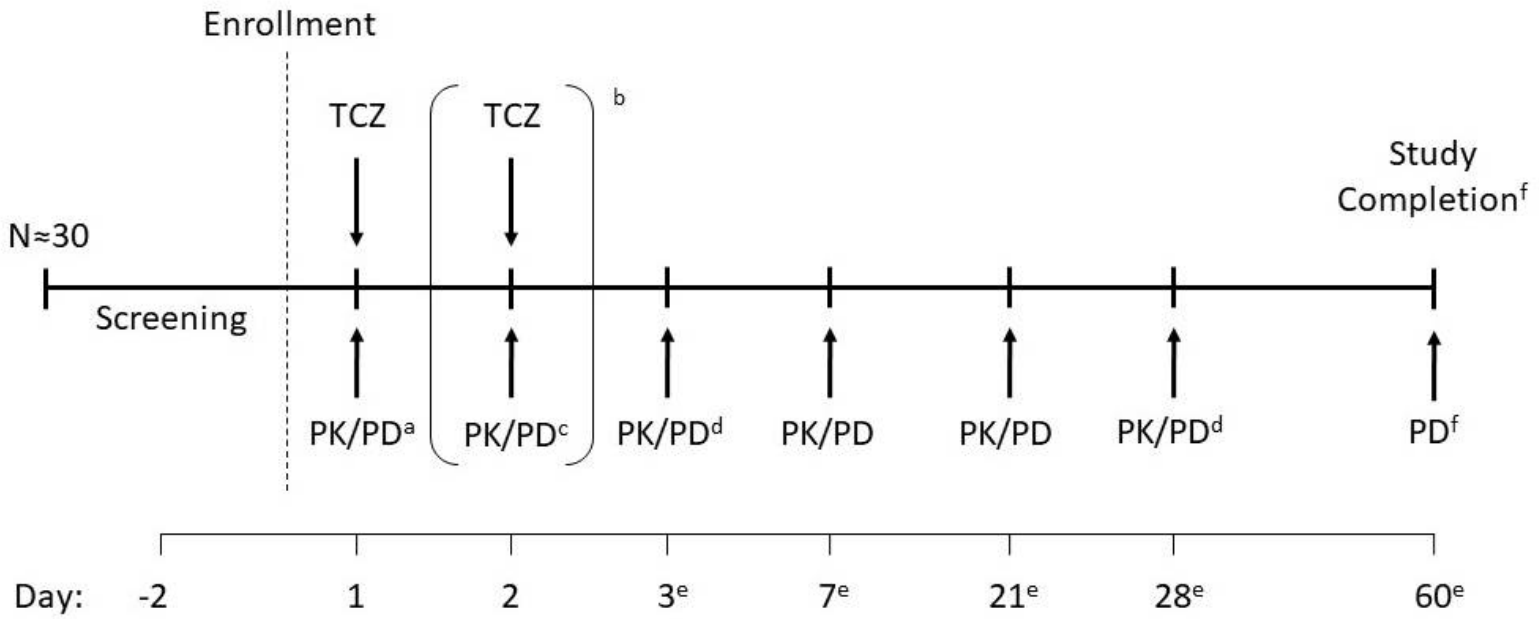
The total duration of study participation for each individual is expected to be approximately 60 days. Participants who are still hospitalized after Day 60 should be followed until hospital discharge.

Independent Data Monitoring Committee

An independent Data Monitoring Committee is not being used.

1.2 STUDY SCHEMA

Figure 1 Study Schema



PD = pharmacodynamic; PK = pharmacokinetic; TCZ = tocilizumab.

[a] Both a predose and a postdose sample (within 15 minutes of completion of the infusion) has to be collected on Day 1.

[b] Optional second dose within 8–24 hours after the first dose, if clinically indicated.

[c] A postdose sample must be collected within 15 minutes of completion of the infusion, if the optional second dose is administered.

[d] Not applicable for participants who weigh < 30 kg.

[e] If a participant receives the optional second dose of TCZ on Day 2, subsequent days may shift to Day 4, Day 8, Day 22, and Day 29. The study completion visit is Day 60 (± 3 days).

[f] Upon study completion, a PD sample must be collected. In case of early study discontinuation before Day 28, both a PK and PD sample must be collected. In case of early study discontinuation after Day 28, only a PD sample must be collected.

1.3 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities at Screening, and on Days 1 and 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]

Table 1 Schedule of Activities at Screening, and on Days 1 and 2 (cont.)

	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	
Central laboratory				
Blood samples for PK and PD		See Table 5.		

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.

Table 1 Schedule of Activities at Screening, and on Days 1 and 2 (cont.)

[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).

Table 2 Schedule of Activities on Days 3–28

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.

Table 2 Schedule of Activities on Days 3–28 (cont.)

[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.

Table 3 Schedule of Activities after Day 28 (for Discharged Participants)

			Study Completion/ Early Discontinuation
Study Day (Assessment Window)	35 [a] (±3 days)	45 [a] (±3 days)	60 [a] (±3 days)
Vital signs, SpO_2, FiO_2, and oxygen flow rate [b]	x	x	x
Oxygen support type [c]	x	x	x
Adverse events [d]	x	x	x
Concomitant medications [e]	x	x	x
Hematology [f]	x	x	x
Chemistry panel [g]	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] Discharged participants should have follow-up visits on Days 35, 45, and 60 (±3 days). The Day 35 and Day 45 visits may be conducted by telephone. Vital signs, SpO_2, FiO_2, oxygen flow rate, and laboratory testing will not be required for telephone visits. Discharged participants should return to the site for the Day 60 visit. If a participant is re-hospitalized during the study duration, then follow Table 4 for hospitalized participants.

[b] Following hospital discharge, vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature), SpO_2, FiO_2, and oxygen flow rate 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.

[c] For participants discharged with supplemental oxygen, it should be assessed during follow-up visits if and when home oxygen use was stopped.

[d] 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).

Table 3 Schedule of Activities after Day 28 (for Discharged Participants) (cont.)

[e] 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.

[f] 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.

[g] 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.

Table 4 Schedule of Activities after Day 28 (for Hospitalized Participants)

Study Day	Days 29–59 [a]																														Day 60 (Study Completion/ Early Discon.)
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	
Vital signs, SpO_2, FiO_2, and oxygen flow rate [b]							x										x															x
Oxygen support type [c]	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	x	x	x	x	x
Ordinal scoring [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	x	x	x	x	x
Adverse events [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	x	x	x	x	x
Concomitant medications [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	x	x	x	x	x
Hematology [g]							x										x															x
Chemistry panel [h]							x										x															x
Central laboratory																																
Blood samples for PK and PD	See Table 5.																															

COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; Discon. = discontinuation; 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 60, then follow Table 3 for discharged participants.

[b] 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. Refer to Section 8.2.2 for detailed information on vital signs measurements.

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

Table 4 Schedule of Activities after Day 28 (for Hospitalized Participants) (cont.)

[d] 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. See Section 8.1.1 for additional details.

[e] 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).

[f] 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.

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

[h] 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.

Table 5 Schedule of Pharmacokinetic and Pharmacodynamic Samples

Visit	Timepoint [a]	Sample Type(s)
Day 1	Predose	Serum PK Serum PD [c]
	After the first infusion (ideally within 15 minutes to maximum 1 hour of completion)	
Day 2 [b]	After the second infusion (ideally within 15 minutes to maximum 1 hour of completion), if applicable [b]	
Day 3 [d, e]	2 days after final TCZ dose	
Day 7 [e]	6 days after final TCZ dose	
Day 21 [e]	20 days after final TCZ dose	
Day 28 [d, e]	27 days after final TCZ dose	
Early study discontinuation (prior to Day 28)		
Day 60 [e] Or Early study discontinuation (after Day 28)		Serum PD

PD = pharmacodynamic; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TCZ = tocilizumab.

Note: All postdose samples must be drawn from the opposite arm as the TCZ infusion was administered.

[a] The timepoint defines the study day or visit when a sample has to be collected. Collection timepoints should be followed as accurately as possible and practical.

[b] 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).

[c] Serum viral load and anti-SARS-CoV-2 antibody titers may also be measured at selected timepoints from the same sample as exploratory biomarkers, if a sufficient blood volume was collected.

[d] Assessment not applicable for participants who weigh < 30 kg.

[e] If a participant receives the optional second TCZ dose on Day 2, then the visit days shift to Day 4, Day 8, Day 22, and Day 29. If the optional second TCZ dose is administered on Day 1, then the original visit days should be kept. The study completion visit is Day 60 (± 3 days).

2. INTRODUCTION

2.1 STUDY RATIONALE

Although an increasing number of treatment options for coronavirus disease 2019 (COVID-19) are becoming available in adults, and vaccines are able to effectively prevent severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) infection and reduce the risk of hospitalization in adults, there are very limited treatment options developed for children and no vaccine has been approved in children less than 12 years old as of the time of study design. Thus, there is an urgent medical need for effective therapies in children with COVID-19, especially those who are hospitalized and who require supplemental oxygen.

Tocilizumab (TCZ) has demonstrated a favorable benefit/risk profile in adults hospitalized with COVID-19 and has an established efficacy and safety profile in approved pediatric indications, making it a potentially effective treatment option for COVID-19 in hospitalized pediatric patients. The purpose of this Phase Ib study is to assess the pharmacokinetics, pharmacodynamics, safety, and exploratory efficacy of TCZ in pediatric patients from birth to less than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

2.2 BACKGROUND

Although a majority of SARS-CoV-2 infections are either asymptomatic or result in mild to moderate disease, a substantial proportion of infected individuals develop respiratory failure, hypoxemia, and multiple organ failure with potentially fatal outcome. Hypoxic respiratory failure in COVID-19 is associated with evidence of systemic inflammation, including release of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor–a (TNF-α), elevated C-reactive protein (CRP), and ferritin (Chen et al. 2020; Del Valle et al. 2020). Clinical signs and symptoms of COVID-19 in pediatric patients are similar to those in adults, with severe and critical cases experiencing similar clinical complications (Rankin et al. 2021; Dong et al. 2020). Consistent with a high level of inflammation, elevated cytokine levels have also been reported, including IL-6 (Wang et al. 2020), and severe disease has been associated with significantly higher CRP levels at admission, as well as elevated peak IL-6 and ferritin levels during hospitalization (Zachariah et al. 2020).

TCZ is a recombinant humanized, anti-human monoclonal antibody of the IgG1 sub-class directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R). TCZ (known as Actemra® or RoActemra®) was approved globally for the treatment of rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis, giant cell arteritis, chimeric antigen receptor (CAR) T cell–induced severe or life-threatening cytokine-release syndrome (CRS) and systemic sclerosis-associated interstitial lung disease (only in the United States). TCZ has IV and SC formulations. The estimated cumulative clinical trial exposure to TCZ

from the Developmental International Birth Date (28 April 1997) and until 10 April 2021 (the data lock point for the Periodic Benefit–Risk Evaluation Report) is 24,790 patients. Since the International Birth Date (11 April 2005), the estimated cumulative market exposure to TCZ until 31 March 2021 is 2,567,502 patients (2,213,381 patient-years).

Given the potential role of IL-6 in COVID-19, TCZ was investigated for the treatment of adults hospitalized with COVID-19 in three Phase III Roche-sponsored double-blind, placebo-controlled studies (WA42380 [COVACTA] (Rosas et al. 2021), ML42528 [EMPACTA] (Salama et al. 2021), and WA42511 [REMDACTA]), one Phase II Study CA42481 (MARIPOSA), and one investigator-initiated, Roche-supported randomized open-label large platform study (RECOVERY) (RECOVERY Collaborative Group 2021). The totality of evidence from these studies showed that TCZ treatment resulted in a significant overall reduction of risk of death, particularly in patients who were also receiving systemic corticosteroids at baseline. Other clinical benefits include shortened hospital stay and reduced need for mechanical ventilation in patients enrolled without ventilation. Safety results from the three Roche-sponsored studies revealed no new safety signals compared with the known safety profiles of other indications. An independent prospective meta analysis performed by the WHO supported these findings (Shankar-Hari et al. 2021). On 24 June 2021, based on the clinical evidence from adults in COVID-19, the similarities of disease pathogenesis between adults and children, and the extensive efficacy and safety of TCZ in approved pediatric indications, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for TCZ for the treatment of adults and pediatric patients ($\geq$2 years old) 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 number of hospitalized children with COVID-19 has been increasing globally; however, as of the time of study design, remdesivir is the only currently approved therapy for children 12 years or older for the treatment of COVID-19 requiring hospitalization in the United States and Europe. No approved therapeutics are available for neonates, infants, and children below 12 years of age. Dexamethasone is recommended in patients with respiratory distress maintained on oxygen or ventilation. Furthermore, as COVID-19 vaccines are at present not approved for use in children less than 12 years old, this may result in an increased percentage of hospitalizations in that age group.

Detailed information on TCZ is provided in the Tocilizumab Investigator's Brochure and the Fact Sheet for Healthcare Providers: Emergency Use Authorization for Actemra® (Tocilizumab).

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the pharmacokinetics, pharmacodynamics, safety, and exploratory efficacy of TCZ for the treatment of pediatric patients from to birth to less

than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

The totality of the evidence from RECOVERY, the Roche-sponsored studies, and other randomized, controlled trials supports a favorable benefit–risk profile of TCZ for the treatment of adult patients hospitalized COVID-19, particularly patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation (see Section 2.2, as well as the Tocilizumab Investigator's Brochure for more detailed information). The similarities in clinical presentation and inflammatory marker elevations between pediatric and adult patients suggest a common disease pathogenesis. Thus, it is expected that TCZ treatment will also be beneficial in pediatric patients, assuming comparable TCZ exposure.

Clinical studies in adults have robustly demonstrated the safety of TCZ in COVID-19 and, furthermore, extensive experience has established the safety of TCZ treatment in pediatric patients for chronic autoimmune indications. Known potential risks for TCZ are serious infections and opportunistic infections, gastrointestinal (GI) perforation, hypersensitivity reactions and anaphylaxis, hematologic abnormalities, liver enzyme abnormalities and liver injury, increased lipids and cardiovascular and cerebrovascular events, and demyelinating disorders.

The vast majority of pediatric patients with COVID-19 are treated successfully with supportive care; however, for severe or complicated COVID-19 in children, treatment options are limited. Besides the recommended dexamethasone in children requiring supplemental oxygen or ventilatory support, the U.S. Food and Drug Administration (FDA) issued an EUA for baricitinib to treat COVID-19 in hospitalized patients aged 2 years or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. However, there still remains an urgent unmet need for more effective therapy that would rapidly resolve the inflammatory response, reduce the requirement for more invasive therapy (mechanical ventilation or extracorporeal membrane oxygenation), and potentially limit damage to the lungs and improve long-term outcomes, particularly in the light of limited experience with baricitinib use in pediatric patients. Based on the known safety profile of TCZ in children in other indications and established clinical benefits in adults with COVID-19, it is expected that TCZ treatment of pediatric patients hospitalized with COVID-19 and receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation will result in a favorable benefit–risk ratio.

Refer to Appendix 3 for information on anticipated risks for TCZ and risk-mitigation measures, including guidelines for managing adverse events associated with TCZ.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of TCZ may be found in the Tocilizumab

Investigator's Brochure, prescribing information, and the Fact Sheet for Healthcare Providers: Emergency Use Authorization for Actemra® (Tocilizumab).

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, safety and exploratory efficacy of TCZ in pediatric participants hospitalized with COVID-19. Specific objectives and corresponding endpoints for the study are outlined in Table 6.

Table 6 Objectives and Endpoints

Primary Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of TCZ through Day 28	• Serum concentrations of TCZ at specified timepoints and derived PK parameters (C_{max}, $AUC_{Days\ 0\text{-}28}$, C_{Day28}, CL, and volume of distribution)
Secondary Objectives	**Corresponding Endpoints**
• To characterize the pharmacodynamics of TCZ through Day 60	• Duration of 90% saturation of sIL-6R through Day 28 • Concentrations of IL-6, sIL-6R, and CRP at specified timepoints
• To evaluate the safety of TCZ through Day 60	• 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 test results
Exploratory Objectives	**Corresponding Endpoint(s)**
• To explore the efficacy of TCZ through Day 60	• Clinical improvement assessed using a 7-category ordinal scale (see details in Section 8.1.1) • Duration of hospitalization (in days) • Duration of PICU or ICU stay (in days) • Mortality • Incidence of mechanical ventilation • Duration of supplemental oxygen
• 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	• Relationship between biomarkers in serum (listed in Section 8.7) and efficacy, safety, PK, or other biomarker endpoints

$AUC_{Days\ 0\text{-}28}$ = area under the concentration–time curve up to Day 28; $C_{Day\ 28}$ = serum concentration on Day 28; CL = total clearance of drug; C_{max} = maximal serum concentration; CRP = C-reactive protein; ICU = intensive care unit; IL-6 = interleukin 6; PICU = pediatric intensive care unit; PK = pharmacokinetic; sIL-6R = soluble interleukin-6 receptor; TCZ = tocilizumab.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase Ib, single-arm, open-label study to assess the pharmacokinetics, pharmacodynamics, safety, and exploratory efficacy of TCZ for the treatment of pediatric patients from birth to less than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The main scope of the study is to characterize the pharmacokinetics of the dosing regimens proposed in the pediatric patient population.

At least 30 pediatric participants will be enrolled from birth to less than 18 years old who are hospitalized with COVID-19, confirmed by positive PCR and a chest X-ray or computed tomography (CT) scan, and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Overall, at least 10 participants in each body weight category (<30 kg, ≥ 30 kg) will be enrolled in the study.

An interim analysis to confirm the dosing regimens (see Section 9.5) will be performed when at least 5 participants in each body weight category (<30 kg, ≥ 30 kg) are enrolled and have completed the study assessments to Day 28. The interim analysis will be considered successful if the duration of 90% saturation of soluble interleukin 6 receptor (sIL-6R) in at least 90% of the pediatric participants included in the interim analysis is greater or equal to the 5th percentile of the distribution of the duration of 90% saturation of sIL-6R observed in adult patients with COVID-19 pneumonia of similar disease severity. If the interim analysis is not successful, then the study will be put on temporary hold while alternative dosing regimens will be assessed (see Section 9.5 for details).

Participants <2 years old may only be enrolled once the interim analysis is concluded.

TCZ will be administered as a single IV infusion. Participants with a body weight ≥ 30 kg will receive TCZ at a dose of 8 mg/kg, and participants with a body weight <30 kg will receive TCZ at a dose of 12 mg/kg. Infusion times and volumes will be adjusted based on patient age (refer to Section 6.1 for details).

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 infusion. The second dose of TCZ must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of TCZ.

All participants will also receive standard of care per local practice for the treatment of COVID-19.

Following a screening period of maximum 3 days, participants will receive a single dose of open-label TCZ on Day 1 (with the option of a second dose 8–24 hours later if clinically indicated), and subsequently followed-up for a total of 60 days after first dose of

study drug. Participants who are still hospitalized after Day 60 should be followed until hospital discharge. Participants who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion (refer to Section 5.4 for further details).

Daily assessments will be performed for as long as the participant is hospitalized, with pharmacokinetic (PK) and pharmacodynamic (PD) samples collected on Days 1, 2, 3, 7, 21, and 28. On Day 1, both a predose and a postdose sample will be collected. A postdose sample on Day 2 will be collected only if the optional second TCZ infusion is administered (i.e., if the second dose is not given, then no sample will be collected on Day 2). If a participant receives the optional second TCZ dose on Day 2, then the PK and PD sample collection days shift to Day 4, Day 8, Day 22, and Day 29. If the optional second TCZ dose is administered on Day 1, then the original sample collection days should be kept (refer to Table 5 for details).

The Day 3 and Day 28 samples will not be collected for participants who weigh <30 kg.

If a participant is discharged from the hospital prior to Day 28, follow-up visits should be conducted on Day 14 (± 1 day), Day 21 (± 1 day), and Day 28 (± 1 day). The follow-up visit on Day 14 may be conducted as a telephone visit. Participants should return to the site for the Day 21 and Day 28 visits in order to collect the PK and PD samples (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). Participants discharged before Day 7 should also return to the site for the Day 7 PK and PD sample collection. On-site follow-up visits should be conducted so that they align with the PK/PD sample collection timepoints outlined in Table 5 as accurately as possible and practical.

After Day 28, all discharged participants should have follow-up visits on Days 35, 45, and 60 (± 3 days). The Day 35 and Day 45 visits may be conducted by telephone. Participants should return to the site for the Day 60 visit, because this is the final PD sample collection timepoint. If a participant discontinues from the study before the Day 60 visit, then an early discontinuation visit should be done, if possible.

In case of early discontinuation from the study before Day 28, both a PK and PD sample must be collected at that visit. In case of early study discontinuation after Day 28, only a PD sample must be collected.

As this is a single-arm, open-label study, no independent Data Monitoring Committee will be used. However, an Internal Monitoring Committee (IMC) consisting of Sponsor representatives who are not part of the study team and Scientific Oversight Committee (SOC) including external experts will be established. The IMC and SOC will periodically review safety data after certain patient numbers have been enrolled or other study

milestones have been reached. Details on responsibilities and operating principles of the IMC and SOC will be described in a charter.

A study schema is provided in Section 1.2 (see Figure 1). The schedules of activities and a sample collection schedule are provided in Section 1.3 (see Table 1–Table 5).

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

TCZ, as an immunomodulatory agent, targets the hyperinflammation stage of the COVID-19 disease development. The totality of clinical evidence from adults also confirmed that the most beneficial patient population is the hospitalized patients who are receiving systemic corticosteroids and on supplemental oxygen or mechanical ventilation (Shankar-Hari et al. 2021). In this study, the targeted pediatric participants (birth to less than 18 years old) will mirror the above mentioned population, which is also consistent with the population that was granted with the FDA EUA for pediatric patients (≥2 years old), who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

The pediatric population in scope of this study ranges from to birth to less than 18 years. TCZ has been approved for use in pediatric patients age ≥2 years in several countries (including the United States and the EU) for conditions such as sJIA and CAR T cell–induced CRS. Furthermore, the FDA EUA for TCZ use in COVID-19 included pediatric patients age 2 years and older. The study will also attempt to enroll participants from birth to 2 years old after the interim analysis is concluded, given that there currently are no treatment options for severe or complicated COVID-19 available in this age range. Experience with IV TCZ in children less than 2 years old is limited. One trial conducted in 11 participants aged 2 years or less with sJIA (NP25737 [Report Number 1080839]) indicated an increased incidence of serious hypersensitivity reactions. The Sponsor proposes to use a longer infusion time for participants age less than 2 years as a risk-mitigation procedure (refer to Section 6.1 for further details). Apart from that, TCZ was well-tolerated and observed adverse events from those <2 years old were consistent with the results obtained previously for patients with sJIA age ≥2 years.

The trial explicitly excludes participants with multisystem inflammatory syndrome in children (MIS-C), which is an inflammatory vascular disorder that appears to have a different pathogenesis and clinical presentation than COVID-19 pneumonia based on the current knowledge. The trial focuses on pediatric patients hospitalized with COVID-19 who present with respiratory distress requiring supplemental oxygen or ventilation, which is considered the pediatric equivalent of severe and critical COVID-19 in adults.

4.2.2 Rationale for Biomarker Assessments

COVID-19 is a heterogeneous disease, and patients with severe COVID-19 have shown various levels of IL-6 pathway activation (Xu et al. 2020). PD biomarkers (IL-6, sIL-6R, CRP) will be assessed to demonstrate evidence of biologic activity of TCZ in participants, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule.

Additional biomarkers such as inflammatory markers associated with disease severity may be assessed to understand the impact of TCZ on disease. Residual samples, if available and adequate volume, may be considered for assessment of serum viral load and antibodies to COVID-19.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

TCZ will be administered as a single IV infusion. 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 infusion. This dosing schedule is in keeping with the dosing schedule used in adult patients with COVID-19. The different doses chosen based on age and body weight are as follows:

- Participants $\geq$2 years old and $\geq$30 kg will receive a 8 mg/kg dose
- Participants $\geq$2 years old and $<$30 kg will receive a 12 mg/kg dose
- Participants $<$2 years old and $<$30 kg will receive a 12 mg/kg dose

The doses for the different age and body weight groups were chosen based on the approved doses for children with CAR T cell-induced CRS. The dose for participants with a body weight of $\geq$30 kg is also the same as used adult patients with COVID-19. Modeling and simulation of PK and sIL-6R profiles was used to support that the approved TCZ doses for children with CAR T cell-induced CRS should also be appropriate in pediatric patients with COVID–19 as it provides a reasonable overlap of TCZ exposure and duration of 90% sIL6R saturation between pediatric patients and adult patients with COVID-19.

The levels of polysorbate 80 (excipient) that would be administered to pediatric patients at birth would be within the European Medicines Agency (EMA) guidelines, and if sodium administration needs to be restricted (e.g., in newborns) the Sponsor is providing the option to use a 0.45% saline infusion bag for administration (rather than the 0.9% saline infusion bag approved in the E.U. for administration of TCZ IV to patients $\geq$2 years old).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last datapoint required for statistical analysis or safety

follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur approximately 60 days after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 60 days. Participants who are still hospitalized after Day 60 should be followed until hospital discharge.

5. STUDY POPULATION

At least 30 pediatric participants will be enrolled from birth to less than 18 years old who are hospitalized with COVID-19, confirmed by positive PCR test, and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. At least 10 participants weighing less than 30 kg and at least 10 participants weighing 30 kg or more will be enrolled. Participants <2 years old may be enrolled after the interim analysis is concluded.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Signed Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Aged less than 18 years at the time of signing Informed Consent Form or Assent (if applicable)

  Eligible participants aged 0 to <2 years may only be enrolled after the interim analysis has been concluded.
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized with COVID-19 confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, or other bodily fluid) and evidenced by chest X-ray or CT scan
- Receiving systemic corticosteroids at baseline
- Oxygen saturation $<93\%$ on room air, or requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO to maintain oxygen saturation $>92\%$ at screening and baseline

- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 90 days after the final dose of TCZ.

  Participants must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of TCZ to avoid exposing the embryo. Male participants must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Gestational age < 37 weeks
- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Active tuberculosis infection
- Uncontrolled active bacterial, fungal, viral, or other infection (besides COVID-19)
- Diagnosis or suspected diagnosis of MIS-C
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 48 hours, irrespective of the provision of treatments
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months prior to enrollment
- ALT or AST $> 10 \times$ upper limit of normal (ULN) detected within 24 hours of screening (according to local laboratory reference ranges)
- ANC $< 1000/\mu L$ at screening (according to local laboratory reference ranges)
- Platelet count $< 50{,}000/\mu L$ at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or intention of becoming pregnant during the study or within 90 days after the final dose of TCZ (only applicable to female participants of childbearing potential)

  Female participants of childbearing potential must have a negative pregnancy test result as part of screening.
- Treatment with an investigational drug within 5 drug-elimination half-lives or 30 days, whichever is longer, of enrollment (except for anti-SARS-CoV-2 antibodies or directly-acting antivirals)
- Participating in another interventional drug clinical trial (except for anti-SARS-CoV-2 antibodies or directly-acting antivirals)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal product (IMP) for this study is IV TCZ.

6.1 STUDY TREATMENTS ADMINISTERED

Table 7 provides a description of assigned study treatments for this study.

Table 7 Study Treatment Description

	Tocilizumab
Use	Experimental
Type of medicinal product	IMP
Drug form	Liquid concentrate
Unit dose strength	20 mg/mL
Dosage level	12 mg/kg (participants $<$ 30 kg) or 8 mg/kg (participants $\geq$ 30 kg)
Formulation	Refer to the pharmacy manual, Tocilizumab Investigator's Brochure, or local prescribing information
Packaging	4.0 mL, 10.0 mL, or 20.0 mL single-use vials
Labeling	Per local requirements
Route of administration	IV infusion
Source	Sponsor

IMP = investigational medicinal product.

TCZ concentrate for solution for infusion will be used, with the instructions for the dilution adapted to minimize risks in participants $<$ 2 years old. Infusion parameters for the different age and body weight categories are described below in Table 8.

Table 8 Tocilizumab Dose Administration and Dilution

Age	Body Weight	TCZ Dose	IV Infusion Bag Size	Volume (20 mg/mL) per Kilogram of Body Weight	Infusion Time	Infusion Rate
≥2 years	≥30 kg	8 mg/kg	100 mL	0.4 mL/kg	1 hour	10 mL/hr for first 15 minutes, then 130 mL/hr
≥2 years	<30 kg	12 mg/kg	50 mL	0.6 mL/kg	1 hour	10 mL/hr for first 15 minutes, then 65 mL/hr
<2 years	<30 kg	12 mg/kg	25 mL	0.6 mL/kg	2 hours	5 mL/hr for first 30 minutes, then 15 mL/hr

TCZ = tocilizumab.

TCZ will be administered by IV infusion with the dose based on a participant's body weight (see Table 8). Dilution should be made into an infusion bag containing 0.9% Sodium Chloride for Injection, USP, using aseptic technique, as outlined in Table 8. Sodium chloride 4.5 mg/mL (0.45%) can be used instead of 0.9% sodium chloride in participants for whom sodium administration is restricted (e.g., newborns). Refer to Section 6.2 for holding times of diluted TCZ solution. The TCZ solution will be administered at room temperature by controlled infusion into a vein over the time period outlined in Table 8. If a participant has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of TCZ can be given 8–24 hours after the first infusion. The maximum dose of TCZ that will be administered per infusion is 800 mg for participants weighing ≥100 kg.

Infusion parameters for participants aged 2 years or older have been established and previously approved by many health authorities (including the FDA and EMA) for different indications such as CAR T cell-induced CRS.

For participants <2 years old (who may be enrolled after the planned interim analysis is concluded), an infusion volume to 25 mL should be used to ensure sufficient remaining daily fluid allowance for administration of nutrition or other medications. The TCZ concentrations in this lower 25-mL infusion volume would be no higher than those achieved with the 50 mL and 100 mL infusions approved for pediatric patients ≥2 years old (see Table 8 for details). However, to reduce the potential risk of extravasation, intolerance or hypersensitivity in neonates (birth to 1 month) or infants (1 month to <2 years), the infusion time should be increased to 2 hours (by decreasing the infusion rate).

Administration of TCZ will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions (see Section 6.8.1). Participants should be monitored for at least 2 hours after the TCZ infusion is completed. For anaphylaxis precautions, see Section A3-1.1 and Appendix 6. If a participant experiences symptoms of anaphylaxis or serious hypersensitivity/serious infusion-related adverse reaction, administration of TCZ should be stopped immediately and permanently discontinued.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events, and guidelines for medical management of infusion-related reactions (IRRs), are provided in Appendix 3.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff. TCZ vials must be stored at a temperature of 2°C–8°C (36°F–46°F). In general, TCZ solution diluted for infusion should be used as soon as possible, but may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours and should be protected from light (storage at room temperature may also be acceptable if allowed in the local prescribing information). Refer to the pharmacy manual for further detail on storage of TCZ.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional SOP or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The

site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Tocilizumab Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a single-arm (non-randomized), open-label study. After initial written informed consent or assent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will enroll the subject through an IxRS.

All participants will receive the same open-label study treatment with the dose determined by body weight.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 2.

6.5 DOSE MODIFICATION

Modification of the TCZ dose is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide Roche IMP (TCZ) or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing TCZ in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 2.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities.

6.8 CONCOMITANT THERAPY

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the final study visit (Day 60 visit or early discontinuation visit) must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. If a participant experiences a hypersensitivity reaction after TCZ infusion, please refer to Section A3-1.1 for full details. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Standard of care for the treatment of COVID-19 as per local guidelines is permitted, including antiviral therapies, COVID-19 convalescent plasma, anti–SARS-CoV-2 monoclonal antibodies, and corticosteroids, at the discretion of the investigator.

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, for molecules that antagonize

cytokine activity, such as TCZ, it is expected that the formation of CYP450 enzymes could be normalized. When starting TCZ therapy, patients taking medications that are individually dose adjusted and metabolized by means of CYP450, CYP3A4, CYP1A2, or CYP2C9 (e.g., atorvastatin, calcium-channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) are recommended to be monitored, as doses may need to be adjusted to maintain their therapeutic effect.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study as described below:

- Treatment with any investigational agent (except for anti-SARS-CoV-2 antibodies or directly-acting antivirals)
- Cell-depleting therapies
- Biologic immunomodulatory agents (e.g., tumor necrosis factor antagonists, anti-cytokine or cytokine receptor therapies including IL-6/IL-6R therapies such as sarilumab, siltuximab)
- Janus kinase inhibitors (e.g., tofacitinib, baricitinib)
- Alkylating agents (e.g., chlorambucil, cyclophosphamide), thalidomide, anti-thymocyte globulin, IV gamma globulin, and azathioprine
- Rifampin
- Bone marrow transplantation with total lymphoid irradiation
- Plasmapheresis or extracorporeal photopheresis

In addition to above prohibited therapies, immunization with a live attenuated vaccine will be prohibited through Day 60.

Please refer to the exclusion criteria (Section 5.2) for prior therapies that are prohibitive of study participation.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- ALT or AST $>10\times$ ULN, ANC $<1000/\mu L$, or platelet count $<50{,}000/\mu L$ detected between screening and a TCZ infusion (either the first infusion or the optional second infusion)
- Symptoms of anaphylaxis or serious hypersensitivity/serious infusion-related adverse reaction after the first TCZ infusion
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants who discontinue from the study treatment should continue in the study and complete all assessments through Day 60.

Refer to the schedules of activities in Section 1.3 (see Table 1–Table 4) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own (or their parent's or guardian's) request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use public information sources to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., CBC) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedules of activities.

Medical history and baseline conditions, including all complications of COVID-19, other clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at baseline. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. COVID-19 vaccinations should also be recorded if received more than 7 days prior to initiation of study treatment. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Ordinal Scale Score Determination

Assessment of clinical status using a 7-category ordinal scale of clinical status will be recorded at baseline on Day 1, and then again once daily every morning (between 8:00 a.m. and 12:00 p.m.) while hospitalized. The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge," as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2 L supplemental oxygen)

2. Non-intensive care unit (ICU) hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen
3. Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Participants who are ready to be discharged but are still hospitalized (e.g., due to non-medical or administrative reasons) will be assigned an ordinal scale category of 1. Participants in a non-ICU hospital ward who are eligible for ICU care based on clinical presentation but are awaiting ICU care will be assigned an ordinal scale category of 4. Participants in an ICU for administrative or non-medical reasons who are ready for a non-ICU hospital ward will be assigned an ordinal scale category of 2 (if not requiring supplemental oxygen), 3 (if requiring supplemental oxygen), or 4 (if requiring non-invasive ventilation or high-flow oxygen). After a participant has been discharged from the hospital, the ordinal scale score should no longer be recorded for follow-up visits. However, if a participant is re-hospitalized, then the same process for ordinal scale score determination should be followed as for the initial hospitalization.

In general, participants with oxygen saturation consistently $\leq 90\%$ should be considered for escalation to a higher clinical status category, whereas patients with oxygen saturation consistently $\geq 96\%$ should be considered for de-escalation to a lower category. Participants on supplemental oxygen should be evaluated at least daily and considered for reduction or discontinuation of oxygen support. Actual changes in level of support will be at the discretion of the clinician(s) treating the patient based on the participant’s overall condition and may be dictated by other clinical and nonclinical considerations.

Normal body temperature is defined as oral, rectal, axillary, temporal, or tympanic temperature 36.1°C–38.0°C. Normal respiratory rate is defined as 12–20 breaths per minute.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination, performed at screening, will include, at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, and neurologic systems. Any abnormality identified at or before baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations may be performed as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Oral, tympanic, rectal, axillary, skin, or temporal artery temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Peripheral oxygen saturation should also be measured at the same time as vital signs. For participants requiring supplemental oxygen, the oxygen flow rate (in liters per minute [L/min]) and/or fraction of inspired oxygen (FiO_2) should be recorded.

Blood pressure and pulse measurements will be assessed while the participant is in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

If feasible, vital signs should be assessed at or close to the time of ordinal scale score determination (refer to Section 8.1.1 for details).

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and/or QT interval corrected through use of Fridericia's formula (QTcF)/QT interval. After screening, additional recordings may be obtained as needed per investigator's discretion. Refer to Appendix 3 for withdrawal criteria and any additional readings that may be necessary.

All ECG recordings must be performed through use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio,

conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Digital recordings will be stored at the site.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 5 for the list of clinical laboratory tests to be performed and to the schedules of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 2).

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline for participants discharged from the hospital within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants of childbearing potential is outlined in Section 1.3 and will be conducted as outlined in Appendix 5.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are

considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 2). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 60 days after the first dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Tocilizumab	Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of TCZ.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 2.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2-5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A2-7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 3.

8.3.9 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor/Emergency Medical Contact:	Min Bao, M.D. (Primary)
Mobile Telephone No.:	+1 650 296-3298
Medical Monitor:	Oliver Gordon, PhD (Secondary)
Mobile Telephone No.:	+44 7876 848699

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Serum samples of approximately 1 mL will be collected for measurement of serum concentrations of TCZ as specified in the schedules of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the study on the basis of newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of TCZ. Samples collected for analyses of TCZ (serum) concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. At visits during which serum samples for the determination of TCZ pharmacokinetics and pharmacodynamics will be taken, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on PD biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

8.7.1 Pharmacodynamic Biomarker Assessments

Serum samples of approximately 2.5 mL will be collected for PD analysis (IL-6, sIL-6R, CRP) at predefined timepoints as specified in the schedules of activities (see Section 1.3).

Samples will be used to evaluate the pharmacodynamics and assessment of the PK-sIL6R relationship after TCZ administration.

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded

PD samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.7.2 Exploratory Biomarker Assessments

Exploratory biomarker research may include, but will not be limited to, SARS-CoV-2 virus and antibodies in any residual serum to understand kinetics of these relative to TCZ treatment. These changes may be assessed in relation to changes in other disease biomarkers, including CRP and ferritin.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 5). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10), biomarker samples will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

Data generated from samples collected for exploratory biomarker research will be analyzed in aggregate rather than on an individual basis. Thus, there will be no

identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

There are no additional assessments and procedures requiring separate consent or that will be performed only at participating sites.

9. STATISTICAL CONSIDERATIONS

Full details of the statistical methods will be described in the Statistical Analysis Plan (SAP).

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.2 SAMPLE SIZE DETERMINATION

The primary objective of this study is to characterize the pharmacokinetics of TCZ in pediatric participants hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

At least 30 participants will be enrolled in this study in order to provide PK- and PD-evaluable data, including at least:

- 10 participants who weigh <30 kg
- 10 participants who weigh ≥ 30 kg

No formal sample size calculations have been performed.

9.3 ANALYSIS SETS

All Patients Population

The all patients population comprises all participants enrolled in the study.

Safety-Evaluable Population

The safety-evaluable population comprises all participants who received any amount of study drug.

Pharmacokinetic- and Pharmacodynamic-Evaluable Population

The PK- and PD-evaluable population comprises all patients in the safety-evaluable population who have at least four postdose drug concentration measurements at a scheduled visit timepoint for participants weighing $\geq$30 kg and at least three postdose drug concentration measurements at a scheduled visit timepoint for participant weighing $<$30 kg. Patients may be excluded from the PK- and PD-evaluable population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol, or if data are unavailable or incomplete (which may influence the PK analysis).

Decisions on patient exclusion from the PK- and PD-evaluable population will be made prior to database closure by the clinical pharmacologist. Excluded patients will be documented, together with the reason for exclusion.

9.4 STATISTICAL ANALYSES

The SAP will be finalized prior to the planned interim analysis and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and key secondary endpoints.

9.4.1 General Considerations

This is a single-arm, open-label study. Therefore, there will be no formal statistical hypothesis testing. All statistical analyses will be descriptive and 95% confidence intervals will be used for analyses, where appropriate.

9.4.2 Primary Endpoint

The pharmacokinetics of TCZ following one or two doses of 8 mg/kg or 12 mg/kg IV TCZ will be characterized through Day 28 in the PK-evaluable population using the following endpoints:

- Maximal serum concentration (C_{max}), serum concentration on Day 28 (C_{Day28}), area under the concentration–time curve up to Day 28 ($AUC_{Days\ 0\text{-}28}$), total clearance, volume of distribution.

The establishment of an integrated population PK-sIL-6R model with all relevant available PK and sIL-6R data in JIA patients and adult RA patients and adult patients with COVID-19 pneumonia (from COVACTA and MARIPOSA) has shown that the pharmacokinetics of TCZ in adult patients with COVID-19 pneumonia is well captured using a two-compartment model with parallel linear and Michaelis Menten elimination. TCZ linear clearance increased with increasing disease severity in adult patients with COVID-19 pneumonia and was higher as compared to adult patients with RA. Consistent with previous analyses in other indications, linear clearance and volume of

distribution were increasing with body weight. No other covariate relationship explored was found to be clinically relevant to TCZ pharmacokinetics.

This integrated PK-sIL-6R model will be used to characterize the TCZ and sIL-6R concentration–time courses of pediatric patients with COVID-19 and to compare the spread of PK exposure parameters and duration of 90% saturation of sIL-6R following a single IV TCZ dose from pediatric participants per body weight category to adult patients at similar disease category.

The ability of the integrated model to describe TCZ data in pediatric patients with COVID-19 will be evaluated by graphical analysis using both goodness-of-fit plots and simulation-based diagnostic plots (e.g., visual predictive check, normalized prediction distribution errors). Any detected obvious bias in the simulation-based diagnostic or goodness-of-fit plots will lead to model adjustment to reduce any potential weaknesses for PK/PD description in pediatric patients with COVID-19.

9.4.3 Secondary Endpoints

The pharmacodynamics of TCZ through Day 60 will be characterized in the safety-evaluable population using the following endpoints:

- Duration of 90% saturation of sIL-6R through Day 28
- Concentrations of IL-6, sIL-6R, and CRP at specified timepoints

IL-6, sIL-6R, CRP data will be presented using descriptive summary statistics, including mean, median, range, and SD. The duration of 90% saturation of sIL-6R will be derived using the integrated PK-sIL-6R model (see Section 9.4.2).

The safety of TCZ through Day 60 will be evaluated in the safety-evaluable population using the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale
- Incidence of serious adverse events
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Study treatment exposure will also be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study discontinuation or study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be listed and summarized

by mapped term and appropriate thesaurus level. Adverse events will also be summarized by severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory and vital sign (including, but not limited to, pulse rate, respiratory rate, blood pressure, and temperature) data will be presented over time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and laboratory tests will be summarized.

9.4.4 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be evaluated in the safety-evaluable population and are summarized in Table 6.

Details of all exploratory analyses will be described in the SAP.

9.4.5 Other Analyses

9.4.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized. The reasons for study discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

9.4.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including, but not limited to, age, sex, race/ethnicity, geographic region, ordinal scale category for clinical status) will be summarized. Baseline data are the last data obtained prior to initiation of study treatment, unless otherwise specified. Descriptive statistics (mean, SD, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables, as appropriate. Summaries will be presented for the safety-evaluable population and may be produced for other populations if there are differences.

Medical history data, including surgery and procedures, and baseline conditions, will be summarized descriptively using the safety-evaluable population.

Previous and concomitant treatments will be summarized descriptively.

9.5 INTERIM ANALYSIS

9.5.1 Planned Interim Analysis

An interim population PK/PD analysis will be conducted once Day 28 data are available from at least 10 PK/PD-evaluable participants (at least 5 participants weighing < 30 kg, and at least 5 participants weighing ≥ 30 kg) to confirm the dosing regimens.

A Bayesian feedback using the integrated PK-sIL-6R model will be performed to derived the PK/PD and PK parameters in participants (as described in Section 9.4.2). The spread of PK exposure parameters and duration of 90% saturation of sIL-6R following a single dose of IV TCZ from participants per body weight category will be compared with that observed in adult patients with COVID-19 who have similar disease severity.

The interim analysis will be considered successful if the duration of 90% saturation of sIL-6R in at least 90% of participants included in the interim analysis is greater or equal to the 5th percentile of the distribution of the duration of 90% saturation of sIL-6R observed in adult patients with COVID-19 pneumonia of similar disease severity. If the interim analysis is successful, then participants under 2 years of age may be enrolled and receive TCZ treatment as outlined in Section 6.1.

In the scenario that the interim analysis is deemed not successful, study enrollment will be put on a temporary hold. Simulations will be conducted using the integrated PK-sIL-6R model to identify alternative dosing regimens that would generate more comparable distributions between pediatric patients and adult patients. If different dosing regimens are identified based on the interim analysis outcome, the remaining participants, including those younger than 2 years of age, will be enrolled after the protocol is amended to incorporate the new dosing regimen(s), and following relevant health authority feedback. All remaining participants will be treated with the new dosing regimen(s).

A similar analysis to the interim analysis will be then conducted on the PK and PD data collected in participants receiving the updated dosing regimen at the end of the study.

Given that the study is a single-arm, open-label study, the interim analysis will be conducted by the study team and reviewed by the IMC and SOC (details on their responsibilities will be outlined in a charter).

The decision to conduct the interim analysis, along with the rationale, timing, and success criteria and additional details for the analysis, will be documented in the SAP.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

A1. TABLE OF CONTENTS

A1-1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Regulation (E.U.) No. 536/2014 (E.U. sites only), and all other applicable local regulations

A1-2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1-3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1-4 DATA PROTECTION

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1-5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites globally will participate to enroll approximately 30 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A1-6 DISSEMINATION OF CLINICAL STUDY DATA

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1-7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study

initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A1-8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1-9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1-10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1-11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating

procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A2. TABLE OF CONTENTS

A2-1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events (with the exception of death due to COVID-19 pneumonia progression as described in Section A2-7.8). These data will be captured as efficacy assessment data only. If there is any

uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A2-2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A2-1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A2-3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A2-5 for reporting instructions).

A2-3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2-3.1 Adverse Event and Serious Adverse Event Recording

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A2-3.2 Assessment of Severity

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table 1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A2-5 for reporting instructions), per the definition of serious adverse event in Section A2-2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A2-5 for reporting instructions), per the definition of serious adverse event in Section A2-2.

A2-3.3 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A2-3.4 Follow-up of Adverse Events and Serious Adverse Events

A2-3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A2-3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A2-4 REPORTING OF SERIOUS ADVERSE EVENTS

A2-4.1 Serious Adverse Event Reporting to the Sponsor via an Electronic Collection Tool

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A2-5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2-5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2-5.

A2-4.2 Serious Adverse Event Reporting to the Sponsor via Paper CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form , as described in Section A2-5.

A2-5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A2-5.1 Events That Occur Prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A2-5.2 Events That Occur After Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 60 days after the first dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 60 days after the first dose of study treatment are provided in Section A2-6.

A2-6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days after the first dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A2-7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A2-7.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction/anaphylactic reaction).

A2-7.2 Diagnosis versus Signs And Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome

at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A2-7.3 Adverse Events that are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A2-7.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A2-5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A2-7.5 Abnormal Laboratory Values

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A2-7.4 for details on recording persistent adverse events).

A2-7.6 Abnormal Vital Sign Values

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an

adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A2-7.4 for details on recording persistent adverse events).

A2-7.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A2-7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A2-5).

A2-7.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the

Adverse Event eCRF and immediately reported to the Sponsor (see Section A2-5). This includes death attributed to progression of COVID-19.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COVID-19, "COVID-19 progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section A2-6.

A2-7.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A2-7.10 Lack of Efficacy or Worsening of COVID-19

Medical occurrences or symptoms of deterioration that are anticipated as part of COVID-19 should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of COVID-19 on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of COVID-19").

A2-7.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse

event (per the definition of serious adverse event in Section A2-2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A2-7.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware

of the event; see Section A2-5). For tocilizumab (TCZ), adverse events associated with special situations should be recorded as described below for each situation:

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

All special situations associated with TCZ, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter TCZ and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter TCZ and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter TCZ and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter TCZ and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

Appendix 3
Safety Plan: Management of Identified and Potential Risks

A3. TABLE OF CONTENTS

A3-1 RISKS ASSOCIATED WITH TOCILIZUMAB

The safety plan for participants in this study is based on clinical experience with tocilizumab (TCZ) in clinical studies and postmarketing experience. The important safety risks for TCZ are outlined below. Please refer to the current Tocilizumab Investigator's Brochure for a complete summary of safety information.

A3-1.1 Hypersensitivity Reactions, Including Anaphylaxis

An infusion reaction is defined as any adverse event that occurs during or within 24 hours after the end of an infusion. This may include hypersensitivity or anaphylactic reactions. Stevens-Johnson syndrome has been reported during treatment with TCZ in the postmarketing setting. Signs of a possible hypersensitivity reaction include, but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

TCZ infusions will be administered to participants at the site under close supervision. Healthcare professionals administering TCZ infusions should be trained in the appropriate procedures for TCZ administration, should be able to recognize the symptoms associated with potential hypersensitivity reactions, including anaphylaxis, and should have the appropriate medication available for immediate use in case of hypersensitivity reaction such as anaphylaxis during or after administration of TCZ. The participant should be treated according to the standard of care for management of the hypersensitivity reaction.

If a participant has symptoms of serious hypersensitivity reactions, such as anaphylaxis, or requires an interruption of the study drug because of symptoms of hypersensitivity, including anaphylaxis, administration of TCZ must be discontinued permanently.

A3-1.2 Serious Infections and Opportunistic Infections

Physicians should exercise caution when considering the use of TCZ in participants at increased risk of infection, such as a history of recurring infections or with underlying conditions (e.g., diabetes mellitus) that may predispose participants to serious infections and opportunistic infections such as tuberculosis and viral reactivations (e.g., hepatitis B virus).

Vigilance for timely detection of serious infection is recommended for participants receiving biologic agents, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase reaction. The effects of TCZ on C-reactive protein (CRP) and neutrophils, and the signs and symptoms of infection, should be considered when evaluating a for a potential infection. It is recommended that

neutropenic participants (ANC $<$ 1000/μL) undergo weekly surveillance blood cultures during the study.

If a participant develops a serious infection, administration of TCZ should be discontinued.

In participants with COVID-19, TCZ should not be administered if participants also have any other concurrent serious active infection.

A3-1.3 Gastrointestinal Perforations

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower gastrointestinal (GI) disease, such as Crohn disease, ulcerative colitis, or other chronic lower GI conditions, might predispose participants to GI perforations. Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus reduce the risk of GI perforations.

Discontinuation of TCZ is required for participants who develop GI perforations.

A3-1.4 Hematologic Abnormalities

Decreases in neutrophil counts, platelet counts, and fibrinogen levels have been observed following treatment with TCZ for labeled indications. Treatment-related neutropenia was not associated with serious infection in clinical trials in any indication and no association between decreases in platelet counts and serious bleeding events has been observed.

In participants with COVID-19 and an ANC below 1000/μL, administration of treatment is not recommended. Neutrophil count should be monitored according to current standard clinical practices.

In all participants, including those with COVID-19, with a platelet count below $50 \times 10^3/\mu$L, treatment is not recommended. Platelets should be monitored according to current standard clinical practices.

A3-1.5 Demyelinating Disorders

The effect of treatment with TCZ on demyelinating disorders is not known; events have been reported rarely. Physicians should exercise caution when considering the use of TCZ in participants with preexisting or recent-onset demyelinating disorders.

Participants should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders.

A3-1.6 Elevated Liver Enzymes

In clinical trials, mild and moderate elevations of hepatic transaminases have been observed with TCZ treatment.

Participants hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer TCZ should balance the potential benefit against the risks of acute treatment with TCZ. In participants with COVID-19 and elevated ALT or AST above $10 \times$ ULN, administration of TCZ treatment is not recommended. ALT or AST should be monitored according to current standard clinical practices.

The optional second infusion of TCZ must not be administered if ALT or AST $> 10 \times$ ULN is measured after the first infusion.

Participants who develop elevated liver function tests during the study must have repeat tests performed as clinically indicated until levels return to baseline, even if they withdraw from the study. If the specialist deems a liver biopsy necessary, the prepared histologic slides will be requested by the Sponsor for central review by a third party, and the biopsy report should be forwarded to the Sponsor.

A3-1.7 CYP450 Enzyme Normalization

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as interleukin 6, that stimulate chronic inflammation. TCZ normalizes expression of these enzymes. The effect of TCZ on CYP450 enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index and/or when the dose is individually adjusted.

When starting or stopping therapy with TCZ, participants taking medicinal products which are individually dose adjusted and are metabolized via CYP450 CYP3A4, CYP1A2, CYP2B6, or CYP2C9 (e.g., atorvastatin, calcium-channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their therapeutic effect.

A3-2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A3-2.1 Dose Modifications

Dose modifications for TCZ are not allowed in this study.

A3-2.2 Treatment Interruption

Treatment interruption guidelines are not applicable for this study.

A3-2.3 Management Guidelines

If ALT or AST $>10\times$ ULN, ANC $<1000/\mu L$, or platelet count $<50{,}000/\mu L$ is detected after the first TCZ infusion, the optional second infusion should not be administered.

Guidelines for management of specific adverse events are outlined in Section A3-1.1.

Appendix 4
Contraceptive and Barrier Guidance

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A4-1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of tocilizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event electronic Case Report Form (eCRF). In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4-2 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2-5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2-5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4-3 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2-5).

Appendix 5
Clinical Safety Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
• Chemistry panel (serum or plasma): 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
• Pregnancy test All female participants of childbearing potential will have a urine or serum pregnancy test performed at screening. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

CRP = C-reactive protein.

Investigators must document their review of each laboratory safety report.

Appendix 6
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 7
Abbreviations

Abbreviation or Term	Definition
$AUC_{Days\ 0-28}$	area under the concentration–time curve up to Day 28
C_{Day28}	serum concentration on Day 28
C_{max}	maximal serum concentration
CAR	chimeric antigen receptor
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine-release syndrome
CT	computed tomography (scan)
EC	Ethics Committee
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EUA	emergency use authorization
FDA	(U.S.) Food and Drug Administration
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
ICH	International Council for Harmonisation
ICU	intensive care unit
IMC	Internal Monitoring Committee
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
JIA	juvenile idiopathic arthritis
LPLV	last participant, last visit
MIS-C	multisystem inflammatory syndrome in children

Appendix 7: Abbreviations

Abbreviation or Term	Definition
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
PD	pharmacodynamic
PK	pharmacokinetic
QTcF	QT interval corrected through use of Fridericia's formula
RA	rheumatoid arthritis
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome corona virus-2
sIL-6R	soluble interleukin 6 receptor
sJIA	systemic juvenile idiopathic arthritis
SOC	Scientific Oversight Committee
TCZ	tocilizumab
ULN	upper limit of normal