06 December 2021
EMA/733881/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## RoActemra

International non-proprietary name: tocilizumab

Procedure No. EMEA/H/C/000955/II/0101

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

# List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ARDS | acute respiratory stress syndrome |
| CL | clearance |
| COVID-19 | coronavirus disease 2019 |
| CRP | C-reactive protein |
| CSR | clinical study report |
| ECMO | extracorporeal membrane oxygen |
| ECMP | Exceptional Change Management Process |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FDA | Food and Drug Administration |
| HR | hazard ratio |
| ICU | intensive care unit |
| IL-6R | interleukin 6 receptor |
| IQR | interquartile range |
| ITT | intent-to-treat |
| IV | intravenous |
| MA | marketing authorization |
| mITT | modified intent-to-treat |
| OR | odds ratio |
| PBO | placebo |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| q4w | every 4 weeks |
| RA | rheumatoid arthritis |
| RDV | remdesivir |
| SoC | standard of care |
| TCZ | tocilizumab |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 27 July 2021 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA and IIIB |

C.I.6 - Extension of indication to include the treatment of coronavirus disease 2019 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation for RoActemra; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC for RoActemra 20 mg/mL concentrate for solution for infusion are updated. The Package Leaflet is updated in accordance. Version 27.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev. 1.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

### *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0333/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0333/2021 was not yet completed as some measures were deferred.

### *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Agnes Gyurasics

| Timetable | Actual dates |
|---|---|
| Submission date | 27 July 2021 |
| Start of procedure: | 16 August 2021 |
| CHMP Rapporteur Assessment Report | 14 September 2021 |
| PRAC Rapporteur Assessment Report | 17 September 2021 |
| PRAC members comments and Co-Rapporteur critique | 22 September 2021 |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC Outcome | 30 September 2021 |
| CHMP members comments | 04 October 2021 |
| ETF meeting | 07 October 2021 |
| Updated CHMP Rapporteur Assessment Report | 07 October 2021 |
| Request for supplementary information | 14 October 2021 |
| CHMP Rapporteur Assessment Report | 17 November 2021 |
| PRAC Rapporteur Assessment Report | 17 November 2021 |
| PRAC members comments and Co-Rapporteur critique | 24 November 2021 |
| Updated PRAC Rapporteur Assessment Report | 25 November 2021 |
| CHMP members comments | 25 November 2021 |
| ETF meeting | 30 November 2021 |
| PRAC Outcome | 02 December 2021 |
| Updated CHMP Rapporteur Assessment Report | 03 December 2021 |
| CHMP Opinion | 06 December 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

Coronaviruses (CoV) are positive-stranded ribonucleic acid viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in the city of Wuhan, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (WHO, 2020) (Zhu, 2020).

Most patients with mild cases of disease recover with symptomatic treatment and supportive care. However, approximately 15% of COVID-19 pneumonia patients with more severe illness frequently require hospitalization (WHO, 2020). Approximately 5% of infected patients experience complications related to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multi-organ failure and death (WHO, 2020).

Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

## *Claimed therapeutic indication*

"*RoActemra is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation*."

## *Epidemiology*

As of 7 June 2021, over 172 million confirmed cases of COVID-19 have been reported globally by the WHO with the cumulative prevalence of 2331 cases per 100,000 population.

In the WHO European region, over 54.5 million cases were confirmed so far with a prevalence of 5963 cases per 100,000 population.

Older adults are more likely to get severely ill from COVID-19. More than 80% of COVID-19 deaths occur in people over age 65, and more than 95% of COVID-19 deaths occur in people older than 45. Long-standing systemic health and social inequities have put various groups of people at increased risk of getting sick and dying from COVID-19, including many racial and ethnic minority groups and people with disabilities. A meta-analysis of 50 studies (42 were from the USA and 8 from the United Kingdom) reported that individuals from Black [Relative Risk (RR): 2.02; 95% CI 1.67-2.44)] and Asian (RR:1.50; 95% CI 1.24-1.83) ethnicities had a higher risk of COVID-19 infection compared to white individuals (Sze et al. 2020). Chronic underlying health conditions also place patients at increased risk for developing severe disease. These include cancer; chronic kidney disease; chronic obstructive pulmonary disease; Down Syndrome; heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies; immunocompromised state (weakened immune system); liver disease; obesity (body mass index [BMI] of 30 kg/$m^2$ or higher but < 40 kg/$m^2$); severe obesity (BMI $\geq$ 40 kg/$m^2$); pregnancy; sickle cell disease; cerebrovascular disease; and Type 2 diabetes mellitus (ECDC High Risk Groups; CDC People with Certain Medical Conditions).

## *Aetiology and pathogenesis*

Coronaviruses (CoV) are enveloped RNA viruses and are important human and animal pathogens. Two coronaviruses have previously been identified as zoonotic infections which have adapted to humans and caused severe respiratory illnesses with high fatality: Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). The S protein mediates binding to the host receptor angiotensin converting enzyme 2 (ACE2), resulting in membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020).

Transmission of SARS-CoV-2 occurs primarily through person-to-person contact and respiratory droplet transmission (Lai, 2020) (Lewis, 2020). A high background rate of lateral transmission has been observed in households with a documented SARS-CoV-2 infected individual quarantining alongside other household members (Madewell, 2020). Compared to other betacoronavirus infections, the incubation period of SARS-CoV-2 infection (i.e., time before symptoms occur) has features that complicate the control of virus transmission: the period is highly variable (range 2 to 14 days) and it is often characterized by high viral loads and viral shedding (Ellington, 2020).

## *Clinical presentation, diagnosis and stage/prognosis*

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness, ranging from a mild upper respiratory tract infection to severe acute respiratory distress syndrome (ARDS) and multiorgan failure (Wiersinga et al. 2020). Severe/critical COVID-19 pneumonia (occurring in about 15% of patients) is associated with high mortality and places extensive burden on intensive care units (ICUs) to provide mechanical ventilation and other advanced forms of life support (Guan et al. 2020; Yang et al. 2020).

Hypoxic respiratory failure in patients with COVID-19 is associated with evidence of systemic inflammation, including release of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6 and TNFα, and elevated levels of D-dimer, ferritin, and C-reactive protein (CRP) (Chen et al. 2020; Del Valle et al. 2020). The host immune response is thought to play a key role in driving a rapid increase in proinflammatory cytokines, an uncontrolled inflammatory response, ARDS and multiple organ failure (Giamarellos-Bourboulis et al. 2020; Vabret et al. 2020). The beneficial effects of dexamethasone in hospitalized COVID-19 requiring supplemental oxygen suggest that other, more specific immunomodulatory agents may provide additional improvements in clinical outcomes (Horby et al. 2021).

## *Management*

### Prevention

To date, four vaccines have been granted conditional marketing authorization (MA) in the EU. Several other are currently under evaluation in Europe.

### Treatments

Treatment options for COVID-19 have been evolving since the pandemic was declared in March 2020. Initially, treatment was largely supportive in the outpatient or hospitalized setting and included the use of antipyretics, fluids, antibiotics if bacterial secondary infection or co-infection was suspected, and supplemental oxygen.

Systemic corticosteroids were not routinely recommended until emerging data from clinical trials, including the RECOVERY trial dexamethasone cohort (Horby et al. 2021), indicated a mortality benefit among patients requiring supplemental oxygen or mechanical ventilation. The EMA issued

recommendations on the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation (art 5(3) procedure 18 September 2020).

Velkury (remdesivir, RDV), a broad spectrum anti-viral, was granted conditional marketing authorisation on 3 July 2020 and is indicated for use in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at the start of treatment).

Regkirona (regdanvimab) is an antiviral, a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection. It has been granted a marketing authorisation on 12/11/2021 for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Ronapreve (casirivimab / imdevimab) is a human IgG1 mAbs that bind simultaneously to the S protein receptor binding domain (RBD) and block its interaction with the host receptor, angiotensin-converting enzyme 2 (ACE2). It has been granted a marketing authorisation on 12/11/2021 for the treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 and the prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

EMA's human medicines committee (CHMP) has issued an opinion (Article 5.3 procedure) on the use of Lagevrio (also known as molnupiravir or MK 4482) for the treatment of COVID-19 on 19/11/2021. The medicine, which is currently not authorised in the EU, can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19. Lagevrio should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. The medicine, which is available as capsules, should be taken twice a day for 5 days.

Several other therapeutics are currently under evaluation in Europe.

### 2.1.2. About the product

Tocilizumab (TCZ, RoActemra) is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1 subclass directed against the human interleukin 6 receptor (IL-6R). TCZ, which is registered as RoActemra in the EU, was first approved in the EU for the treatment of rheumatoid arthritis (RA) on 16 January 2009.

Roactemra is already approved in the EU for treating the inflammatory conditions rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis and cytokine release syndrome (CRS).

TCZ has been approved in over 120 countries worldwide; there have been nearly 25,000 patients exposed to TCZ in clinical trials (over 40,000 patient-years of exposure) and over 2.5 million patients exposed (over 2.2 million patient-years of exposure).

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice for this procedure.

### 2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 1 Tocilizumab Clinical Studies that Form the Basis of the Type II Variation**

| Study Number | Overall Design | Patient Population/ Number of Patients | Primary Objective | Status |
|---|---|---|---|---|
| RECOVERY[a] | Investigator-initiated, randomized, controlled, open-label, platform trial | 4116 hospitalized patients with COVID-19 | To evaluate the effects of TCZ in adult patients admitted to hospital with COVID-19 with both hypoxia and systemic inflammation (TCZ cohort) | Ongoing<br>Results from TCZ Cohort published<br>(RECOVERY Collaborative Group 2021) |
| WA42380/ COVACTA | Phase III, double-blind, placebo-controlled, multicenter, randomized | 452 hospitalized patients with severe COVID-19 pneumonia | To evaluate the efficacy of TCZ compared with placebo in combination with SoC for the treatment of severe COVID-19 pneumonia on the basis of clinical status assessed on a 7-category ordinal scale at Day 28 | Completed<br>Final CSR available<br>Results published<br>(Rosas et al 2021) |

| | | | | |
|---|---|---|---|---|
| ML42528/ EMPACTA | Phase III, double-blind, placebo-controlled, multicenter, randomized | 389 hospitalized patients with COVID-19 pneumonia not on either invasive ventilation or CPAP/BiPAP at baseline | To evaluate the efficacy of TCZ compared with placebo in combination with SoC for the treatment of COVID-19 pneumonia on the basis of cumulative proportion of patients with death or requiring mechanical ventilation by Day 28 | Completed<br>Final CSR available<br>Results published<br>(Salama et al 2021) |
| WA42511/ REMDACTA | Phase III, double-blind, placebo-controlled, multicenter, randomized | 649 hospitalized patients with severe COVID-19 pneumonia | To evaluate the efficacy of TCZ plus remdesivir compared with placebo plus remdesivir for the treatment of severe COVID-19 pneumonia on the basis of time to discharge/ready for discharge up to Day 28 | Completed<br>Final CSR available |
| CA42481/ MARIPOSA[b] | Phase II, open-label, multicenter study, randomized | 100 hospitalized patients with moderate and severe COVID-19 pneumonia | To evaluate the PK and PD of two doses of TCZ (4 mg/kg and 8 mg/kg) in combination with SoC in hospitalized patients with severe or moderate COVID-19 pneumonia | Completed<br>Final CSR available |

BiPAP=bilevel-positive airway pressure; CPAP=continuous positive airway pressure; CSR=clinical study report; PD=pharmacodynamics; PK=pharmacokinetics; SoC=standard of care; TCZ=tocilizumab.
[a] RECOVERY is a Roche-supported, investigator-initiated trial.
[b] Supportive study.

### 2.3.2. Pharmacokinetics

Pharmacokinetics of TCZ in adult patients with severe COVID-19 was assessed based on data from two clinical studies WA42380 (COVACTA) and CA42481 (MARIPOSA). The key PK and pharmacodynamics results are derived from the following analyses on studies conducted by the MAH:

- Observed PK and pharmacodynamics data over 60 days following one or two doses TCZ in patients with COVID-19 pneumonia from studies COVACTA and MARIPOSA.
- Population PK (popPK) and PK-sIL6R analysis of TCZ and sIL6R concentrations in adult patients with COVID-19 (COVACTA and MARIPOSA) collected over 60 days.

The proposed posology for treatment of COVID-19 was "*a single 60-minute intravenous infusion of 8 mg/kg BW. If clinical signs or symptoms worsen or do not improve after the first dose, 1 additional infusion of RoActemra 8 mg/kg may be administered. There should be an interval of at least 8 hours between these two infusions. Doses exceeding 800 mg per infusion are not recommended in patients with COVID-19.*"

**Table 2 Overview of studies contributing clinical pharmacology data**

| Study Number (Phase) | Study Design | Patient Population | Dose, Route, Regimen | Number of Patients |
|---|---|---|---|---|
| WA42380<br>Phase III | Randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SoC compared with matching placebo in combination with SoC in hospitalized adult patients with severe COVID-19 pneumonia. | Patients ≥ 18 years with severe COVID-19 pneumonia | TCZ IV 8 mg/kg, 1 or 2 doses 8 to 24 hours apart<br>or<br>Matching PBO IV<br>Maximum dose capped at 800 mg | 452 pts randomized<br>438 pts treated<br>295 pts TCZ (65 pts with 2 doses) / 143 pts PBO (43 pts with 2 doses)<br>284 pts PKPD analysis population[a] |
| CA42481<br>Phase II | Open-label, randomized, multicenter study to assess the pharmacodynamics, pharmacokinetics, safety, and efficacy of two different doses of TCZ in combination with SoC in hospitalized adult patients with moderate to severe COVID-19 pneumonia. | Patients ≥ 18 years with moderate to severe COVID-19 pneumonia | TCZ IV 8 mg/kg, 1 or 2 doses 8 to 24 hours apart<br>or<br>TCZ IV 4 mg/kg, 1 or 2 doses 8 to 24 hours apart<br>Maximum dose capped at 800 mg | 100 pts randomized<br>97 pts treated<br>49 pts TCZ 4 mg/kg (12 pts with 2 doses)/ 48 pts TCZ 8 mg/kg (9 pts with 2 doses)<br>96 pts PKPD analysis population[b] |

COVID-19 = coronavirus disease 2019; IV = intravenous; PBO=placebo; PK=pharmacokinetic; pts=patients; SoC = standard of care; TCZ = tocilizumab.

[a] Patients treated with TCZ who presented at least one evaluable TCZ PK and/or sIL-6R sample.

[b] Among 96 subjects two subjects did not have evaluable TCZ or sIL-6R concentrations; one subject had TCZ concentrations but did not have evaluable sIL-6R concentrations; one subject had sIL-6R concentrations but did not have evaluable TCZ concentrations.

***Analytical methods***

Determination of tocilizumab concentrations in human serum samples was conducted using the established and validated enzyme-linked immunosorbent assay (ELISA). The limit of quantitation was 0.1 µg/mL for tocilizumab.

Determination of sIL-6R concentrations in human serum samples was conducted using the established and validated ELISA. Measurements of sIL-6R do not distinguish between unbound sIL-6R and sIL-6R bound to tocilizumab: sIL-6R assay measures the total concentration that is the sum of the unbound sIL-6R and sIL-6R bound to tocilizumab. The limit of quantitation was 1 µg/mL for sIL-6R.

***Study WA42380 (COVACTA)***

Patients (≥18 years of age) were randomized at a 2:1 ratio to receive blinded treatment of either tocilizumab or a matching placebo, respectively. Study treatment must have been given in combination with SoC. The randomization was stratified by geographic region and mechanical ventilation to ensure that the treatment arms were balanced for any differences in regional SoC across global sites, and for baseline disease severity.

The proportion of patients who were supported by mechanical ventilation at the time of randomization was capped at no more than 50% of the overall study population. Patients assigned to the tocilizumab arm received one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm received one infusion of placebo. For both arms, if the clinical signs or symptoms worsened or did not improve one additional infusion of blinded treatment of TCZ or placebo could be given, 8–24 hours after the initial infusion.

The optimal TCZ dose regimen for the treatment of COVID-19 pneumonia was not known at the time of initiation of Study WA42380. The TCZ dose regimen chosen in this study is consistent with the approved TCZ dose for patients experiencing CRS induced by CAR-T cell therapy who weigh ≥30 kg. The additional dose authorized in case of lack of clinical improvement, was based on clinical experience from off-label use and the fact that up to three additional infusions of TCZ (with at least 8 hours in between infusions) are allowed for CAR-T induced CRS.

Serum samples were obtained according to the following schedule: Day 1 pre-dose, Day 1 end-of-infusion, 24 and 36 hours after infusion, and then at Day 3 (sIL-6 only), 7, 14, 21, 28, 35, and at study completion (Day 60) or discontinuation.

Patients were followed up for a total of 60 days after first dose of TCZ.

Observed TCZ Pharmacokinetic Results

Serum TCZ concentrations peaked at the end of each infusion and then declined (Figure 1).

As expected, the peak following the second infusion was higher than the peak following the first infusion. TCZ concentrations were close to or below the limit of quantification (0.1 µg/mL) from approximately Day 21 in patients who received one dose of 8 mg/kg TCZ and from approximately Day 35 in patients who received two doses of 8 mg/kg TCZ.

The fluctuations observed following the peak in the average profile for patients who received two doses of 8 mg/kg TCZ was due to the different times when the second infusion was actually administered, between 8 to 24 hours after the initial dose as allowed per protocol.

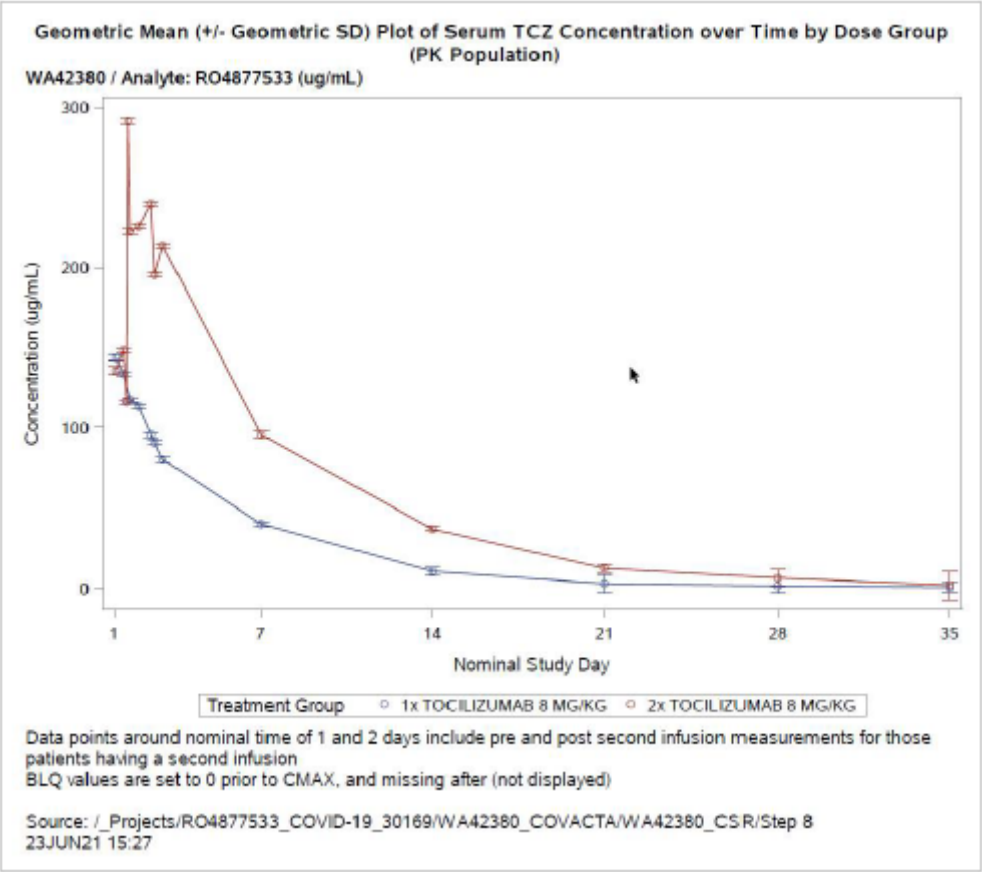



**Figure 1 Geometric mean (+/- Geometric SD) plot of serum TCZ concentration over time by dose group (PK population)**

***Study CA42481 (MARIPOSA)***

Patients (≥18 years of age) categorized as having severe or moderate COVID-19 pneumonia as per protocol were randomized in a 1:1 ratio to receive open-label treatment with either 4 mg/kg or 8 mg/kg IV TCZ plus SoC per local practice.

Randomization was stratified by COVID-19 pneumonia disease severity (moderate or severe). The planned sample size was 100 patients, with 50 patients per treatment group and no more than 50 patients with moderate disease in total.

Each patient received one IV infusion of 4 or 8 mg/kg TCZ, with a maximum dose of 800 mg. If the patient had a sustained fever or clinically significant worsening of signs or symptoms, one additional TCZ infusion at the same dose as the initial infusion was administered, at the discretion of the investigator, within 8 to 24 hours after the initial TCZ infusion.

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

Off-label use of TCZ in China for the treatment of COVID-19 pneumonia indicated that a TCZ dose lower than the dose recommended in the CAR T cell-induced CRS label might also be efficacious for the treatment of COVID-19 pneumonia (Xu et al. 2020). The dose regimen used in China was a single fixed dose of 400 mg IV TCZ (which equates to between 4 and 8 mg/kg TCZ based on the body weight range of the Chinese adult population), with a maximum single dose of 800 mg and an additional dose within 12 hours if clinical signs and symptoms did not improve.

Understanding of the PK-PD relationship of TCZ and predictions from a well-established PK/sIL-6R model for RA supported the choice of testing 4 mg/kg IV TCZ in patients presenting with COVID-19 pneumonia. The model predicted that the 4 mg/kg IV dose would elicit a similar onset and magnitude of IL-6 pathway inhibition as the 8 mg/kg IV dose but for a shorter duration as shown by the sIL-6R time course, although it was acknowledged that the model may not accurately predict the PK and PD of TCZ in patients with COVID-19 pneumonia. The choice of the 4 mg/kg dose was further supported by the possibility of administering a second infusion of TCZ.

Patients were followed up until 60 days after the first TCZ IV administration.

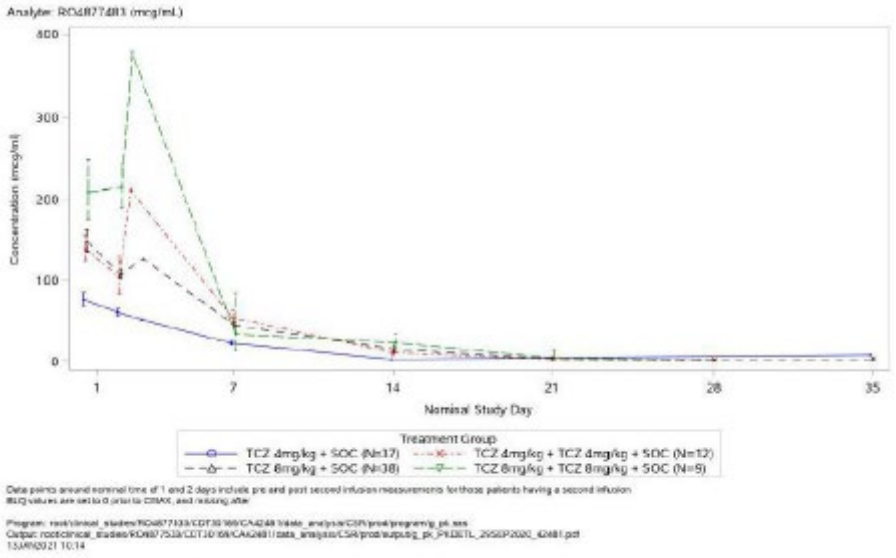
Observed TCZ Pharmacokinetic Results

Serum TCZ concentrations peaked at the end of each infusion and then declined (Figure 2).

As expected, the peak following the second infusion was higher than the peak following the first infusion, and peak TCZ concentrations were highest in patients who received two doses of 8 mg/kg TCZ and lowest in patients who received one dose of 4 mg/kg.

TCZ concentrations were close to or below the limit of quantification (0.1 µg/mL) from approximately Day 14 in patients who received one dose of 4 mg/kg TCZ and from approximately Day 21 in patients who received two doses of 4 mg/kg TCZ or one or two doses of 8 mg/kg TCZ.

The apparent second lower peak in the average profile for patients who received one dose of 8 mg/kg TCZ was due to a single patient with data at Day 3; the patient showed the expected decrease in TCZ concentration over time but the concentration on Day 3 was higher than the geometric mean for all patients at Day 2.




PK=pharmacokinetic; SD=standard deviation; TCZ=tocilizumab.

**Figure 2 Geometric mean (+/- geometric SD) plot of serum TCZ concentration over time by dose group (PK population)**

***Population PK and PK-sIL6R model analysis***

A joint population PK- sIL6R model that describes the pharmacokinetics of tocilizumab and total sIL6R concentrations following intravenous administration in adult patients with COVID-19 was established.

Overall, 380 patients from WA42380 and CA42481 were included in the analysis. A total of 1860 PK observations and 2929 sIL-6R observations from 369 and 377 patients, respectively, were available for the analysis.

Model development

Tocilizumab population PK-sIL6R model was first developed using data from multiple studies in adult patients with RA and paediatric patients with sJIA and pcJIA following fix and weight-based dosing of tocilizumab administered SC and IV. Tocilizumab concentrations were described by a two-compartment model with parallel linear and Michaelis- Menten elimination, and the first-order subcutaneous absorption. Total (unbound and bound to tocilizumab) sIL-6R concentrations were described by equations of quasi-steady-state (QSS) approximation of the target-mediated drug disposition (TMDD) model. Joint fit of tocilizumab and sIL-6R data was performed (non-COVID model).

Modelling started with the fit of the prior model supplemented by the COVID-19 effects (effects of studies COVACTA and MARIPOSA) on model parameters of linear clearance (CL), central and peripheral volumes (VC and VP), maximum target-mediated elimination rate (VM), elimination rate of bound sIL-6R (kint), and degradation rate of free (unbound) sIL-6R (kdeg), and COVID-19 severity (SCALE) effects on CL and kint. In addition, the effect of age on kdeg (noticed on diagnostic plots for patients with AGE > 50 years) was added. Then, covariate effects not supported by the model were removed to arrive at the final model. The significance level of 0.01 (change of objective function of 6.63 points for one estimated parameter) was used to compare models.

Final model

The serum concentration-time course of tocilizumab following multiple IV administration in adult patients with COVID-19 was described by a two-compartment pharmacokinetic model with parallel linear and Michaelis-Menten elimination.

**Table 3 Parameter estimates of the tocilizumab population PK-sIL-6R Model 018mar**

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

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

Model evaluation

Goodness-of-fit plots (Model 018mar) are shown in Figure 3 and Figure 4 for tocilizumab PK and sIL-6R, respectively.

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

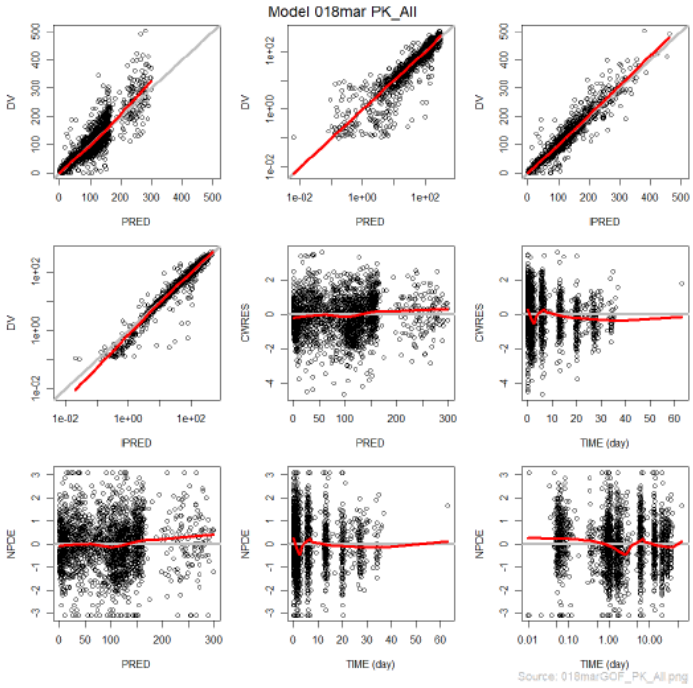



**Figure 3** **Goodness of fit for Model 018mar: TCZ**

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

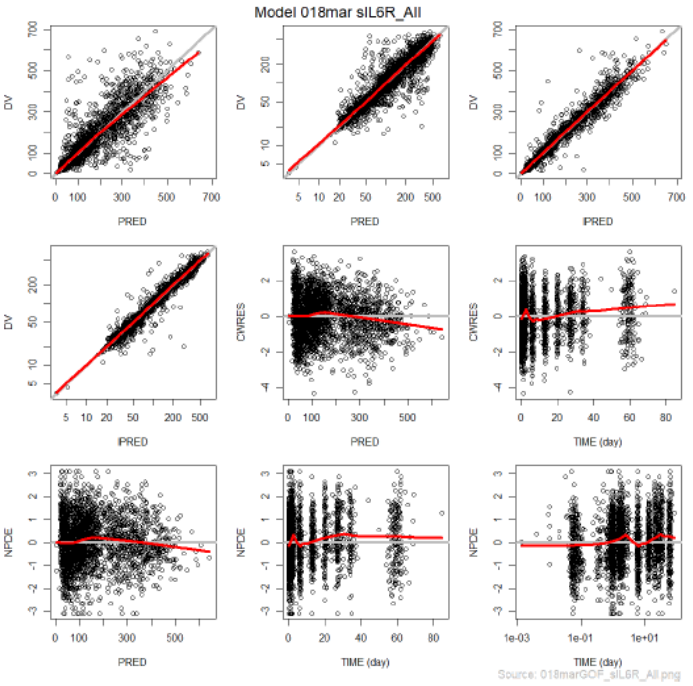



**Figure 4** **Goodness of fit for Model 018mar: sIL6R**

The results of the shrinkage calculation are presented in Figure 5 and Figure 6 below.

Density histograms of the inter-individual random effect distributions. The y-axis shows the density of observations that fall into respective bins. The solid black lines illustrate the density of the random effect distributions. The vertical lines show medians of these distributions. The dashed red lines show the density of the random effect distributions as estimated by the model. Shrinkage calculations are described in the Methods section. ETA1: the random effect on linear clearance (CL); ETA2: the random effect on central volume ($V_C$); ETA3: the random effect on volume of the peripheral compartment ($V_P$); ETA4: the random effect on inter-compartment clearance (Q) ; ETA5: the random effect on maximum Michaelis-Menten elimination rate ($V_{MAX}$) ; ETA6: the random effect on Michaelis-Menten constant ($K_M$); ETA10: the random effect on elimination rate of sIL6R-TCZ complex ($k_{int}$); ETA11: the random effect on unbound sIL6R degradation rate ($k_{deg}$) ; ETA12: the random effect on QSS constant ($K_{SS}$).

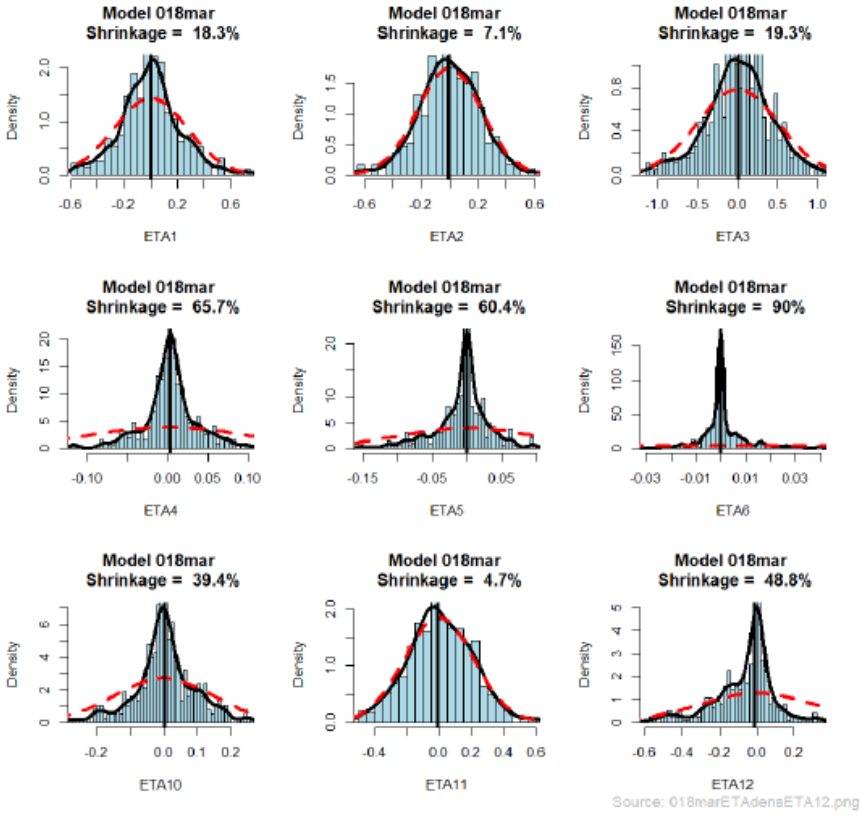



**Figure 5** **Density of inter-individual random effect distributions for Model 018mar**

Density histograms of the inter-individual random effect distributions. The y-axis shows the density of observations that fall into respective bins. The solid black lines illustrate the density of the random effect distributions. The vertical lines show medians of these distributions. The dashed red lines show the density of the random effect distributions as estimated by the model. Shrinkage calculations are described in the Methods section. ETA13: the random effect on standard deviation of TCZ residual error ($\sigma_{TCZ}$); ETA14: the random effect on standard deviation of sIL6R residual error ($\sigma_{sIL6R}$).

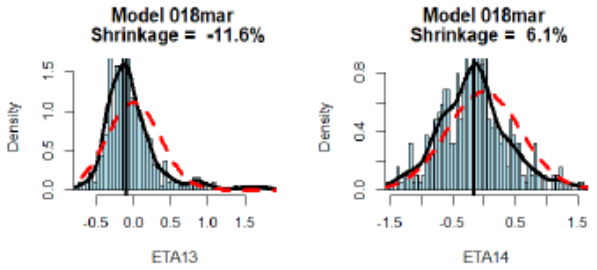



**Figure 6** **Density of inter-individual random effect distributions for Model 018mar**

Visual predictive check plots are presented in Figure 7 to Figure 11.

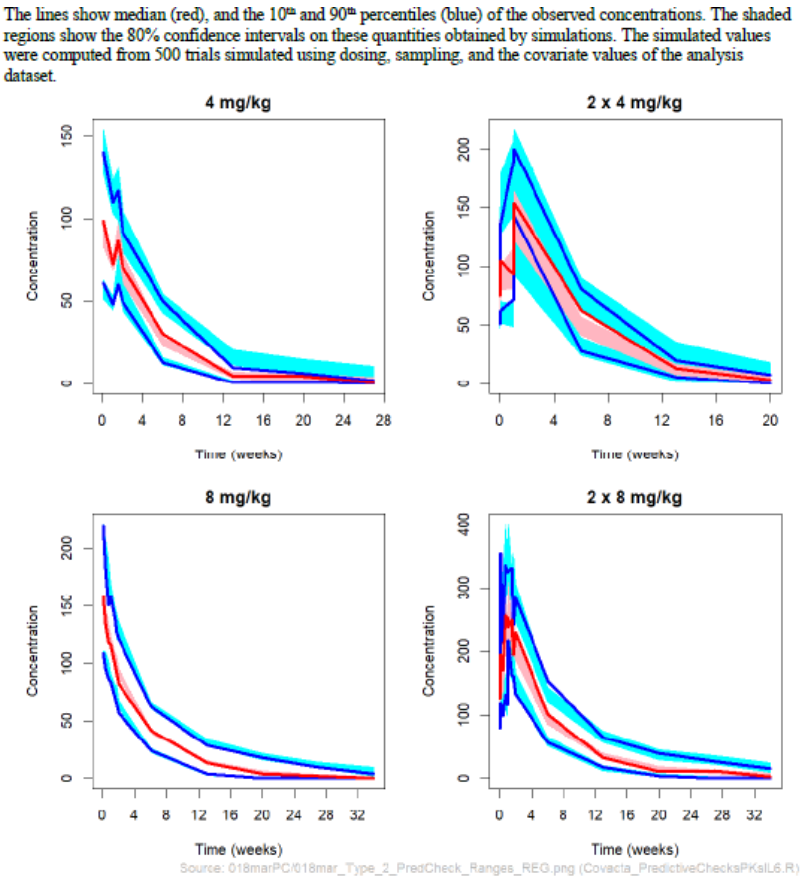



**Figure 7 Visual predictive check for model 018mar, by dose group: TCZ**

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

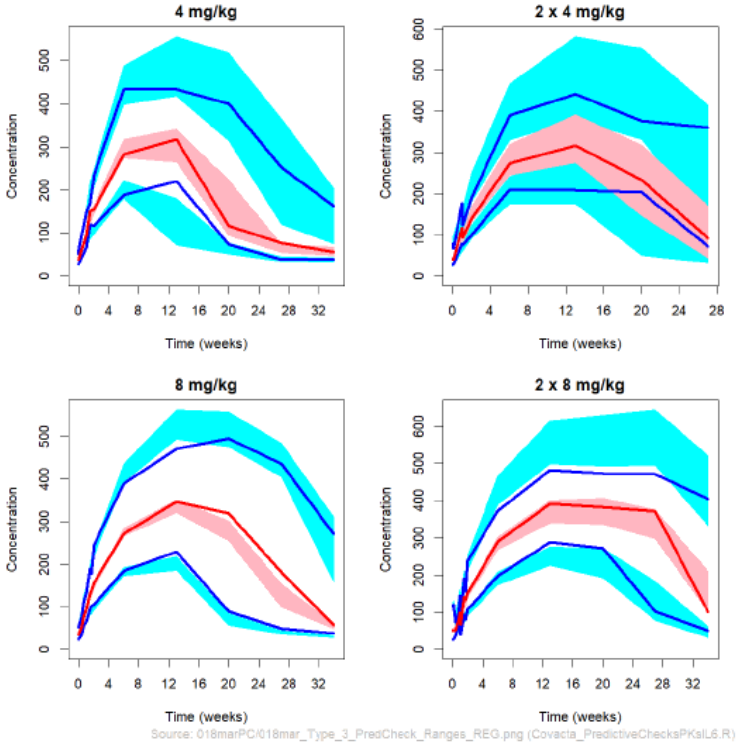



**Figure 8** **Visual predictive check for model 018mar, by dose group: sIL6R**

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

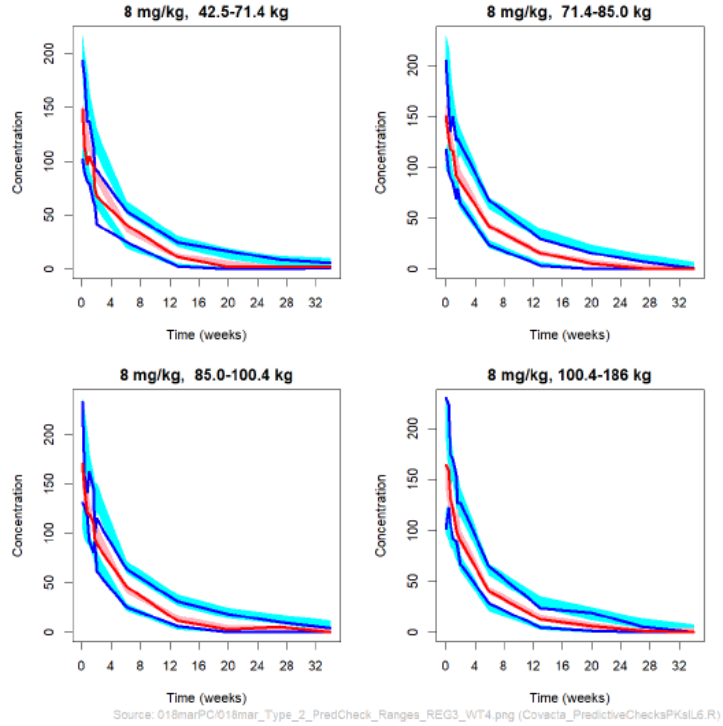



**Figure 9** **Visual predictive check for model 018mar, by weight group, 8mg/kg dose: TCZ**

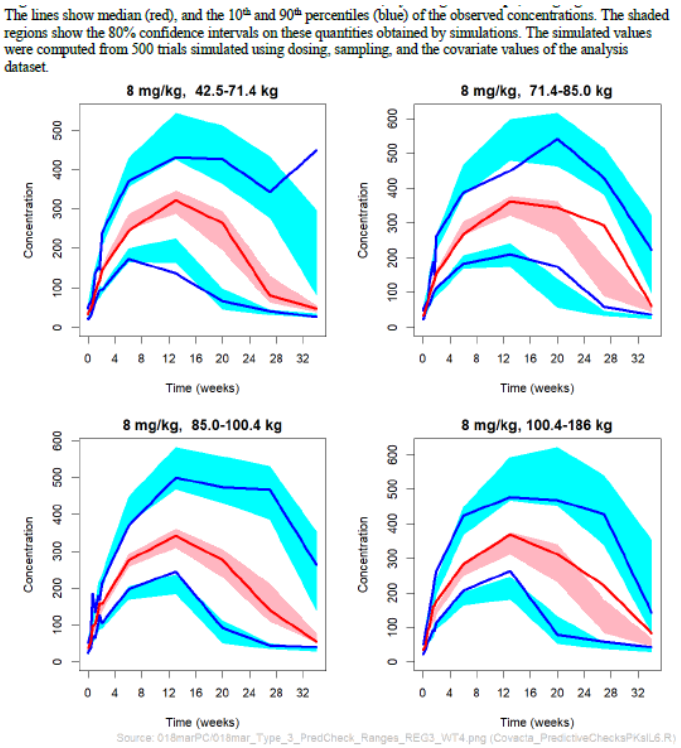



**Figure 10 Visual predictive check for model 018mar, by weight group, 8mg/kg dose: sIL6R**

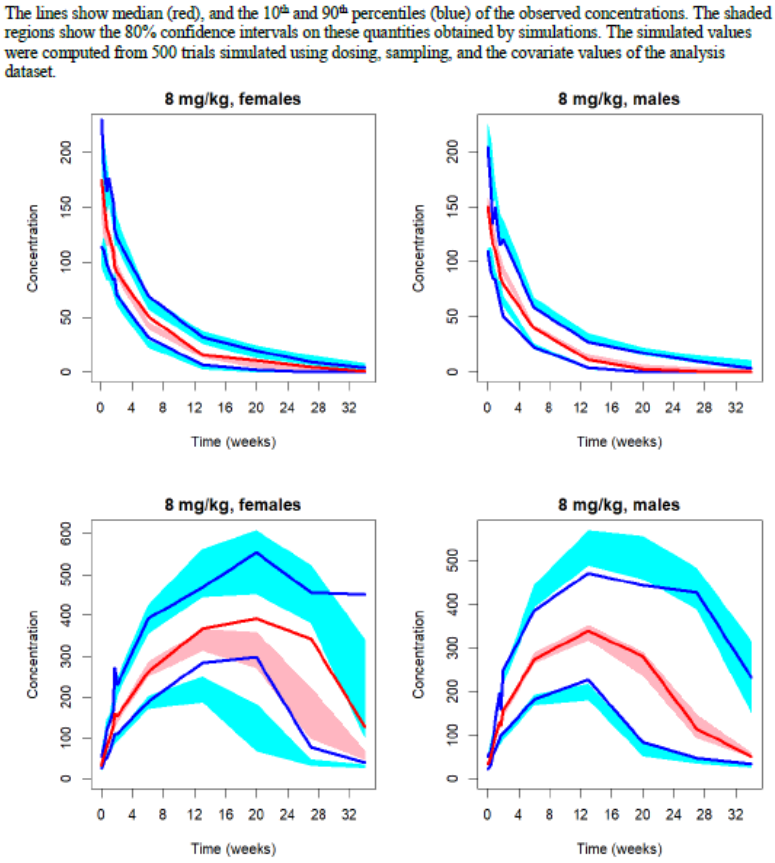



**Figure 11 Visual predictive check for model 018mar, by sex, 8mg/kg dose: TCZ (top) and sIL6R (bottom)**

Model predications/applications

The final population PK model was used to simulate the typical tocilizumab and sIL-6R concentration-time courses and evaluate the spread of the concentration-time curves in the study population. In addition, the individual concentration-time profiles were simulated for patients in the dataset using their individual posthoc PK parameters and per protocol dosing. Simulated profiles were used to calculate the individual derived PK parameters such as area under the serum concentration time curve (AUC) over 28 days (AUC28), AUC from zero to infinity (AUCinf), and maximum drug concentration (Cmax) using Bayesian posthoc parameters and per-protocol dosing. The parameters were summarized (mean, median, range, and standard deviation) by dosing regimens.

**Table 4 Covid-19 related covariate effects of tocilizumab as estimated by the population PK-sIL6R Model 018mar**

| Parameter | Covarate | Reference | Value | Effect [95%CI] |
|---|---|---|---|---|
| VC | COVID-19 | No COVID-19 | No COVID-19 | 10.9 [8.2;13.7] |
| CL | Scale7 | No COVID-19 | COVID-19 with Scale7 = 1 | 22.3 [21.2;23.4] |
| | | | COVID-19 with Scale7 = 2 | 49.6 [47;52.4] |
| | | | COVID-19 with Scale7 = 3 | 83.1 [78.2;88.1] |
| | | | COVID-19 with Scale7 = 4 | 123.9 [116;132.2] |
| | | | COVID-19 with Scale7 = 5 | 173.9 [161.8;186.6] |
| | | | COVID-19 with Scale7 = 6 | 235.1 [217.4;253.7] |
| $k_{deg}$ | Age | Age < 50 years | 87 years | -25.3 [-31.2;-19] |
| | COVID-19 | No COVID-19 | COVID-19 | 68.8 [62.2;75.8] |
| $k_{int}$ | COVID-19 | COVID-19 with Scale7 = 4 | No COVID-19 | -59.1 [-60.5;-57.8] |
| | Scale7 | COVID-19 with Scale7 = 4 | COVID-19 with Scale7 = 0 | -23.2 [-27;-19.1] |
| | | | COVID-19 with Scale7 = 1 | -17.9 [-21;-14.7] |
| | | | COVID-19 with Scale7 = 2 | -12.3 [-14.6;-10.1] |
| | | | COVID-19 with Scale7 = 3 | -6.4 [-7.6;-5.2] |
| | | | COVID-19 with Scale7 = 5 | 6.8 [5.4;8.2] |
| | | | COVID-19 with Scale7 = 6 | 14.1 [11.2;17.1] |

**Table 5 Estimates of tocilizumab exposure parameters**

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

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

**Table 6 Estimates of Tocilizumab PK parameters**

Dose group: 1 = 4 mg/kg; 2 = 2 x 4 mg/kg; 3 = 8 mg/kg; 4 = 2 x 8 mg/kg. Clearance was computed at baseline value of Scale 7 severity score (SCALE7B). Statistics of SCALE7B are provided for the reference.

| Study | Dose Group | N | CL (L/day) | $V_C$ (L) | $V_P$ (L) | $V_M$ (µg/mL /day) | $K_M$ (µg/mL) | SCALE | Weight (kg) |
|---|---|---|---|---|---|---|---|---|---|
| **Mean (Standard Deviation)** | | | | | | | | | |
| 42380 | 3 | 224 | 0.593 (0.235) | 4.55 (1.24) | 4.33 (1.97) | 2.09 (0.379) | 0.414 (0.00473) | 4.26 (1.2) | 88.7 (24.6) |
| 42380 | 4 | 60 | 0.627 (0.289) | 4.49 (1.11) | 4.19 (1.9) | 2.07 (0.421) | 0.414 (0.00259) | 4.48 (1.1) | 90 (21.5) |
| 42481 | 1 | 35 | 0.459 (0.107) | 4.31 (1) | 3.93 (1.48) | 2.09 (0.528) | 0.414 (0.0028) | 3.31 (0.963) | 87.7 (22.4) |
| 42481 | 2 | 12 | 0.489 (0.11) | 4.13 (0.803) | 4 (1.25) | 2.15 (0.3) | 0.416 (0.00341) | 3.92 (0.515) | 91.4 (25.1) |
| 42481 | 3 | 38 | 0.53 (0.199) | 4.57 (1.13) | 4.05 (1.62) | 2.17 (0.366) | 0.414 (0.00422) | 3.66 (0.994) | 92.2 (22.3) |
| 42481 | 4 | 9 | 0.653 (0.206) | 4.91 (1.23) | 4.16 (1.31) | 2.19 (0.376) | 0.414 (0.00155) | 4.22 (0.833) | 105 (43.1) |
| **Median (Range)** | | | | | | | | | |
| 42380 | 3 | 224 | 0.565 (0.245-1.47) | 4.37 (1.88-8.93) | 3.93 (1.15-12.8) | 2.17 (1.13-2.76) | 0.414 (0.398-0.437) | 4 (2-6) | 84.1 (43.5-186) |
| 42380 | 4 | 60 | 0.572 (0.255-2.23) | 4.34 (2.61-8.24) | 3.98 (1.4-9.62) | 2.09 (1.15-2.79) | 0.414 (0.407-0.423) | 4 (3-6) | 89.1 (48.6-139) |
| 42481 | 1 | 35 | 0.451 (0.261-0.697) | 4.14 (2.47-7.11) | 3.66 (1.31-7.51) | 2.17 (1.17-2.84) | 0.414 (0.41-0.425) | 3 (2-5) | 89 (45.4-152) |
| 42481 | 2 | 12 | 0.468 (0.327-0.701) | 4.2 (2.54-5.17) | 3.85 (1.7-5.85) | 2.15 (1.4-2.48) | 0.414 (0.413-0.422) | 4 (3-5) | 83.8 (54.4-129) |
| 42481 | 3 | 38 | 0.487 (0.179-1.16) | 4.34 (3.08-7.88) | 3.75 (1.55-8.47) | 2.19 (1.25-2.73) | 0.414 (0.407-0.43) | 4 (2-6) | 88.6 (62.2-153) |
| 42481 | 4 | 9 | 0.629 (0.376-1.02) | 4.57 (3.59-7.27) | 4.11 (2.21-6.29) | 2.14 (1.67-2.82) | 0.414 (0.412-0.418) | 4 (3-6) | 96 (59-181) |
| **Geometric Mean (Coefficient of Variation)** | | | | | | | | | |
| 42380 | 3 | 224 | 0.552 (0.376) | 4.4 (0.263) | 3.94 (0.438) | 2.06 (0.197) | 0.414 (0.0114) | 4.09 (0.293) | 85.7 (0.256) |
| 42380 | 4 | 60 | 0.581 (0.378) | 4.36 (0.241) | 3.81 (0.441) | 2.03 (0.219) | 0.414 (0.00625) | 4.35 (0.249) | 87.5 (0.239) |
| 42481 | 1 | 35 | 0.447 (0.238) | 4.2 (0.232) | 3.66 (0.39) | 2.01 (0.283) | 0.414 (0.00672) | 3.17 (0.305) | 84.9 (0.261) |
| 42481 | 2 | 12 | 0.477 (0.224) | 4.05 (0.211) | 3.8 (0.351) | 2.13 (0.156) | 0.416 (0.00816) | 3.88 (0.137) | 88.2 (0.281) |
| 42481 | 3 | 38 | 0.496 (0.369) | 4.45 (0.236) | 3.76 (0.39) | 2.13 (0.186) | 0.414 (0.0101) | 3.52 (0.289) | 89.9 (0.226) |
| 42481 | 4 | 9 | 0.624 (0.32) | 4.79 (0.235) | 3.97 (0.332) | 2.16 (0.171) | 0.414 (0.00373) | 4.15 (0.188) | 97.3 (0.407) |

TCZ exposure and parameter estimates following one or two 8 mg/kg IV doses, with a maximum dose of 800 mg (second dose administered 8 hours after the first dose), are presented in popPK Report 1107025, Table 7, overall and by study. Following two 8 mg/kg TCZ IV doses, with a maximum of 800 mg per dose, tocilizumab mean Cmax, AUC28 and C28 were approximately 1.9-fold, 2.3-fold, and 9.6-fold higher, respectively, than following a single 8 mg/kg IV dose.

**Table 7 Estimates of tocilizumab exposure one or two 8mg/kg doses, with a maximun of 800mg per dose**

Inter-dose interval: 8 hours. Individual parameter estimates were used to compute exposure. Individual PK parameters were computed at baseline value of Scale 7 severity score (SCALE7B).

| Study | Number of Doses | N | $AUC_{28}$ (µg/mL* day) | $C_{max}$ (µg/mL) | $C_{28}$ (µg/mL) | Duration >LLOQ (day) | CL (L/day) | $V_C$ (L) | $V_P$ (L) |
|---|---|---|---|---|---|---|---|---|---|
| **Mean (Standard Deviation)** | | | | | | | | | |
| 42380 | 2 | 284 | 1700 (479) | 294 (66.7) | 8.07 (8.03) | 46.5 (10.5) | 0.614 (0.26) | 4.54 (1.21) | 4.3 (1.95) |
| 42380 | 1 | 284 | 740 (216) | 153 (35.9) | 0.823 (1.66) | 33.6 (6.86) | 0.614 (0.26) | 4.54 (1.21) | 4.3 (1.95) |
| 42481 | 2 | 96 | 1920 (445) | 301 (58.6) | 11.5 (9.36) | 48.4 (10.3) | 0.533 (0.241) | 4.45 (1.05) | 4 (1.46) |
| 42481 | 1 | 96 | 832 (204) | 157 (31.6) | 1.26 (2.55) | 35.2 (6.96) | 0.533 (0.241) | 4.45 (1.05) | 4 (1.46) |
| All | 2 | 380 | 1760 (480) | 296 (64.7) | 8.94 (8.5) | 47 (10.5) | 0.593 (0.257) | 4.52 (1.17) | 4.23 (1.84) |
| All | 1 | 380 | 763 (216) | 154 (34.9) | 0.934 (1.93) | 34 (6.91) | 0.593 (0.257) | 4.52 (1.17) | 4.23 (1.84) |
| **Median (Range)** | | | | | | | | | |
| 42380 | 2 | 284 | 1660 (614-3850) | 287 (152-604) | 5.87 (0.0384-40) | 45.8 (25.3-81.6) | 0.552 (0.192-1.58) | 4.36 (1.88-8.93) | 3.95 (1.15-12.8) |
| 42380 | 1 | 284 | 712 (288-1780) | 150 (77.5-319) | 0.204 (0.00687-11.9) | 33 (18.1-54.2) | 0.552 (0.192-1.58) | 4.36 (1.88-8.93) | 3.95 (1.15-12.8) |
| 42481 | 2 | 96 | 1950 (922-3170) | 297 (189-497) | 10.4 (0.00474-54.8) | 47.7 (20.1-78.1) | 0.479 (0.222-1.81) | 4.24 (2.47-7.88) | 3.77 (1.31-8.47) |
| 42481 | 1 | 96 | 830 (409-1450) | 155 (98.5-267) | 0.318 (0.00119-19.4) | 34.7 (16.2-54.7) | 0.479 (0.222-1.81) | 4.24 (2.47-7.88) | 3.77 (1.31-8.47) |
| All | 2 | 380 | 1720 (614-3850) | 290 (152-604) | 7.04 (0.00474-54.8) | 46.3 (20.1-81.6) | 0.538 (0.192-1.81) | 4.34 (1.88-8.93) | 3.9 (1.15-12.8) |
| All | 1 | 380 | 745 (288-1780) | 151 (77.5-319) | 0.229 (0.00119-19.4) | 33.6 (16.2-54.7) | 0.538 (0.192-1.81) | 4.34 (1.88-8.93) | 3.9 (1.15-12.8) |
| **Geometric Mean (Coefficient of Variation)** | | | | | | | | | |
| 42380 | 2 | 284 | 1640 (0.288) | 286 (0.224) | 3.7 (1.57) | 45.3 (0.227) | 0.565 (0.403) | 4.39 (0.258) | 3.91 (0.438) |
| 42380 | 1 | 284 | 710 (0.291) | 149 (0.23) | 0.265 (1.39) | 32.9 (0.204) | 0.565 (0.403) | 4.39 (0.258) | 3.91 (0.438) |
| 42481 | 2 | 96 | 1870 (0.241) | 296 (0.195) | 6.84 (1.43) | 47.3 (0.22) | 0.49 (0.406) | 4.33 (0.231) | 3.75 (0.372) |
| 42481 | 1 | 96 | 807 (0.252) | 154 (0.201) | 0.409 (1.55) | 34.5 (0.203) | 0.49 (0.406) | 4.33 (0.231) | 3.75 (0.372) |
| All | 2 | 380 | 1690 (0.282) | 289 (0.217) | 4.32 (1.55) | 45.8 (0.226) | 0.545 (0.408) | 4.37 (0.251) | 3.87 (0.422) |
| All | 1 | 380 | 733 (0.286) | 150 (0.223) | 0.295 (1.44) | 33.3 (0.205) | 0.545 (0.408) | 4.37 (0.251) | 3.87 (0.422) |

***Absorption***

Tocilizumab in was given via the IV route of administration in hospitalized patients with moderate to severe COVID-19 pneumonia.

Due to IV administration, tocilizumab is 100% bioavailable. $C_{max}$ for the 8 mg/kg dose in COVID-19 patients (popPK estimate for 1 dose at 8 mg/kg: 154 µg/mL) was slightly lower but still similar to maximum concentrations described for already approved indications (SmPC $C_{max}$: 182 µg/mL).

***Distribution***

Referring to the population PK analysis, in COVID-19 adult patients, the central volume of distribution was 4.52 L, the peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Volume of distribution (Vd) in COVID-19 patients was slightly higher than Vd described for RA patients (the central volume of distribution was 3.72 L, the peripheral volume of distribution was 3.35 L resulting in a volume of distribution at steady state of 7.07 L).

***Elimination***

For tocilizumab, a dual mechanism of elimination has been described with linear clearance at higher concentrations where the non-linear, concentration-dependent pathway is already saturated. At lower concentrations, as seen in the terminal elimination phase of the tocilizumab concentration-time curve, non-linear clearance predominates.

In COVID-19 adult patients, the linear clearance was 17.6 mL/h in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL/h in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL/h in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL/h in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support).

As compared to RA patients (linear CL = 9.5 mL/h), CL in COVID-19 patients was higher (OS 3: CL = 17.6 mL/h, OS 6: CL = 35.4 mL/h) and generally increased with disease severity, see PK in special populations.

***Dose proportionality and time dependencies***

**Table 8 Estimates of tocilizumab exposure parameters**

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

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

***Special populations***

The ratios of the typical parameters and their 95% CI for subpopulations to the typical parameters for a reference patient (as specified in the figure title) are illustrated. For categorical covariates and for continuous covariates with a specific value, point estimates are represented by open circles, and 95% CI are represented by horizontal bars. The hatched area represents typical values ± 20%.

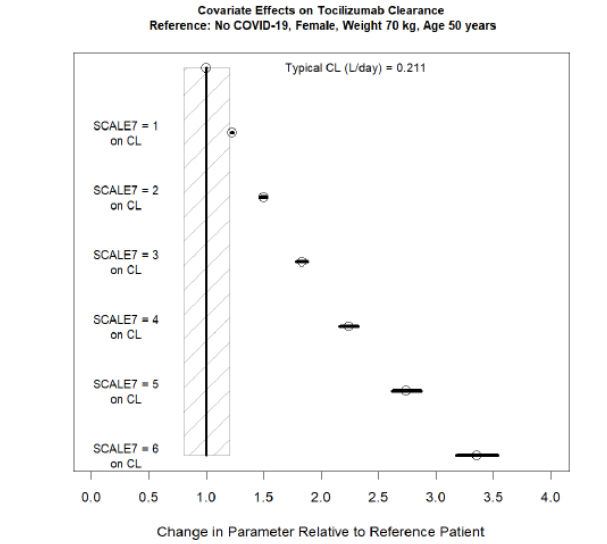



**Figure 12 Covariate effects on linear clearance for model 018mar**

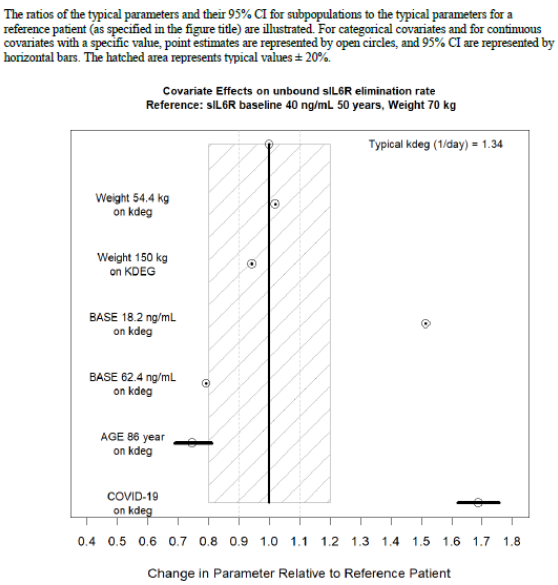



**Figure 13 Covariate effects on unbound sIL6R elimination rate constant for Model 018mar**

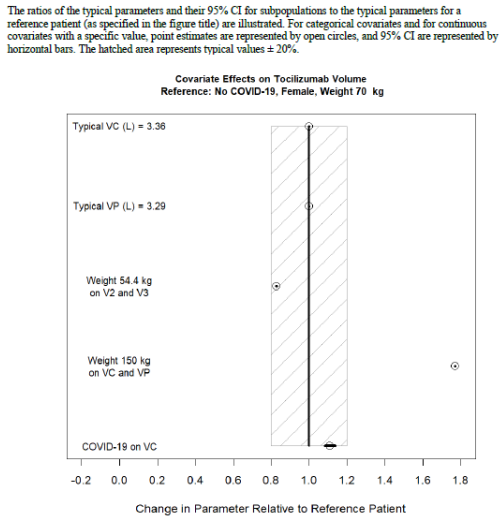



**Figure 14 Covariate effects on volumes for model 018mar**

The ratios of the typical parameters and their 95% CI for subpopulations to the typical parameters for a reference patient (as specified in the figure title) are illustrated. For categorical covariates and for continuous covariates with a specific value, point estimates are represented by open circles, and 95% CI are represented by horizontal bars. The hatched area represents typical values ± 20%.

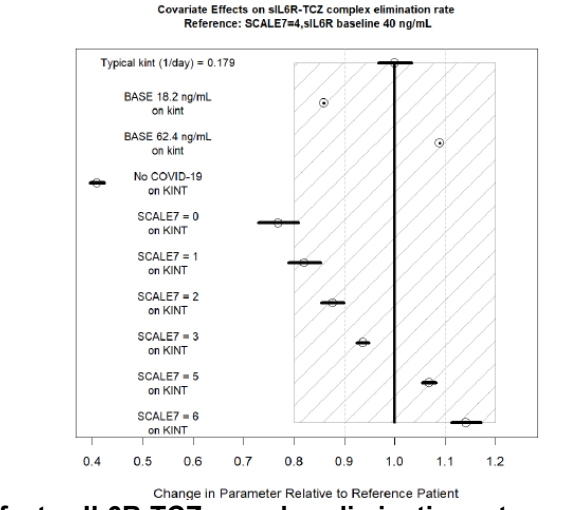



**Figure 15 Covariate effects sIL6R-TCZ complex elimination rate constant for model 018mar**

Results of the population PK analysis for COVID-19 patients confirmed that body weight and disease severity are both covariates which have an substantial impact on the linear clearance of tocilizumab (Figure 12-15).

Infection with COVID-19 and severity of the disease had major effects on elimination rate of tocilizumab and sIL6R bound to tocilizumab. Specifically, linear clearance in patients with COVID-19 was on average 124% (95%CI: 116-132%) higher than in patients with RA. Clearance increased by 22.3% (95%CI: 21.2-23.4%) for each point on a 7-level SCALE. The mean CL for COVID-19 pneumonia patients with a baseline disease severity of Category 4 was 22.4 mL/h and increased to 35.4 mL/h in patients in Category 6 (Table 9).

**Table 9 Tocilizumab clearance at baseline by disease severity**

Clearance was computed at baseline value of Scale 7 severity score (SCALE7B).

| SCALE7B | N | CL (L/day) |
|---|---|---|
| **Mean (Standard Deviation)** | | |
| 2 | 21 | 0.356 (0.079) |
| 3 | 100 | 0.423 (0.103) |
| 4 | 135 | 0.540 (0.148) |
| 5 | 51 | 0.696 (0.177) |
| 6 | 71 | 0.849 (0.273) |
| **Median (Range)** | | |
| 2 | 21 | 0.362 (0.179-0.504) |
| 3 | 100 | 0.403 (0.245-0.856) |
| 4 | 135 | 0.517 (0.255-1.16) |
| 5 | 51 | 0.659 (0.439-1.34) |
| 6 | 71 | 0.778 (0.468-2.23) |
| **Geometric Mean (Coefficient of Variation)** | | |
| 2 | 21 | 0.347 (0.238) |
| 3 | 100 | 0.411 (0.235) |
| 4 | 135 | 0.521 (0.266) |
| 5 | 51 | 0.676 (0.238) |
| 6 | 71 | 0.816 (0.275) |

Similarly, elimination rate of the TCZ/sIL-6R complex (kint) was 145% (95% CI: 137%-153%) higher in patients with COVID-19 pneumonia Category 4, than in patients with RA. kint was also higher in patients with more severe disease: it increased by 7% (95% CI: 5%-8%) for each point/category increase on the ordinal scale (Table 3).

The non-linear part of TCZ clearance (Michaelis-Menten elimination) was not affected by the COVID-19 disease severity effect and was similar to what was reported in RA.

Degradation rate of free (unbound) sIL-6R (kdeg) was 68.8% (95%CI: 62.2%-75.8%) higher in patients with COVID-19 pneumonia than in patients with RA, with no noticeable dependence on disease severity. COVID-19 pneumonia effect on VC was relatively minor (10.9% increase, 95%CI: 8.2%-13.7%).

Mechanical ventilation and the use of systemic corticosteroids at baseline had no effect on tocilizumab PK-sIL-6R parameters.

Unlike in the model previously developed in arthritis patients, albumin and protein concentrations were not correlated with tocilizumab VC in patients with COVID-19 pneumonia. It is possible that acute disease influenced albumin concentrations nullifying the correlation between albumin and Vc observed in patients with RA.

Exposure was higher in heavier patients. As expected, tocilizumab Cmax was independent of the disease severity while AUC28 decreased by about 13% when disease severity increased by 1 point/category on the 7-category ordinal scale (Table 10).

**Table 10 Estimates of mean (SD) TCZ exposure following 8mg/kg dose, with a maximum dose of 800mg, for patients ranging from ordinal scale category 3 to 6, overall and by weight**

| Weight | N | $AUC_{28}$ (µg/mL*day) | $C_{max}$ (µg/mL) | $C_{28}$ (µg/mL) | Weight (kg) |
|---|---|---|---|---|---|
| Ordinal Scale Category 3 | | | | | |
| All | 380 | 883 (222) | 154 (34.9) | 1.59 (2.32) | 89.6 (24.2) |
| < 60 kg | 20 | 700 (156) | 124 (32.8) | 0.793 (0.751) | 53.7 (5.38) |
| 60-100 kg | 261 | 889 (210) | 156 (32.8) | 1.63 (2.27) | 80.2 (10.8) |
| > 100 kg | 99 | 905 (250) | 156 (38.1) | 1.64 (2.63) | 122 (20.2) |
| Ordinal Scale Category 4 | | | | | |
| All | 380 | 773 (190) | 154 (34.9) | 0.706 (1.26) | 89.6 (24.2) |
| < 60 kg | 20 | 614 (131) | 124 (32.8) | 0.319 (0.249) | 53.7 (5.38) |
| 60-100 kg | 261 | 778 (180) | 156 (32.8) | 0.716 (1.19) | 80.2 (10.8) |
| > 100 kg | 99 | 793 (212) | 156 (38.1) | 0.758 (1.51) | 122 (20.2) |
| Ordinal Scale Category 5 | | | | | |
| All | 380 | 671 (161) | 154 (34.8) | 0.311 (0.597) | 89.6 (24.2) |
| < 60 kg | 20 | 535 (110) | 124 (32.7) | 0.174 (0.0977) | 53.7 (5.38) |
| 60-100 kg | 261 | 674 (153) | 156 (32.7) | 0.307 (0.533) | 80.2 (10.8) |
| > 100 kg | 99 | 689 (179) | 156 (38) | 0.349 (0.785) | 122 (20.2) |
| Ordinal Scale Category 6 | | | | | |
| All | 380 | 579 (136) | 154 (34.8) | 0.16 (0.239) | 89.6 (24.2) |
| < 60 kg | 20 | 463 (92.7) | 124 (32.7) | 0.12 (0.0617) | 53.7 (5.38) |
| 60-100 kg | 261 | 581 (129) | 156 (32.7) | 0.156 (0.19) | 80.2 (10.8) |
| > 100 kg | 99 | 595 (150) | 155 (38) | 0.176 (0.353) | 122 (20.2) |

Individual estimates of the random effects were used to compute exposure. However, severity per category of the ordinal scale was assumed for all patients at all times.

## 2.3.3. Pharmacodynamics

Pharmacodynamics (CRP, IL-6, sIL-6R) of TCZ in adult patients with severe COVID-19 was assessed based on data from two clinical studies COVACTA and MARIPOSA.

### *Mechanism of action*

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

### *Primary and secondary pharmacology*

#### *Study WA42380 (COVACTA)*

sIL-6R

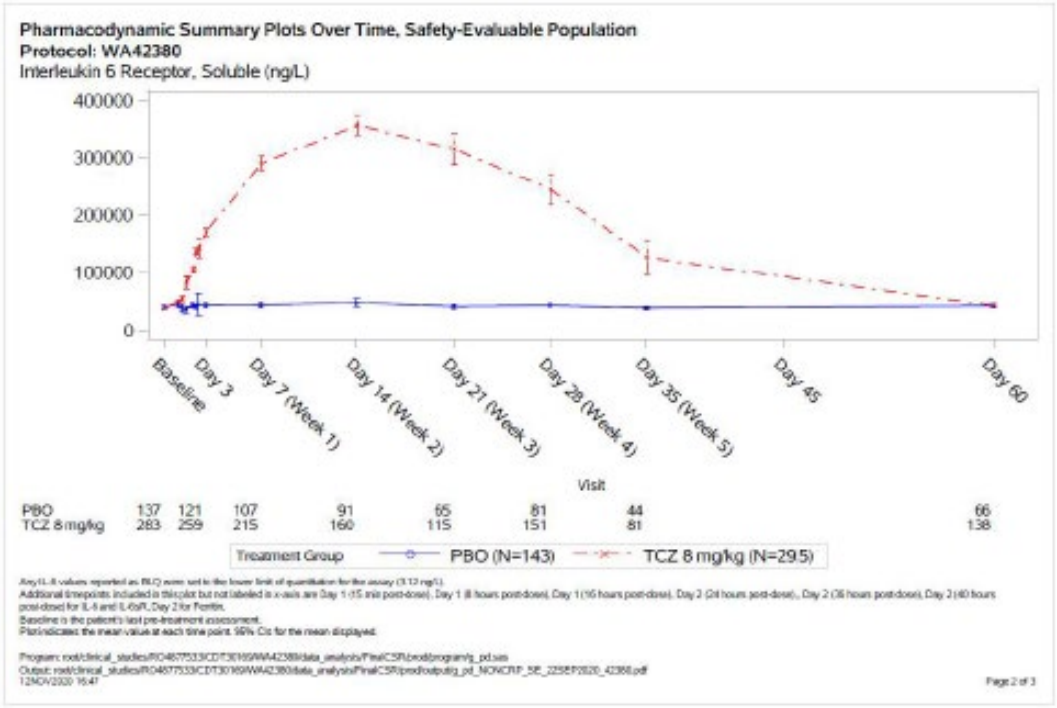
In the TCZ+SoC arm, the mean sIL-6R concentration, measuring total (bound and unbound to TCZ) sIL-6R, increased rapidly after the first dose of study treatment (15 minutes post-dose) and the

increase generally continued through Day 14 after which the median sIL-6R concentration declined through to Day 60.

In the PBO+SoC arm, the mean sIL-6R concentration increased slightly after the first dose of study treatment (15 minutes post-dose) and declined from 8 hours through 16 hours post-dose. An increase in the median sIL-6R concentration was again recorded 24 hours post-dose followed by a decline 36 hours post-dose. Several fluctuations in the median sIL-6R concentration were observed at later timepoints through Day 60.

Mean (SD) serum sIL-6R levels in the TCZ arm were 36.98 (12.55) ng/mL (median: 35.2 ng/mL) at baseline and 244.9 (164.4) ng/mL (median: 260.00 ng/mL) at Day 28.

The mean increases from baseline in sIL-6R concentration were higher in the TCZ+SoC arm compared to the PBO+SoC arm.




PBO = placebo; TCZ= tocilizumab.

**Figure 16 Plot of mean (+/- CI 95%) sIL-6R concentration by visit (safety population)**

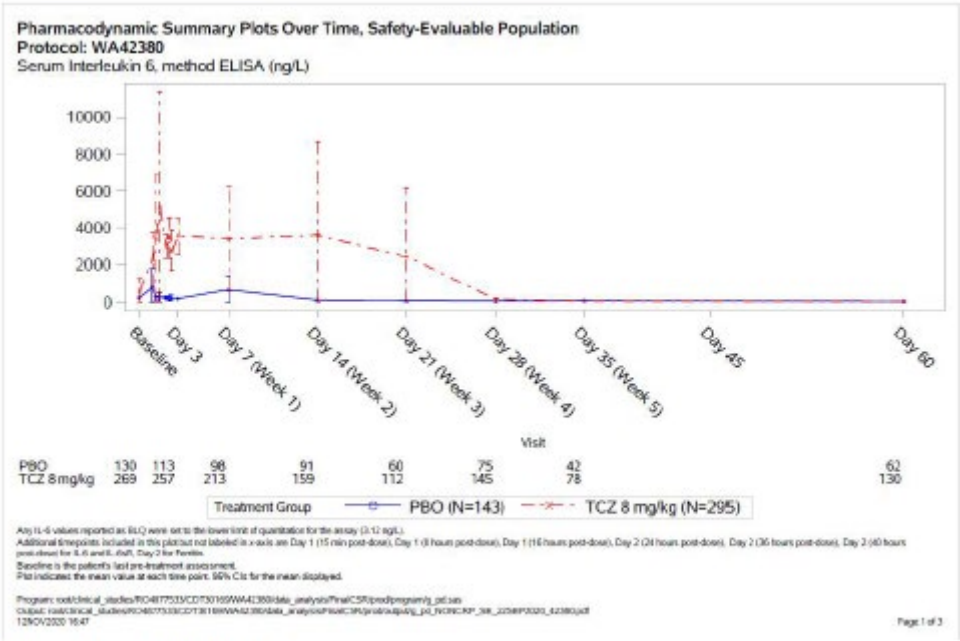
IL-6

In the TCZ+SoC arm, the mean serum IL-6 concentration increased rapidly following the first dose of study treatment (15 min post-dose) through Day 2 (36 hours post-dose), declined slightly 40 hours post-dose and increased again on Day 3. A significant drop in the median IL-6 concentration was recorded on Day 7 after which a steady decline in the median IL-6 concentration levels was observed through Day 60.

In the PBO+SoC arm, the mean IL-6 concentration increased slightly following the first dose of study treatment (15 min post-dose), fluctuated slightly between Day 1 (8 hours post-dose) and Day 3, and declined steadily from Day 7 through Day 60.

Mean (SD) serum IL-6 levels in the TCZ arm were 577.4 (6080) ng/L (median: 87.90 ng/L) at baseline and 120.02 (486.5) ng/L (median: 25.40 ng/L) at Day 28.

The mean increases from baseline in the serum IL-6 concentration were significantly higher in the TCZ+SOC arm compared to the PBO+SOC arm.




PBO = placebo; TCZ= tocilizumab.

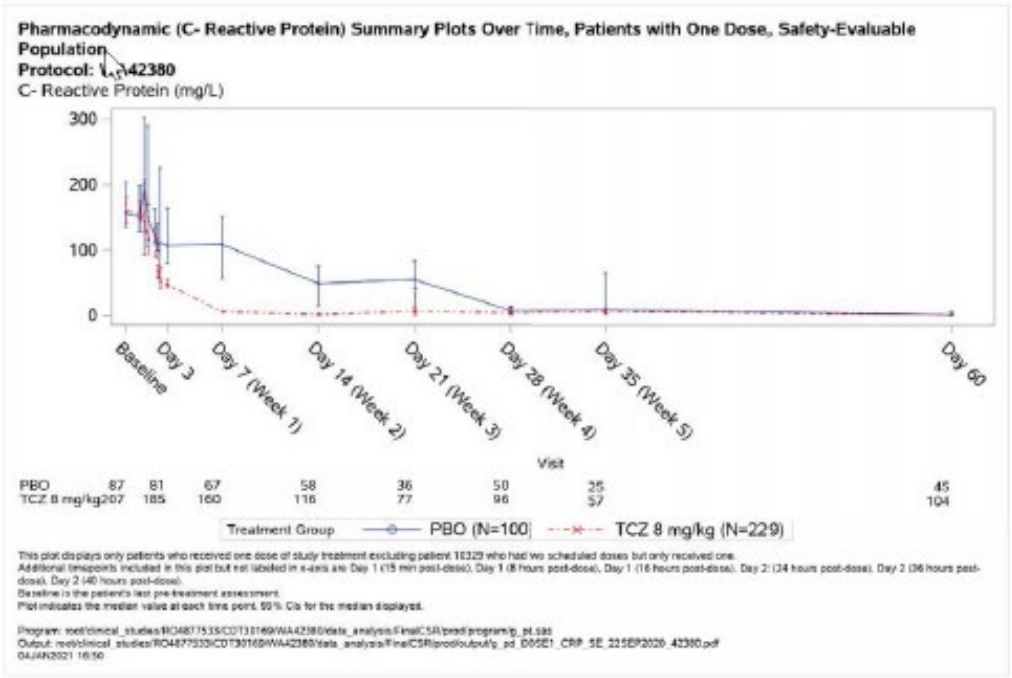
**Figure 17 Plot of mean (+/- CI 95%) IL-6 concentration by visit (safety population)**

CRP

The median CRP levels were above the ULN (10 mg/L) at baseline in both treatment arms.

Patients who received one dose of study treatment:

Following administration of study treatment, median CRP levels decreased at a faster rate in the TCZ+SoC arm compared to the PBO+SoC arm (Table 18).




PBO = placebo; TCZ= tocilizumab.

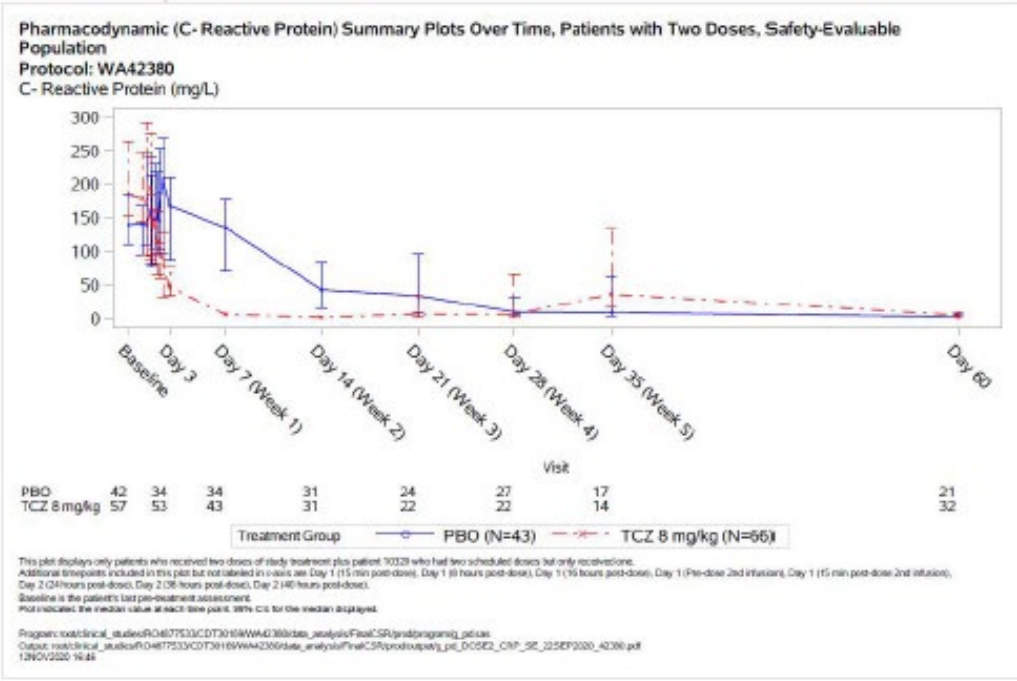
**Figure 18 Plot of median (=/- CI 95%) CRP concentration by visit after one dose of TCZ (safety population)**

Among patients in the TCZ+SoC arm, who received one dose of study treatment (N=229), median CRP levels decreased steadily following administration of study treatment through Day 3, normalized by Day 7, and remained below the ULN from Day 7 to Day 60. Mean (SD) CRP concentrations were 177.36 (109.34) mg/L (median 159.60 mg/L) at baseline and 37.12 (62.53) mg/L (median 4.25 mg/L) at Day 28.

Among patients in the PBO+SoC arm, who received one dose of study treatment (N=100), median CRP levels generally decreased steadily (except for 8 hours post-dose) following administration of study treatment, normalized by Day 28, and remained close to or below the ULN from Day 28 to Day 60. Mean (SD) CRP concentrations were 175.04 (113.85) mg/L (median 155.7 mg/L) at baseline and 28.39 (51.72) mg/L (median 7.75 mg/L) at Day 28.

Patients who received two doses of study treatment

Similarly, among patients who received two doses of study treatment, median CRP levels decreased at a faster rate in the TCZ+SoC arm compared to the PBO+SoC arm (Figure 19).




CRP = c reactive protein; PBO = placebo; TCZ= tocilizumab.

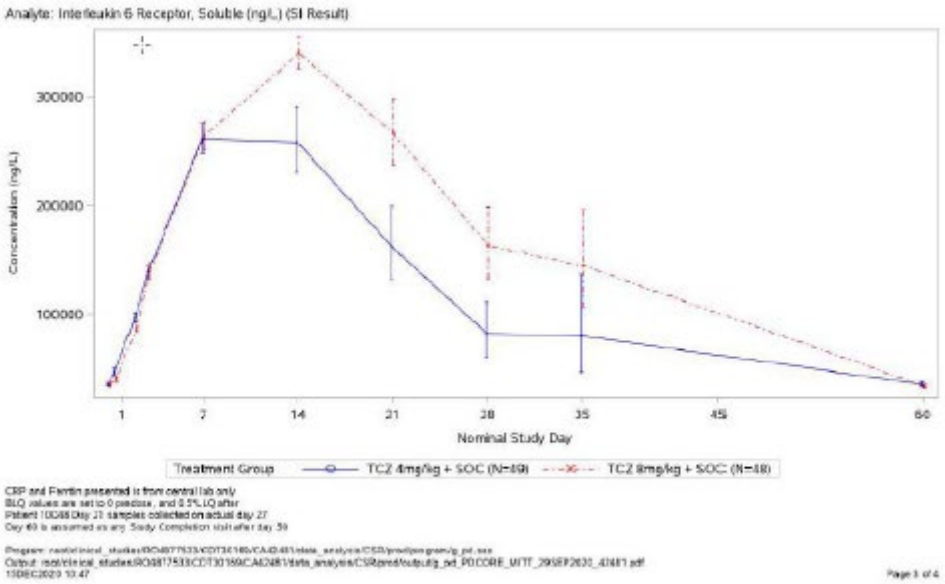
**Figure 19 Plot of median (+/- CI 95%) CRP concentration by visit after two doses of TCZ (safety population)**

In the TCZ+SoC arm, among patients who received two doses of study treatment (N=65), median CRP levels generally decreased steadily from baseline through Day 3, normalized by Day 7, and generally (except for Day 35) remained below the ULN from Day 7 to Day 60. Mean (SD) CRP concentrations were 202.92 (126.94) mg/L (median 183.70 mg/L) at baseline and 59.03 (100.23) mg/L (median 5.50 mg/L) at Day 28.

In the PBO+SoC arm, among patients who received two doses of study treatment (N=43), median CRP levels generally increased from baseline through Day 3 (with peak concentration recorded on Day 2) and decreased afterwards. Median CRP levels stabilized by Day 28 and remained close to or below the ULN from Day 28 to Day 60. Mean (SD) CRP concentrations were 180.23 (121.97) mg/L (median 139.05 mg/L) at baseline and 38.87 (62.20) mg/L (median 9.00 mg/L) at Day 28.

***Study CA42481 (MARIPOSA)***

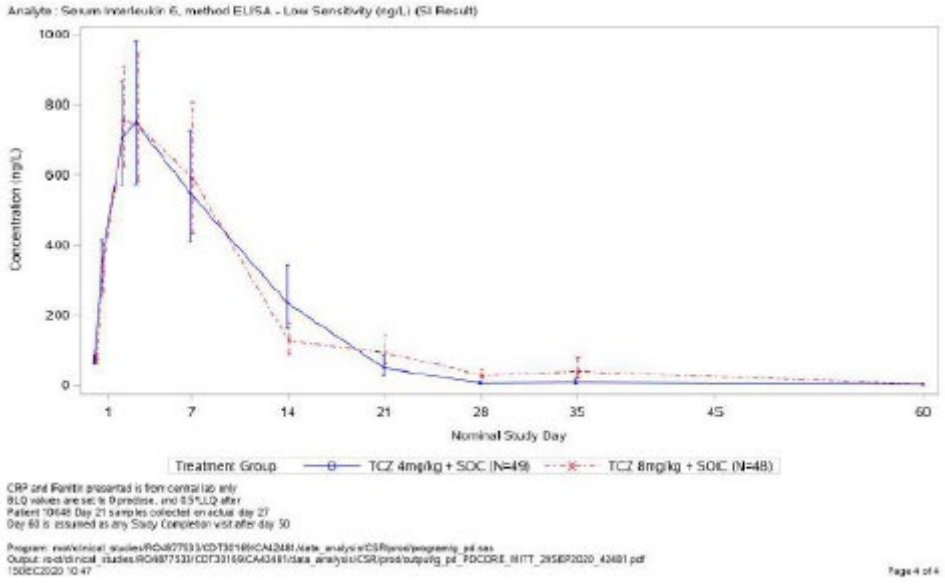
Serum sIL-6R concentrations increased immediately following IV administration of TCZ, with a similar rate of sIL-6R-TCZ complex production up to Day 7 in both treatment groups (Figure 20). Maximum geometric mean serum concentrations were recorded on Day 7 for the 4 mg/kg + SoC group and on Day 14 for the 8 mg/kg + SoC group. Thereafter, the geometric mean sIL-6R serum concentrations declined in both treatment groups, returning to baseline levels by Day 60. Geometric mean serum sIL-6R concentrations were lower in the 4 mg/kg + SoC group than in the 8 mg/kg+SoC group between Days 14 and 35. Inter-subject variability was low to moderate over time in both dose groups.




mITT=modified intent-to-treat; SD=standard deviation; sIL-6R=soluble interleukin 6 receptor.

**Figure 20 Plot of geometric mean (+/- geometric SD) sIL-6R concentration by visit (mITT population)**

Serum IL-6 concentrations increased immediately following the IV administration of TCZ, peaking at Day 3 for both TCZ doses. No notable differences were observed between the two TCZ dose levels in the IL-6 serum concentration-time profiles up to Day 60 (Figure 21).

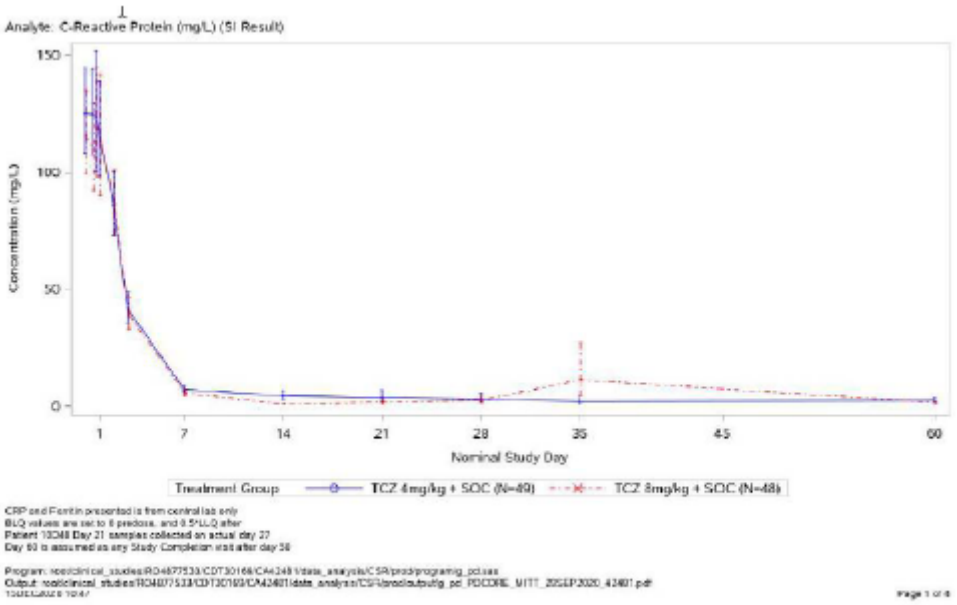



IL-6=interleukin 6; mITT=modified intent-to-treat; SD=standard deviation.

**Figure 21 Plot of geometric mean (+/- geometric SD) IL-6 concentration by visit (mITT population)**

Geometric mean serum CRP concentrations were above the ULN at baseline in both treatment groups. Following IV administration of TCZ, the geometric mean concentrations decreased rapidly to below the ULN and remained close to or below the ULN from Day 7 to Day 60. No notable differences were

observed between the two TCZ treatment groups in the CRP concentration-time profiles up to Day 60 (Figure 22).




CRP=c-reactive protein; mITT=modified intent-to-treat; SD=standard deviation.

**Figure 22 Plot of geometric mean (+/- geometric SD) Concentration by visit (mITT population)**

***Immunogenicity***

Immunogenicity was not considered a concern in a setting of single dose or an additional dose 8-24 hours after the first infusion of TCZ IV; hence anti-drug antibodies were not measured in any of the COVID-19 pneumonia clinical studies.

## 2.3.4. PK/PD modelling

**POPULATION PK-sIL-6R ANALYSIS**

The PK/PD relationship between TCZ and the sIL-6R was characterized by the analysis of the duration of 90% saturation of sIL-6R.

The duration of 90% sIL-6R occupancy was prolonged by approximately 5 days following 2 doses of TCZ IV 8 mg/kg as compared to one dose in Study WA42380 (COVACTA), increasing from 21.9 to 26.7 days, and by 3 days in Study CA42481 (MARIPOSA), increasing from 23.6 to 26.4 days. Duration of 90% sIL-6R saturation increased by 8 days after one single dose of 8 mg/kg as compared to one dose of 4 mg/kg (increasing from 15.6 to 23.6 days in Study CA42481). The duration of 90% sIL-6R saturation was similar following one single dose of 8 mg/kg and 2 doses of 4 mg/kg (23.6 and 23.8 days, respectively, in Study CA42481). In addition, the duration of 90% sIL-6R occupancy was dependent on the level of disease severity represented by the 7-category ordinal scale, reflecting the increase in the elimination rate of TCZ-sIL-6R complex shown by the popPK-sIL-6R analysis: in the most severe COVID-19 patients, i.e., rated Category 6 on the 7-category ordinal scale, 90% sIL-6R occupancy was maintained for approximately 12 and 18 days following one dose of 4 mg/kg and one dose of 8 mg/kg, respectively. The duration of 90% sIL-6R saturation was approximately 17 and 25 days following one dose of 4 mg/kg and one dose of 8 mg/kg, respectively, for COVID-19 patients in Category 3 (Figure 23).

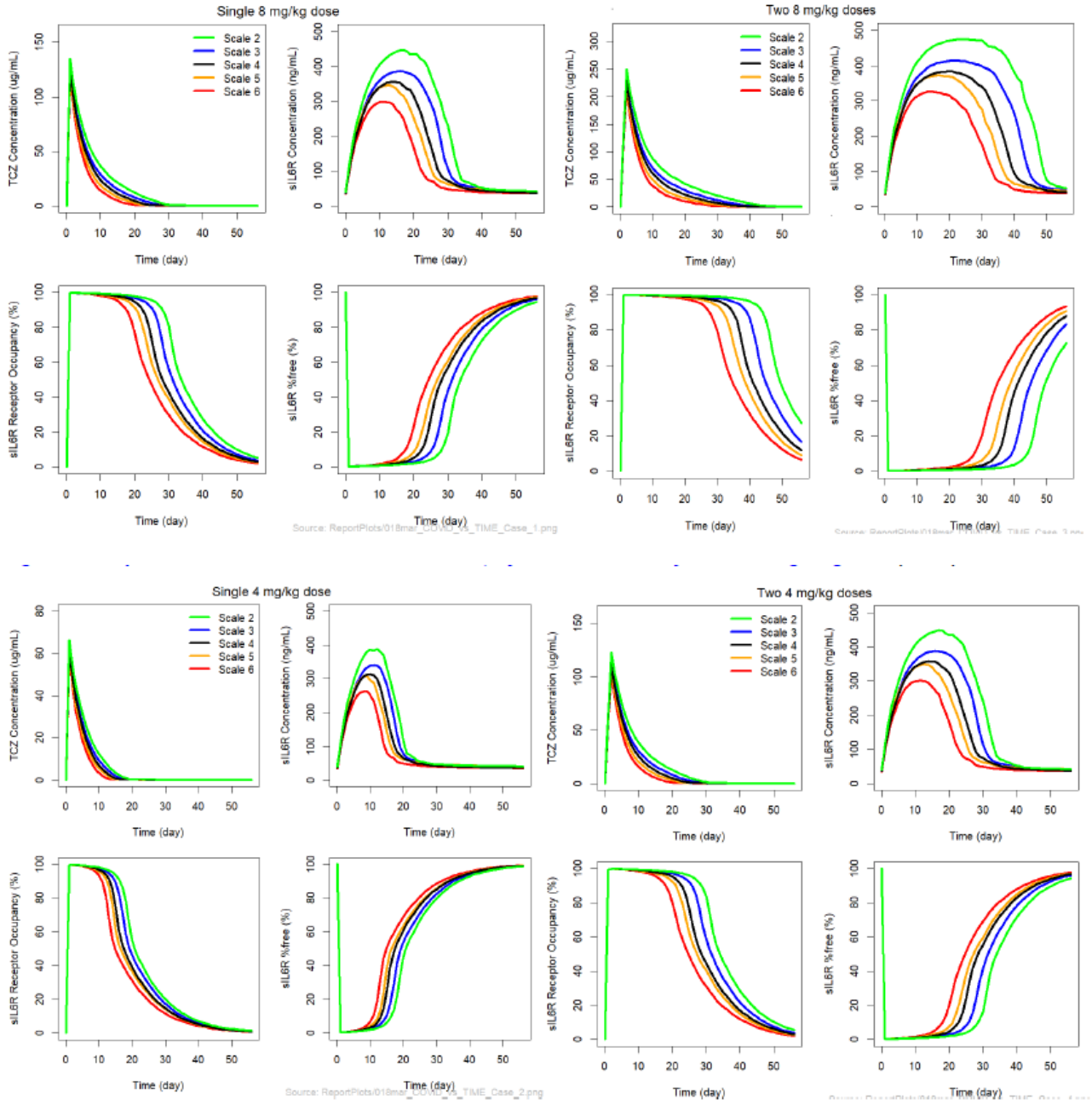



**Figure 23 Population predications of model 018mar, by disease severity and dosing regimen**

## 2.3.5. Discussion on clinical pharmacology

Pharmacokinetics of TCZ in adult patients with severe COVID-19 was assessed based on data from two clinical studies WA42380 (COVACTA) and CA42481 (MARIPOSA).

Pharmacokinetics

Bioanalytical methods used for determination of tocilizumab and sIL-6R concentrations in human serum are those already established and validated. Thus, no new or updated method validation reports were submitted which was considered acceptable to the CHMP.

In general, PK following one or two IV doses of TCZ 8 mg/kg was comparable in study WA42380 and study CA42481.

The 4 mg/kg dose was included in study CA42481 (MARIPOSA) based on off-label use of TCZ in China indicating that a TCZ dose lower than the dose recommended in the CAR T cell-induced CRS label might also be efficacious for the treatment of COVID-19 pneumonia (Xu et al. 2020). In addition, understanding of the PK-PD relationship of TCZ and predictions from a well-established PK/sIL-6R model for RA supported the choice of testing 4 mg/kg IV TCZ in patients presenting with COVID-19 pneumonia. The model predicted that the 4 mg/kg IV dose would elicit a similar onset and magnitude of IL-6 pathway inhibition as the 8 mg/kg IV dose but for a shorter duration as shown by the sIL-6R time course. However, given the shorter duration of sIL-6R occupancy with the 4 mg/kg tocilizumab dose and considering the lower exposure of tocilizumab in COVID-19 patients with further increasing CL with worsening of disease, the selection of the 8 mg/kg dose instead of the 4 mg/kg dose is reasonable to the CHMP.

The concentration-time profile for tocilizumab dosed either once or twice (with at least 8 hours separating the two doses) at 8 mg/kg in hospitalized adult patients with moderate to severe COVID-19 pneumonia revealed typical non-linear clearance of tocilizumab. $C_{max}$ after the first dose was about 150 µg/mL, similar to $C_{max}$ described in the current SmPC (steady state Cmax already reached after first administration: 182 ± 50.4 µg/mL). Peak concentrations following the second infusion were significantly higher than the peak following the first infusion, and peak TCZ concentrations were highest in patients who received two doses of 8 mg/kg TCZ (up to 400 µg/mL) and lowest in patients who received one dose of 4 mg/kg (below 100 µg/mL).

According to population PK analysis, at the intended dose of 8 mg/kg, mean tocilizumab $AUC_{0-28}$ was 18312 h•µg/mL, mean $C_{28}$ was 0.934 µg/mL and mean $C_{max}$ was 154 µg/mL. Following a second dose at 8 mg/kg tocilizumab separated by 8 hours, mean $AUC_{0-28}$ was 42240 h•µg/mL and mean $C_{28}$ and $C_{max}$ were 8.94 µg/mL and 296 µg/mL, respectively. In general, AUC and $C_{min}$ after one dose of 8 mg/kg tocilizumab were lower in COVID-19 patients as compared to steady state values achieved with Q4W dosing regimen as applied for already approved indications such as RA. However, similar values for AUC and $C_{min}$ were reached in COVID-19 patients with the second tocilizumab dose.

In COVID-19 adult patients, the central volume of distribution (Vd) was 4.52 L, the peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L. Volume of distribution in COVID-19 patients was slightly higher than Vd described for RA patients (the central volume of distribution was 3.72 L, the peripheral volume of distribution was 3.35 L resulting in a volume of distribution at steady state of 7.07 L).

As compared to RA patients (linear CL = 9.5 mL/h), CL in COVID-19 patients was higher (OS 3: CL = 17.6 mL/h, OS 6: CL = 35.4 mL/h) and generally increased with disease severity. Referring to population PK analysis, clearance increased by 22.3% (95%CI: 21.2-23.4%) for each point on a 7-level SCALE. Clearance in patients with OS category 6 was increased by 2-fold as compared to patients with OS category 3. While $C_{max}$ was comparable between the different disease categories, $AUC_{28}$ was 883 µg/ml*day in OS category 3 and 579 µg/mL*day in OS category 6. $AUC_{28}$ decreased by about 13% when disease severity increased by 1 point/category on the 7-category ordinal scale. In comparison to RA patients (AUCss = 1583 µg/mL*day), exposure in COVID-19 patients was generally lower and even more reduced in patients with higher disease severity. The MAH clarified that mainly linear CL of tocilizumab is increased in COVID-19 patients, while VM/KM parameters describing TMDD were similar between COVID-19 patients and RA patients. It is believed that higher linear elimination is due to an induction of protein catabolism in acute inflammatory conditions. This was comprehensible to the CHMP.

Exposure of tocilizumab was higher in heavier patients, also reflecting the body weight based dosing regimen.

Relevant time-dependent effects are not expected given that only 1 – 2 doses will be given separated by at least 8 hours.

In COVID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab IV 8 mg/kg.

The CHMP recommends the MAH to provide a discussion on the fixed dose of 600 mg tocilizumab in Covid-19 patients from the recently published PK/PD study (Moes et al., Clin Pharmacokinet. 2021 Oct 11;1-17. doi: 10.1007/s40262-021-01074-2) as a post authorisation measure (recommendation).

Population PK-sIL-6R model

A joint population PK- sIL6R model that describes the pharmacokinetics of tocilizumab and total sIL6R concentrations following intravenous administration in adult patients with COVID-19 was established.

Overall, 380 patients from the studies COVACTA and MARIPOSA were included in the analysis, resulting in a total of 1860 PK observations and 2929 sIL-6R observations from 369 and 377 patients, respectively, available for the analysis.

Given the high degree of non-linear PK and the disease effects (PD) on PK, as well as the weight effect on PK (weight ranged from 43.5 to 186 kg), the % of BLQ samples (COVID-19 studies) is likely to increase in comparison to the previously investigated indications. BLQ values were excluded from the analysis. Thus, the definite number of BLQ samples and outliers observed in studies COVACTA and MARIPOSA were to be provided with a discussion of why those values have been excluded from PK and PK/PD analyses. The MAH provided further information about number of BLQ samples (<0.1 µg/mL) defined in studies COVACTA and MARIPOSA and samples that have been excluded from analysis have been summarized (N=312 in total) but not stratified by Study. In total 13% of PK samples and 1.3% of PD samples (sIL-6R concentrations) have been excluded from further analysis, which can be agreed.

As expected due to the prominent TMDD effect, all tocilizumab samples (BLQ) were collected between week 2 and week 12 post-dose. BLQ values (N=312) were either predicted to be BLQ or very low (< 0.5 µg/mL) by the final pop PK model. It is agreed that this slight overprediction of observed BLQ values is not expected to have relevant effect and to change the model-based conclusions.

Tocilizumab population PK-sIL6R model was first developed using data from multiple studies in adult patients with RA and paediatric patients with sJIA and pcJIA following fix and weight-based dosing of tocilizumab administered SC and IV. Model parameter were partly fit to the data collected from the studies COVACTA and MARIPOSA, indicating disease effects on tocilizumab PK.
Previous modelling also indicate high inter-individual variability and shrinkage values up to 74% and negative shrinkage values. In addition, some %RSE need to be fixed, indicating highly variable data and problems with regard to model convergence and in capturing non-linear CL. In consequence, re-estimation of some model parameters based on the PK data (IV treatment, COVID-19 studies) and based on the non-COVID model necessitated some further discussion and analyses. PK data in adult subjects following IV treatment in RA is rich. To avoid the confounding with Age and study effects as well as the uncertainty in absorption and to render the model more parsimonious and predictive for COVID-19, results from a pop PK-sIL6R model that is based on PK and PD data following IV data in adults only was requested by the CHMP. Covariates, in particular weight effect and disease effects on PK (CL (linear and non-linear) were to be estimated and compared with the current final model. The MAH provided an integrated pop PK-sIL6R model based on PK and PD following tocilizumab IV administration only (RA patients, model 142saemIVRA) at the CHMP request. This model was then used to integrate IV PK and PD data following tocilizumab IV in adult COVID-19 patients (model 018marIVRA). Model 142saemIVRA was compared to the previous model 142saemFCS4, and model 018marIVRA was compared to the previous model 018mar – together with respective GOF plots provided. From this comparison, the CHMP agreed that the detectable differences in estimated

parameters and GOF plots are not expected to have a meaningful impact on model-based predictions. Thus, the integration of SC data was considered appropriate.

Shrinkage is very high for several Ω especially for those describing the non-linear clearance (Michaelis-Menten constant KM and maximum target-mediated elimination rate VM). In addition, also negative shrinkage values have been calculated (ETA13, random effect on SD of tocilizumab residual error), which is not usual and indicates together with the GOF plots presented the high variability in the data.

VPC plots have been presented showing the 80% confidence intervals (data observed and predicted). Whilst for this level, the VPC plots are of acceptable quality, this might be different when investigating the 90% CI. VPC stratified by gender shows that the model under-predicts the observed median and $10^{th}$ percentile of sIL-6R following 8 mg/kg IV.

Thus, VPC plots stratified for the weight ranges 100-120 kg, 120-140 kg, 140-160 kg and 160 – 185 kg were presented, showing the 80% and 90% confidence and prediction intervals respectively. Patients weighing at least 100 kg receive 800 mg flat dose. At the CHMP's request, the MAH provided VPC plots for tocilizumab and sIL-6R stratified by body weight ranges (100-120 kg, 120 – 140 kg, 140-160 kg and 160 -185 kg) with 80% and 90% of confidence and prediction intervals. In addition, population prediction of the sIL-6R occupancy by disease level and weight bands have been provided. VPC plots indicated that except for the very high weight range (small sample size), the diagnostic plots are of acceptable quality. Population predictions of receptor occupancy following single 800 mg dose, stratified by weight and by disease severity scale show an additive effect of disease scale and weight. Median duration of receptor occupancy ranges from over 30 days of receptor occupancy (>90%) for a 100 kg weighing patient (scale 2) to less than 20 days for a 180 kg weighing patient (scale 6), reflecting the high degree of variability in PK and PD response.

Pharmacodynamics

In clinical studies COVACTA and MARIPOSA, the concentration-time profile of sIL-6R, IL-6 and CRP was investigated. In COVACTA, sIL-6R concentrations increased rapidly after administration of tocilizumab, similar to what has been described in RA. Given the single- or two-dose regimen applied in COVID-19 patients, sIL-6R concentrations continuously declined after the peak at Day 14, resembling the elimination of (sIL-6R half-life prolonging) tocilizumab and thereby increased elimination of sIL-6R due to reduced sIL-6R occupation by tocilizumab. IL-6 concentrations were already high at baseline and further increased after treatment with tocilizumab to approx. 3000 – 4000 ng/L between Day 3 and Day 21. In COVID-19 patients, IL-6 concentrations, although highly variable, were significantly higher as compared to other already approved indications. This seems reasonable given that patients already presented with high IL-6 concentrations at baseline. Median CRP levels were above the ULN (10 mg/L) at baseline in both treatment arms. Following administration of tocilizumab, median CRP levels decreased at a faster rate in the TCZ+SoC arm compared to the PBO+SoC arm, normalized by Day 7, and remained below the ULN from Day 7 to Day 60. In comparison, median CRP levels in patients in the PBO+SoC arm generally decreased steadily following administration of study treatment, normalized by Day 28, and remained close to or below the ULN from Day 28 to Day 60.

Findings on sIL-6R, IL-6 and CRP concentrations after treatment with tocilizumab were largely similar in the MARIPOSA as compared to the COVACTA study. Soluble IL-6R concentrations increased immediately after dosing and peaked on Day 14 in case of the 8 mg/kg dose, while the peak was observed already on Day 7 with the 4 mg/kg dose. IL-6 concentrations were generally lower (up to 800 ng/L) in MARIPOSA as compared to COVACTA, presumably reflecting the less severely ill patient population included in this study. No difference in IL-6 concentrations was seen between the 4 mg/kg and the 8 mg/kg dose. The same applies to the CRP concentrations, which were reduced in a similar timely manner and to the same extent comparing the 4 mg/kg and 8 mg/kg dose.

Immunogenicity has not been investigated in COVID-19 patients. The CHMP agreed that the development of ADA against tocilizumab is of minor relevance given the short term treatment comprising only 1 -2 doses of tocilizumab. In addition, based on historical data, the incidence of ADA in treatment with tocilizumab is generally low. The issue was therefore not further pursued by the CHMP.

The median duration of 90% sIL-6R occupancy was calculated based on the integrated PK-sIL-6R model assuming different dosing regimen and disease scales, showing that the duration of 90% receptor occupancy was longer following 2 doses of TCZ IV 8 mg/kg compared to a single dose, as well as after one dose of 8 mg/kg compared to one dose of 4 mg/kg. The median duration of 90% sIL-6R saturation was simulated to be comparable following one single dose of 8 mg/kg and 2 doses of 4 mg/kg.

Following a single 8 mg/kg IV dose, median 90% sIL-6R occupancy was estimated to be maintained over approximately 18 days in patients with the most severe COVID-19 disease (Scale 6), following 4 mg/kg IV dose, this median duration is still estimated to be 12 days.

Simulations for the duration of receptor occupancy were submitted without any measure of variability (e.g. 80% or 90% prediction interval). It was assumed that simulation results are highly overlapping. Simulation results were requested, stating the 5th and 95th percentiles, respectively, for each disease scale. The MAH provided the predictions of receptor occupancy by disease severity together with the 90% prediction intervals for a typical patient stratified by disease severity scales. As expected, the 90% prediction intervals overlap across the range of ordinal scale disease severity. Fifth ($5^{th}$) and $95^{th}$ borders (receptor occupancy above 90%) range from 20 – 35 days (scale 2) to about 15-25 days (scale 6). Thus, for subjects at higher weight than the typical patient, duration of receptor occupancy >90% is expected to be even lower.

High variability and lower exposure as compared to other indications, with further increasing CL in more severely ill patients, was observed in COVID-19 patients. In this regard, it was questioned whether the proposed dosing regimen would lead to sufficiently efficacious exposure in COVID-19 patients. A proper justification for dose selection including a discussion on the correlation of PD with clinical efficacy endpoints was requested by the CHMP. The selection of 8 mg/kg (not exceeding 800 mg flat) IV for treatment was considered acceptable to the CHMP due to the experience and knowledge (safety data) available from other indications. Exposure simulations and exposure-response analyses indicate that duration of sIL-6R occupancy at a certain % is decreasing with weight and disease severity. However, correlation between longer duration of sIL-6R saturation and better efficacy should be interpreted with caution as, based on efficacy data from MARIPOSA and COVACTA, formally, no quantitative relation between efficacy and PD marker could be established. The CHMP also acknowledged the uncertainties related to the inverse relationship between disease severity and tocilizumab exposure (and receptor occupancy, respectively) and the influence of baseline disease status. Overall, the dosing recommendation of 8 mg/kg (not exceeding 800 mg flat) IV for treatment was considered acceptable to the CHMP.

## 2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of tocilizumab was characterized using a population pharmacokinetic analysis of a database composed of 380 adult COVID-19 patients in Study WA42380 (COVACTA) and Study CA42481 (MARIPOSA) that treated with a single infusion of 8 mg/kg tocilizumab or two infusions separated by at least 8 hours.

PK and PD of tocilizumab at the proposed dose of 8 mg/kg has been extensively described in the past procedures.

The population PK/PD model (population PK- sIL6R model) was developed by fitting of the prior model supplemented by COVID-19 effects. Overall, the CHMP concluded that the integrative model predicted the data acceptably well.

The selection of 8 mg/kg (not exceeding 800 mg flat) IV for treatment was considered acceptable to the CHMP due to the experience and knowledge (safety data) available from other indications. Results of the population PK analysis for COVID-19 patients confirmed that body weight and disease severity are both covariates which have an appreciable impact on the linear clearance of tocilizumab. However, correlation between longer duration of sIL-6R saturation and better efficacy should be interpreted with caution.

In conclusion, based on the data submitted, the CHMP endorsed the proposed dosing regimen for treatment of COVID-19: "*a single 60-minute intravenous infusion of 8 mg/kg. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of RoActemra 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours*."

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study

MARIPOSA (CA42481) was a Phase II, open-label, randomized, multicenter study conducted in the United States to assess the PD, PK, safety and efficacy of two different doses of TCZ in combination with SoC in hospitalized adult patients with moderate and severe COVID-19 pneumonia.

Patients (≥ 18 years) were enrolled with confirmed SARS-CoV-2 (COVID-19) infection, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, and other bodily fluids) and radiographic findings of pneumonia. At the time of enrolment, patients were categorized as having severe or moderate COVID-19 pneumonia: Severe patients had to have SpO2 ≤ 93% or PaO2/FiO2 < 300 mmHg despite being on SoC, which could include anti-viral treatment, low-dose steroids, and supportive care. Moderate patients did not need to meet these oxygen requirements but had to have elevated CRP levels of at least 2 times the upper limit of normal (ULN).

Patients were randomized in a 1:1 ratio to receive open-label TCZ treatment with either 4 mg/kg or 8 mg/kg in addition to SoC per local practice. Randomization was stratified by disease status: moderate or severe. The proportion of patients with moderate symptoms was capped at no more than 50% of the overall study population.

For both arms, if the clinical signs or symptoms worsened or did not improve (e.g., a patient had a sustained fever or experienced clinically significant worsening of signs or symptoms such as an increased supplemental oxygen requirement), one additional infusion of unblinded treatment of either 4 or 8 mg/kg could be given within 8 to 24 hours after the initial infusion. The maximum dose per infusion was 800 mg.

Exploratory efficacy outcomes were evaluated at Day 28 and patients were followed for a total of 60 days. As all efficacy assessments were exploratory, this study was not included in the side-by-side analyses of efficacy or in the pooled meta-analysis of efficacy data.

**Patient Disposition and Baseline Characteristics**

A total of 100 patients were enrolled into the study by 22 investigators across 23 sites in the US. Of the 100 randomized patients, 50 were randomized into the 4 mg/kg+SoC group and 50 were randomized into the 8 mg/kg+SoC group. All except 3 patients received study drug, 1 in the 4 mg/kg+SoC group and 2 in the 8 mg/kg+SoC group. The majority of patients in both treatment groups

completed to Day 28 (35 [70.0%] patients in the 4 mg/kg+SoC group vs. 39 [78.0%] patients in the 8 mg/kg+SoC group); 30 (60.0%) patients in the 4 mg/kg+SoC group and 35 (70.0%) patients in the 8 mg/kg+SoC group completed the study up to Day 60.

The median age at baseline was 57.0 years (range: 25 to 86 years) in the 4 mg/kg+SoC group and 62.0 years (range: 27 to 91 years) in the 8 mg/kg+SoC group, and the median body weight was 86 kg (range: 45 to 152 kg) and 89 kg (range: 59 to 181 kg), respectively. Most patients in both groups were White (15/49 patients [30.6%] vs. 23/48 patients [47.9%] in the 4 mg/kg+SoC and 8 mg/kg+SoC groups, respectively) or Black or African American (20/49 patients [40.8%] vs. 13/48 patients [27.1%], respectively).

The baseline disease characteristics for the mITT population were overall similar in the two TCZ treatment groups and no notable differences were observed between the treatment groups in terms of the days from first COVID-19 symptom at baseline (median 8.0 vs. 9.0 days in the 4 mg/kg + SOC and 8 mg/kg + SOC groups, respectively). The majority of patients in both groups were in ordinal scale Category 3 (in a non-ICU ward, or ready for a non-ICU ward, requiring supplemental oxygen) or Category 4 (in an ICU or non-ICU ward requiring non-invasive ventilation or high-flow oxygen) at baseline (36/49 patients [73.5%] vs. 35/48 patients [72.9%] in the 4 mg/kg+SoC and 8 mg/kg+SoC groups, respectively).

Systemic steroid treatment at baseline (Day -7 to Day 1) was reported for 11 patients in each treatment group (22.4% in the 4 mg/kg + SOC vs. 22.9% in the 8 mg/kg + SOC group), whereas anti-viral treatment at baseline (defined as lopinavir, ritonavir, remdesivir, chloroquine, hydroxychloroquine, or hydroxychloroquine sulphate use between Day -7 and Day 1) was reported for a higher proportion of patients in the 4 mg/kg + SOC group (25 patients [51.0%] vs. 19 patients [39.6%], respectively). The most common pre-existing conditions at baseline were hypertension, hyperlipidemia, diabetes mellitus and obesity.

**Efficacy**

All efficacy analyses were exploratory because the main objectives of the study were related to PK and PD. Thus, no formal statistical comparisons between the 4 mg/kg+SoC and 8 mg/kg+SoC treatment groups were conducted. Efficacy results from this study are provided for completeness.

The mortality rate at Day 28 was similar in both treatment groups; 7/49 (14.3%) patients in the 4 mg/kg+SoC group and 5/48 (10.4%) patients in the 8 mg/kg+SoC group, with a weighted difference between the treatment groups of -4.5% (95% CI: -18.2%, 9.2%).

The 7-category ordinal scale distribution favored the 8 mg/kg+SoC group from Day 2 until Day 7. However, the significance of this finding is unclear and there was no difference between the two TCZ treatment groups at later time points.

The cumulative incidence functions over time for hospital discharge (ordinal scale Category 1) indicated a potential benefit in patients with severe COVID-19 pneumonia in the 8 mg/kg+SoC group at Day 7 (21.1% vs. 41.0% in the 4 mg/kg+SoC and 8 mg/kg+SoC groups, respectively). However, the significance of this finding is unclear and there was no difference between the two TCZ treatment groups at later time points.

In a post hoc analysis, the cumulative incidence functions over time for recovery (ordinal scale Category 1 and 2) indicated a potential benefit in the 8 mg/kg+SoC group at Day 7, most notably in patients with severe COVID-19 pneumonia (23.7% vs. 43.6% in the 4 mg/kg+SoC and 8 mg/kg+SoC groups, respectively). However, the significance of this finding is unclear and there was no difference between the two TCZ treatment groups at later time points.

## 2.4.2. Main studies

### *2.4.2.1. RECOVERY TCZ cohort: Tocilizumab in patients admitted to hospital with COVID-19(RECOVERY): a randomized, controlled, open-label, platform trial*

**Methods (from the RECOVERY Study Protocol and the Publication in Lancet "Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial" Published: 2021-05)**

This randomized, controlled, open-label, platform trial (Randomized Evaluation of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg–800 mg (depending on weight) given intravenously. A second dose could be given 12–24 h later if the patient's condition had not improved. The primary outcome was 28-day mortality, assessed in the intention-to-treat population.

In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine (which has now been done). A World Health Organization (WHO) expert group issued broadly similar advice. These groups also advised that other treatments will soon emerge that require evaluation.

This protocol describes a randomised trial among patients hospitalised for COVID-19. All eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment *vs* colchicine *vs* corticosteroids (children only) *vs* intravenous immunoglobulin (children only). In a factorial design (in the UK alone), eligible patients are allocated simultaneously to no additional treatment *vs* convalescent plasma *vs* synthetic neutralising antibodies (REGN-COV2). Separately, all participants aged 18 years or older will be allocated to either aspirin *vs* control. The study allows a subsequent randomisation for patients with progressive COVID-19 (evidence of hyper-inflammatory state): No additional treatment *vs* tocilizumab. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The most important task for the DMC will be to assess whether the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Regardless, follow-up will continue for all randomised participants, including those previously assigned to trial arms that are modified or ceased. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

***Objectives/Outcomes/Endpoints***

The main outcomes will be death, discharge, need for ventilation and need for renal replacement therapy. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to

medical databases where available (such as those managed by NHS Digital and equivalent organisations in the devolved nations).

***Study participants***

Between April 23, 2020, and Jan 24, 2021, 4116 adults of 21550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 (82%) patients receiving systemic corticosteroids.

Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Written informed consent was obtained from all patients, or their legal representative if they were too unwell or unable to provide consent.

***Treatments***

Patients allocated to tocilizumab were to receive tocilizumab as a single intravenous infusion over 60 min. The dose of tocilizumab was established by bodyweight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12–24 h later if, in the opinion of the attending clinician, the patient's condition had not improved.

***Objectives***

The primary objective is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

***Outcomes/endpoints***

Outcomes were assessed at 28 days after randomisation to tocilizumab versus usual care alone, with further analyses specified at 6 months. The primary outcome was all-cause mortality. Secondary outcomes were time to discharge from hospital, and, among patients not receiving invasive mechanical ventilation at randomisation, receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were use of non-invasive respiratory support (defined as high-flow nasal oxygen, continuous positive airway pressure, or non-invasive ventilation), time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of renal dialysis or haemofiltration. Prespecified safety outcomes included cause-specific mortality and major cardiac arrhythmia.

Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements.

***Sample size***

A total of 21 550 patients were enrolled into the RECOVERY trial at one of the 131 sites in the UK participating and underwent the initial (main) randomization. Between April 23, 2020, and Jan 24, 2021, 4116 (19%) of the 21 550 patients underwent the second randomization in the tocilizumab

cohort.2022 patients were randomly allocated to tocilizumab plus usual care and 2094 were randomly allocated to usual care.

According to the study protocol, realistic, appropriate sample sizes could not be estimated at the start of the trial. However, according to the publication, before commencement of the randomization to tocilizumab versus usual care, the trial steering committee determined that if 28-day mortality in the usual care group was above 25% then recruitment of around 4000 patients to this comparison would provide 90% power at two-sided alpha=0.01 to detect a proportional reduction in 28-day mortality of one-fifth. Consequently, Roche Products provided sufficient treatment for 2000 patients to receive tocilizumab. The trial steering committee, masked to the results, closed recruitment to the tocilizumab comparison at the end of Jan 24, 2021, as over 4000 patients had been randomly assigned.

***Randomisation***

RECOVERY is an ongoing randomised trial among patients hospitalized for COVID-19. All eligible patients were planned to receive usual standard of care in the participating hospital and were planned to be randomly allocated between no additional treatment and one of several active treatment arms.

All eligible and consenting patients received usual standard of care and underwent an initial (main) randomisation comprising up to three parts in a factorial design. A single participant could be randomised at most to 1 arm from each of part A, B, and C of the three factorial randomisations, and thus receive 0, 1, 2, or 3 treatments on top of usual standard of care: part A, no additional treatment versus either dexamethasone, lopinavir–ritonavir, hydroxychloroquine, azithromycin, or colchicine; part B, no additional treatment versus either convalescent plasma or REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-CoV-2 spike protein); and part C, no additional treatment versus aspirin. Over time, treatment groups were added to and removed from the protocol, and not all treatments were available at every hospital. Similarly, not all treatments were suitable for some patients (eg, owing to comorbid conditions or concomitant medication). In any of these cases, randomisation was between fewer groups.

The following tables display the randomization parts and dates when each respective treatment arm was introduced or closed (according to supplementary methods, presumingly reflecting protocol version 12.1, dated 16 December 2020):

**Part A** (from 19 March 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 19 March 2020 | Ongoing |
| Dexamethasone | 19 March 2020 | 8 June 2020 |
| Lopinavir-ritonavir | 19 March 2020 | 29 June 2020 |
| Hydroxychloroquine | 23 March 2020 | 5 June 2020 |
| Azithromycin | 7 April 2020 | 27 November 2020 |
| Colchicine | 27 November 2020 | Ongoing |

**Part B** (from 14 May 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 14 May 2020 | Ongoing |
| Convalescent plasma | 14 May 2020 | Ongoing |
| REGN-COV2* | 18 September 2020 | Ongoing |

* monoclonal neutralising antibody cocktail

**Part C** (from 1 November 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 1 November 2020 | Ongoing |
| Aspirin | 1 November 2020 | Ongoing |

Up to 21 days after the main randomisation and regardless of treatment allocation, RECOVERY trial participants with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) could be considered for randomisation to tocilizumab versus usual care alone. For some patients, tocilizumab was unavailable at the hospital at the time of enrolment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. In such cases, the patients were not eligible for the tocilizumab randomisation.

Patients who were eligible for randomisation to tocilizumab were assigned to either usual standard of care or usual standard of care plus tocilizumab in a 1:1 ratio by means of web-based simple randomization (without stratification or minimisation) with allocation concealed until after randomisation. This second randomization was introduced in April 2020:

*Second randomisation for adults (from 14 April 2020)*

From 14 April 2020, a participant could be randomised to one of the following arms and thus receive 0 or 1 treatment on top of those allocated in the initial randomisation and usual standard of care:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 14 April 2020 | 24 January 2021 |
| Tocilizumab | 14 April 2020 | 24 January 2021 |

***Blinding (masking)***

RECOVERY is an ongoing open label study. Participants and local study staff were not planned to be masked to the allocated treatment. The steering committee, investigators, patients and all others involved in the trial were planned to be masked to the outcome data during the trial. The interim trial

results were monitored regularly by an independent Data Monitoring Committee (DMC) which was unblinded. The most important task for the DMC was to assess whether the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies.

***Statistical methods***

*Analysis set*

Comparisons were planned to be made between all patients randomized to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses). Accordingly, an intention-to-treat comparison was done between tocilizumab versus usual care.

Pairwise comparisons within each randomisation were planned to be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation part A, B or C, and second randomisation). However, since not all treatments might have been available or suitable for all patients, those in the no additional treatment arm were planned to be included in a given comparison only if, at the point of their randomisation, they could alternatively have been randomised to the active treatment of interest.

*Primary outcome variable and analysis model*

For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were planned to be used to test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio. Kaplan-Meier survival curves were planned to be constructed to display cumulative mortality over the 28-day period.

The main analyses described above were planned to be unadjusted for baseline characteristics.

*Missing values and censoring*

For the primary outcome (death within 28 days of randomisation), discharge alive before 28 days was planned to assume safety from the event (unless there is additional data confirming otherwise).

*Secondary endpoints*

The same methods were used to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right censored on day 29. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation) and the subsidiary clinical outcomes of receipt of ventilation and receipt of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead.

*Significance level and Multiplicity*

Evaluation of the primary trial (main randomisation) and secondary randomisation was planned to be conducted independently, and no adjustments have been made for these. Formal adjustment were not planned for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses.

*Interim analysis*

The independent Data Monitoring Committee was planned to review unblinded analyses of the study data and any other information considered relevant at intervals of around 2 to 4 weeks. The committee was charged with determining if, in their view, the randomised comparisons in the study provide evidence on mortality that is strong enough (with a range of uncertainty around the results that was

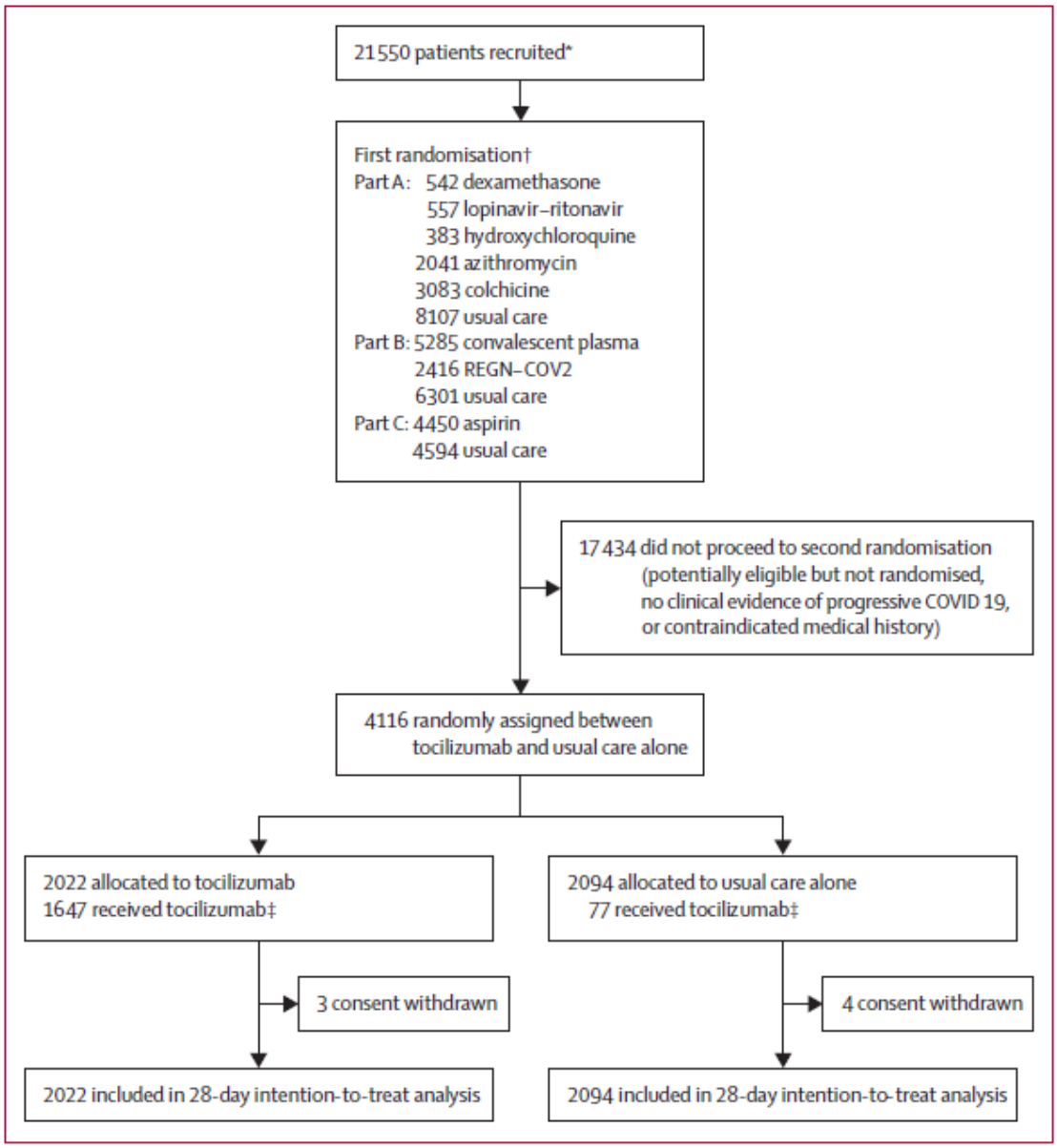
narrow enough) to affect national and global treatment strategies. In such a circumstance, the Committee was planned to inform the Steering Committee who would make the results available to the public and amend the trial arms accordingly. Unless that happened, the Steering Committee, investigators, and all others involved in the trial were planned to remain blinded to the interim results until 28 days after the last patient had been randomised to a particular intervention arm. The Data Monitoring Committee determined that to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality. The Committee concluded that examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate.

*Subgroup analysis*

Prespecified analyses of the primary outcome were planned to be done in subgroups defined by six characteristics at the time of randomisation: age, sex, ethnicity, amount of respiratory support, days since symptom onset, and use of systemic corticosteroids (including dexamethasone). Observed effects within subgroup categories were planned to be compared by means of a $\chi^2$ test for heterogeneity or trend.

**Results**

***Participant flow***




REGN-COV2=a combination of two monoclonal antibodies directed against SARS-CoV-2 spike protein. *Number of adult patients recruited at a site activated for the tocilizumab comparison. †The first randomisation comprised up to three factorial elements such that an eligible patient could be entered into between one and three randomised comparisons, depending on the then current protocol, the patient's suitability for particular treatments, and the availability of the treatment at the site. Median time between first and second randomisation was 0·3 h (IQR 0·1–25·3). ‡1964 (97%) of 2022 patients of those allocated to tocilizumab and 2049 (98%) of 2094 of those allocated to usual care had a completed follow-up form at time of analysis.

**Figure 24 Participant flow - RECOVERY**

***Recruitment***

The trial is being conducted at 177 National Health Service (NHS) hospital organizations in the United Kingdom.

***Conduct of the study***

The trial was conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Cambridge East Research Ethics Committee. The trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

Over time, additional treatment arms have been added (Table 11).

**Table 11 Protocol changes to treatment comparisons**

| Protocol version | Date | Randomisation | Treatment arms |
|---|---|---|---|
| 1.0 | 13-Mar-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Nebulised Interferon-ß-1a (never activated) |
| 2.0 | 23-Mar-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine |
| 3.0 | 07-Apr-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d] |
| 4.0 | 14-Apr-2020 | Main (part A)<br><br><br><br><br>Second[e,f] | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d]<br><br>No additional treatment<br>Tocilizumab[f] |

| | | | |
|---|---|---|---|
| 5.0 | 24-Apr-2020 | - | (no change – extension to children <18 years old) |
| 6.0 | 14-May-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 7.0 | 18-Jun-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 8.0 | 03-Jul-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 9.1 | 18-Sep-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV2 |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |

| | | | |
|---|---|---|---|
| 10.1 | 01-Nov-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV2 |
| | | Main (part C factorial) | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 11.1 | 27-Nov-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV2 |
| | | Main (part C factorial) | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 12.1 | 16-Dec-2020 | Main (part A)[h] | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine |
| | | Main (part B factorial)[h] | No additional treatment<br>Convalescent plasma<br>REGEN-COV2 |
| | | Main (part C factorial)[h] | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |

[a] enrolment ceased 29 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[b] enrolment of adults ceased 8 June 2020 as more than 2,000 patients had been recruited to the active arm
[c] enrolment ceased 5 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[d] enrolment of adults ceased 27 November 2020 as more than 2,500 patients had been recruited to the active arm

Following randomization, 16% of patients in the TCZ group reportedly did not receive this treatment and the reasons for this were not recorded.

***Baseline data***

**Table 12 Baseline data – RECOVERY**

| | Tocilizumab group (n=2022) | Usual care group (n=2094) |
|---|---|---|
| Age, years | 63·3 (13·7) | 63·9 (13·6) |
| ≥18 to <70 | 1331 (66%) | 1355 (65%) |
| ≥70 to <80 | 478 (24%) | 480 (23%) |
| ≥80 | 213 (11%) | 259 (12%) |
| Sex | | |
| Male | 1337 (66%) | 1437 (69%) |
| Female* | 685 (34%) | 657 (31%) |
| Ethnicity | | |
| White | 1530 (76%) | 1597 (76%) |
| Black, Asian, or minority ethnic | 354 (18%) | 378 (18%) |
| Unknown | 138 (7%) | 119 (6%) |
| Number of days since symptom onset | 9 (7–13) | 10 (7–14) |
| Number of days since hospitalisation | 2 (1–5) | 2 (1–5) |
| Oxygen saturation | 94% (92–96) | 94% (91–95) |
| Respiratory support at second randomisation | | |
| No ventilator support† | 935 (46%) | 933 (45%) |
| Non-invasive ventilation‡ | 819 (41%) | 867 (41%) |
| Invasive mechanical ventilation§ | 268 (13%) | 294 (14%) |
| Biochemistry at second randomisation | | |
| Latest C-reactive protein, mg/L | 143 (107–203) | 144 (106–205) |
| Ferritin, ng/mL | 947 (497–1599) | 944 (507–1533) |
| Creatinine, µmol/L | 77 (62–98) | 77 (62–100) |
| Previous diseases | | |
| Diabetes | 569 (28%) | 600 (29%) |
| Heart disease | 435 (22%) | 497 (24%) |
| Chronic lung disease | 473 (23%) | 484 (23%) |
| Tuberculosis | 3 (<1%) | 5 (<1%) |
| HIV | 7 (<1%) | 8 (<1%) |
| Severe liver disease¶ | 14 (1%) | 10 (<1%) |
| Severe kidney impairment‖ | 118 (6%) | 99 (5%) |
| Any of the above | 1100 (54%) | 1163 (56%) |

(Table 1 continues in next column)

| | Tocilizumab group (n=2022) | Usual care group (n=2094) |
|---|---|---|
| (Continued from previous column) | | |
| SARS-CoV-2 test result | | |
| Positive | 1922 (95%) | 2005 (96%) |
| Negative | 69 (3%) | 71 (3%) |
| Not known | 31 (2%) | 18 (1%) |
| First randomisation** | | |
| Number of days since first randomisation | 0 (0–1) | 0 (0–1) |
| Part A allocation | | |
| Usual care | 839 (41%) | 869 (41%) |
| Lopinavir–ritonavir | 51 (3%) | 64 (3%) |
| Dexamethasone | 49 (2%) | 45 (2%) |
| Hydroxychloroquine | 37 (2%) | 38 (2%) |
| Azithromycin | 197 (10%) | 177 (8%) |
| Use of systemic corticosteroids†† | | |
| Yes | 1664 (82%) | 1721 (82%) |
| No | 357 (18%) | 367 (18%) |
| Unknown | 1 (<1%) | 6 (<1%) |

Data are mean (SD), n (%), or median (IQR). Information on sex, ethnicity, and SARS-CoV-2 test result were recorded on the main randomisation form when patients first entered the study. All other information was recorded on the second randomisation form (when patients were randomly assigned to tocilizumab vs usual care alone). *Includes ten pregnant women. †Includes nine patients not receiving any oxygen and 1859 patients receiving low-flow oxygen. ‡Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation. §Includes patients receiving invasive mechanical ventilation or extracorporeal membranous oxygenation. ¶Defined as requiring ongoing specialist care. ||Defined as estimated glomerular filtration rate <30 mL/min per 1·73 $m^2$. **2631 participants were randomly assigned into part B and 1615 into part C of the first randomisation. ††Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids.

***Numbers analysed***

Between April 23, 2020, and Jan 24, 2021, 4116 adults of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 (82%) patients receiving systemic corticosteroids.

***Outcomes and estimation***

Between April 23, 2020, and Jan 24, 2021, 4116 (19%) of 21550 patients enrolled into the RECOVERY trial at one of the 131 sites in the UK participating in the tocilizumab comparison were eligible for random assignment. 2022 patients were randomly allocated to tocilizumab and 2094 were randomly allocated to usual care. The mean age of these participants was 63 · 6 years (SD 13 · 6). At

randomisation, 562 (14%) of 4116 patients were receiving invasive mechanical ventilation, 1686 (41%) of 4116 were receiving non-invasive respiratory support (including high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation), and 1868 (45%) of 4116 were receiving no respiratory support other than simple oxygen therapy (nine of these patients were reportedly not receiving oxygen at randomisation. Median CRP was 143 (IQR 107-204) mg/L. 82% of patients were reported to be receiving corticosteroids at randomisation (and 97% of the patients enrolled since the announcement of the dexamethasone result from RECOVERY in June, 2020).

**Primary endpoint**

A statistically significant reduction in 28-day mortality was demonstrated in the TCZ+Usual Care arm compared with the Usual Care arm. Overall, 621 (31%) of 2022 patients in the TCZ+Usual Care arm and 729 (35%) of 2094 patients in the Usual Care arm died within 28 days (hazard ratio 0.85; 95% CI: 0.76-0.94; p=0.0028).

The proportions of participants experiencing the binary endpoint of 28-day mortality (estimated using the Zee & Xie methodology) were 30.7% in the tocilizumab arm and 34.9% in the Usual Care arm. The difference in proportions was -4.1% (95% CI -7.0% to -1.3%) with a 2-sided p-value of 0.005. In an exploratory analysis restricted to the 3927 (95%) patients with a positive SARS-CoV-2 test result, the result was similar (rate ratio 0・86, 95% CI 0・77-0・97; p=0・0098).

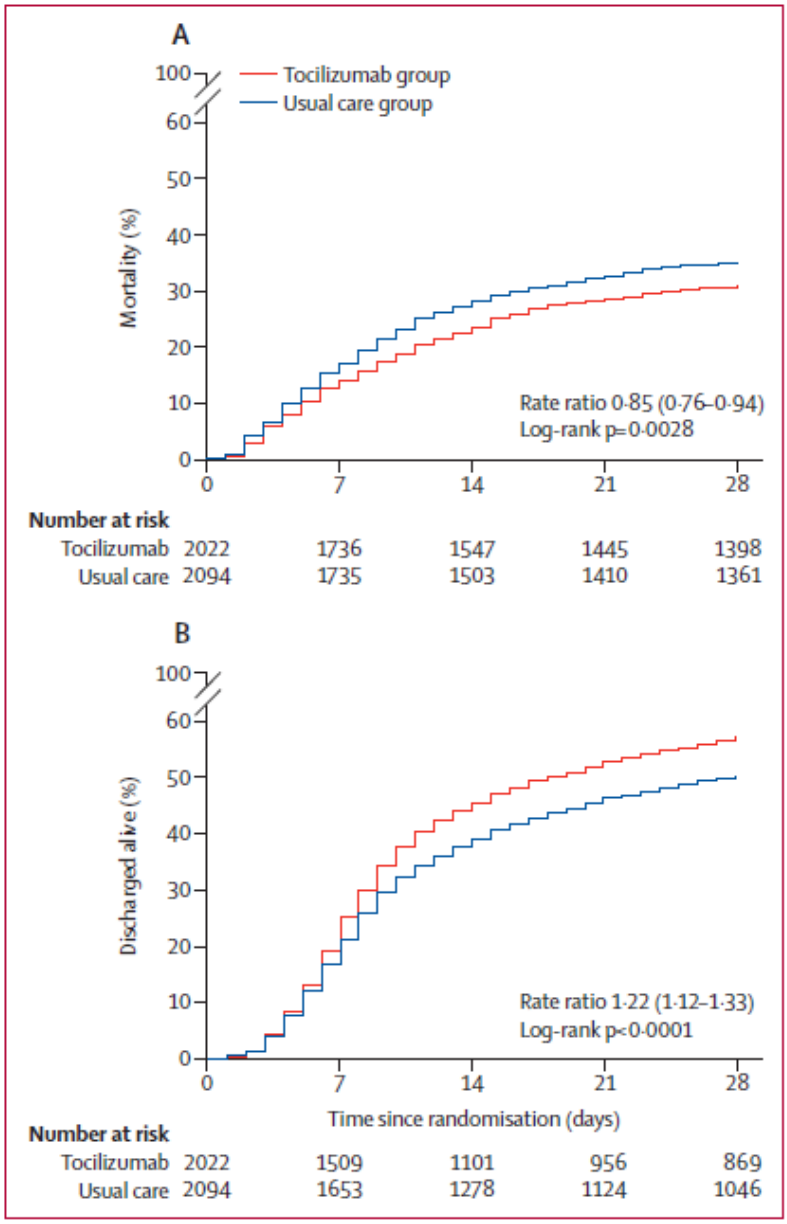
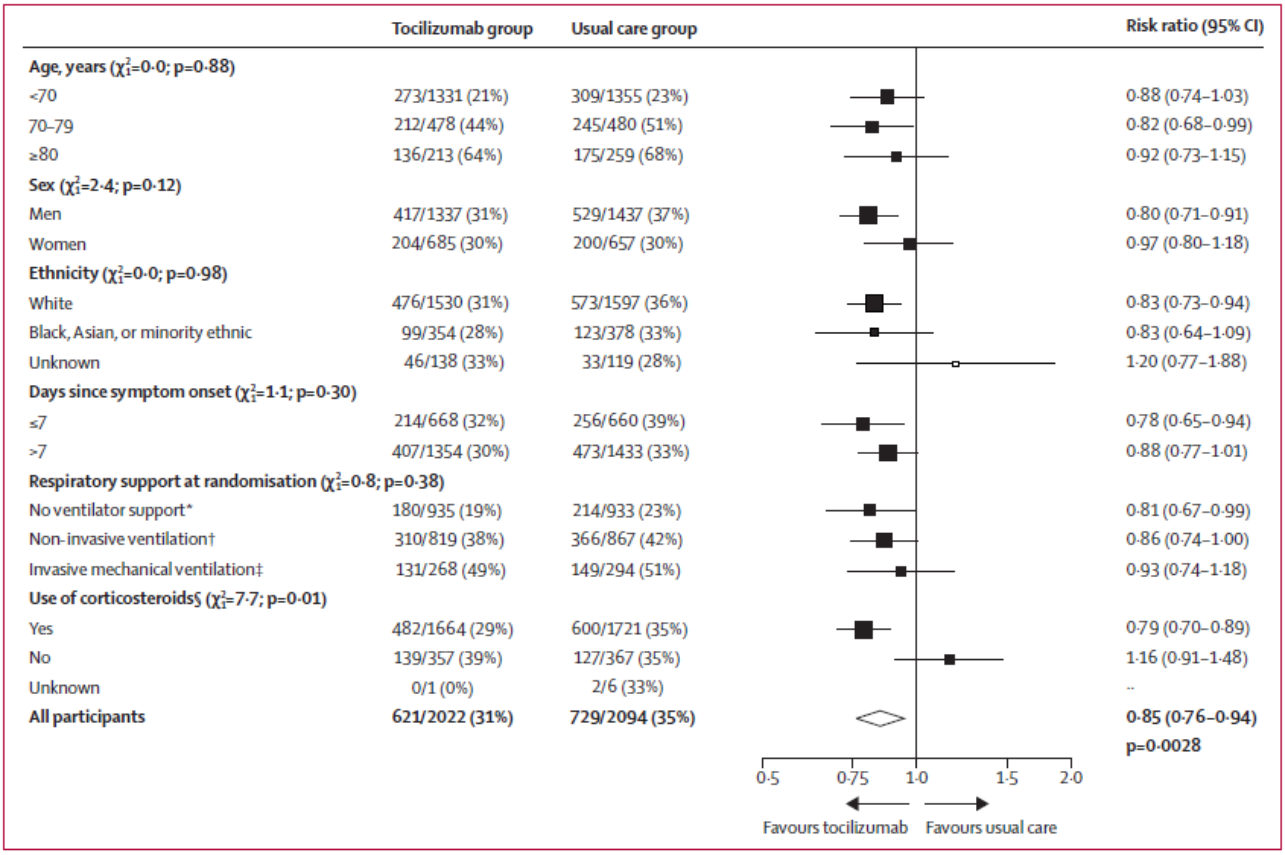



**Figure 25 Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomization (B)**

Allocation to tocilizumab was associated with a greater probability of discharge from hospital within 28 days (57% vs 50%; rate ratio 1 · 22, 1 · 12-1 · 33, p<0 · 0001; figure 25 and table 13). Among those not on invasive mechanical ventilation at baseline, allocation to tocilizumab was associated with a reduction in the risk of progressing to the prespecified composite secondary outcome of invasive mechanical ventilation or death when compared with usual care alone (35% vs 42%, risk ratio 0 · 84, 0 · 77-0 · 92, p<0 · 0001; Table 13).

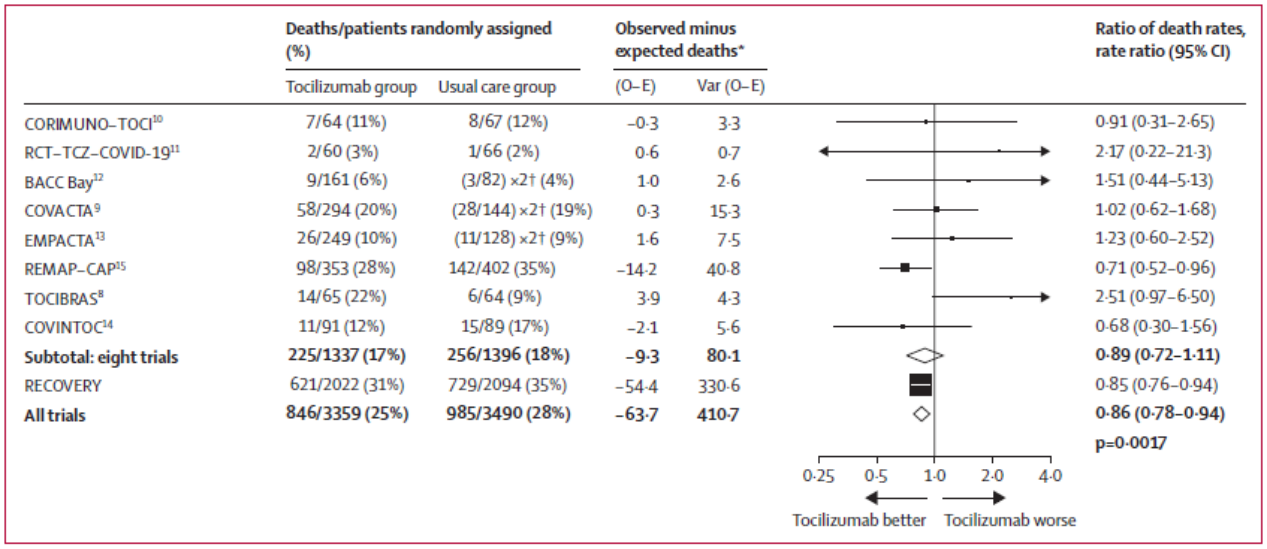
Similar results were observed across all pre-specified subgroups including the amount of respiratory support at randomisation (Figure 26).




Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. *Includes nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only. †Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation. ‡Includes patients receiving invasive mechanical ventilation and extracorporeal membranous oxygenation. §Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids. In a model adjusted for all six baseline subgroups (in the categories shown) the overall rate ratio was 0·88 (95% CI 0·79–0·98).

**Figure 26 Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics**

Given the number of hypothesis tests done, the suggestion of a larger proportional mortality reduction among those receiving a corticosteroid compared with those not (interaction p=0 · 01) might reflect the play of chance. An exploratory analysis showed that the effects of tocilizumab on 28-day mortality were similar for those randomly assigned ≤2 or >2 days since hospitalization (interaction p=0 · 89). In eight previous trials of tocilizumab versus usual care, which included a total of 439 deaths among 2379 patients, allocation to tocilizumab was associated with a non-significant 11% reduction in mortality (rate ratio 0 · 89, 0 · 72-1 · 11; Figure 27).

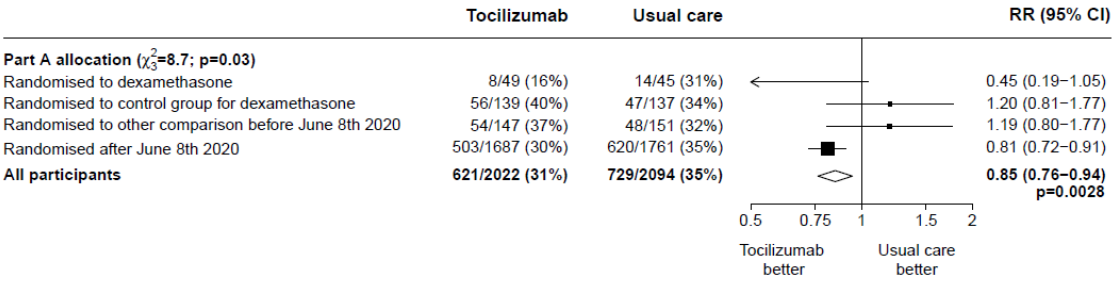



O–E=observed–expected. Var=variance. *Log–rank O–E for RECOVERY, O–E from 2 × 2 contingency tables for the other trials. Rate ratio is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O–E or V values. Heterogeneity between RECOVERY and eight previous trials combined, $\chi_1^2$=0·2 (p=0·7).

**Figure 27 Meta-analysis of mortality in randomized, controlled trials of tocilizumab in patients hospitalized with Covid-19**

After inclusion of the 28-day mortality results from RECOVERY into this metaanalysis, the mortality rate ratio from the nine trials was 0 · 86 (0 · 78-0 · 94), p=0 · 0017. In prespecified subsidiary analyses, no significant effect of tocilizumab on subsequent receipt of non-invasive respiratory support or invasive mechanical ventilation among those on no respiratory support at randomization were found. Nor was there a significant effect on the rate of successful cessation of invasive mechanical ventilation among those on invasive mechanical ventilation at randomisation. However, allocation to tocilizumab reduced the use of haemodialysis or haemofiltration (6% vs 8%, risk ratio 0 · 72, 0 · 58-0 · 90, p=0 · 0046) among those not receiving haemodialysis or haemofiltration at randomisation. There was no evidence of excess deaths from non-COVID infections or other causes. No significant differences in the frequency of new cardiac arrhythmias were observed. There were three reports of serious adverse reactions believed to be related to tocilizumab: one each of otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess, all of which resolved with standard treatment.

At the CHMP's request, the MAH clarified that the major determinant of corticosteroid use is date of enrolment with respect to the announcement of the dexamethasone result from RECOVERY. Prior to 16 June 2020, only 13% of patients in the tocilizumab comparison received corticosteroids. After 16 June 2020 dexamethasone became standard care in the NHS for hypoxic patients and its use was nearly universal with only 3% of patients not receiving dexamethasone at baseline in the tocilizumab comparison. In addition, the MAH provided the analyses in Figure 28 (note that enrolment in the dexamethasone cohort closed on 8 June 2020). The randomizations between dexamethasone and usual care, and between tocilizumab and usual care were entirely independent. Given the post hoc nature of this analysis and the number of other subgroup analyses conducted, the p value for heterogeneity of 0.03 does not provide good evidence of effect modification.




Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs.

**Figure 28 Effect of allocation to tocilizumab on 28-day mortality by allocation in first randomization (RECOVERY)**

### Secondary Endpoints

**Table 13 Effect of allocation to tocilizumab on main study outcomes**

| | Treatment allocation | | RR (95% CI) | p value |
|---|---|---|---|---|
| | Tocilizumab group (n=2022) | Usual care group (n=2094) | | |
| **Primary outcome** | | | | |
| 28-day mortality | 621 (31%) | 729 (35%) | 0·85 (0·76–0·94) | 0·0028 |
| **Secondary outcomes** | | | | |
| Median time to being discharged, days | 19 | >28 | .. | .. |
| Discharged from hospital within 28 days | 1150 (57%) | 1044 (50%) | 1·22 (1·12–1·33) | <0·0001 |
| Receipt of invasive mechanical ventilation or death* | 619/1754 (35%) | 754/1800 (42%) | 0·84 (0·77–0·92) | <0·0001 |
| Invasive mechanical ventilation | 265/1754 (15%) | 343/1800 (19%) | 0·79 (0·69–0·92) | 0·0019 |
| Death | 490/1754 (28%) | 580/1800 (32%) | 0·87 (0·78–0·96) | 0·0055 |
| **Subsidiary clinical outcomes** | | | | |
| Receipt of ventilation† | 290/935 (31%) | 323/933 (35%) | 0·90 (0·79–1·02) | 0·10 |
| Non-invasive ventilation | 281/935 (30%) | 309/933 (33%) | 0·91 (0·79–1·04) | 0·15 |
| Invasive mechanical ventilation | 67/935 (7%) | 86/933 (9%) | 0·78 (0·57–1·06) | 0·11 |
| Successful cessation of invasive mechanical ventilation‡ | 95/268 (35%) | 98/294 (33%) | 1·08 (0·81–1·43) | 0·60 |
| Use of haemodialysis or haemofiltration§ | 120/1994 (6%) | 172/2065 (8%) | 0·72 (0·58–0·90) | 0·0046 |

Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

### Time to discharge alive from hospital

Allocation to the TCZ+Usual Care arm was associated with a greater probability of discharge from hospital within 28 days (57% vs. 50%; hazard ratio 1.22, 95% CI: 1.12 to 1.33, p<0.0001). Median

time to discharge alive was shorter in the TCZ+Usual Care arm compared with the Usual Care arm (TCZ: 19 days and Usual Care: >28 days).

**Use of invasive mechanical ventilation (including ECMO) or death (among patients not on invasive mechanical ventilation or ECMO at time of randomisation)**

Among patients not requiring invasive mechanical ventilation at baseline (1754 patients in TCZ+Usual Care arm and 1800 in Usual Care arm), allocation to the TCZ+Usual Care arm was associated with a reduction in the risk of progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death when compared to Usual Care alone (35% vs. 42%, risk ratio 0.84, 95% CI: 0.77 to 0.92, p<0.0001).

**Subsidiary Endpoints**

Among patients not requiring respiratory support (other than low-flow oxygen) at randomization (935 patients in TCZ+Usual Care arm and 933 in the Usual Care arm) (a pre-specified subgroup analyses), no significant effect of tocilizumab was observed on subsequent receipt of non-invasive ventilation (30% vs. 33%, risk ratio 0.91, 95% CI: 0.79 to 1.04, p=0.15) or invasive mechanical ventilation (7% vs. 9%, risk ratio 0.78, 95% CI: 0.57 to 1.06, p=0.11).

However, among those not receiving hemodialysis or hemofiltration at the second randomization (1994 patients in TCZ+Usual Care arm and 2065 in the Usual Care arm), the percentage of patients requiring hemodialysis or hemofiltration was lower in the TCZ+Usual Care treatment arm compared with the Usual Care arm (6% vs. 8%, risk ratio 0.72, 95% CI 0.58 to 0.90, p=0.0046).

#### *2.4.2.2. COVACTA - A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab inPatients with Severe COVID-19 Pneumonia.*

**Methods**

COVACTA was a global, multicenter, randomized, double-blind, placebo-controlled, Phase III trial investigating the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia.

***Study participants***

The COVACTA study recruited patients with severe COVID-19 pneumonia, defined by a positive polymerase chain reaction (PCR) result, radiographic evidence of pneumonia and the presence of hypoxia (blood oxygen saturation [$SpO_2$] ≤ 93% or partial pressure of $O_2$ [$PaO_2$]/fraction of inspired $O_2$ [$FiO_2$] <300 mmHg), but also patients with critical disease, including those requiring mechanical ventilation, with or without other advanced life support. Patients were excluded if progression to death was imminent and inevitable within 24 hours as determined by the treating physician or they had any suspected active bacterial, fungal, or viral infection other than COVID-19.

***Treatments***

Patients (≥18 years of age) who fulfilled the study entry criteria were randomly assigned at a ratio of 2:1 to one of two treatment arms, tocilizumab (8 mg/kg, with a maximum dose of 800 mg) in combination with SoC (TCZ + SoC) or placebo in combination with SoC (PBO + SoC), using a permuted-block randomization method.

***Objectives /Outcomes/endpoints***

| Objectives | Endpoints/Outcome Measures |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia | • Clinical status assessed using a 7-category ordinal scale at Day 28 |
| **Secondary** | |
| • To evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia | • Time to clinical improvement (TTCI) defined as a National Early Warning Score 2 (NEWS2) of ≤2 maintained for 24 hours<br>• Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status<br>• Incidence of mechanical ventilation<br>• Ventilator-free days to Day 28<br>• Incidence of intensive care unit (ICU) stay<br>• Duration of ICU stay<br>• Clinical status assessed using a 7-category ordinal scale at Day 14<br>• Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death<br>• Mortality at Days 7, 14, 21, 28, and 60<br>• Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and |

| | |
|---|---|
| | respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen)<br>• Time to recovery defined as hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen), or Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen<br>• Duration of supplemental oxygen |
| **Exploratory** | |
| To evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia | • Incidence of vasopressor use<br>• Duration of vasopressor use<br>• Incidence of extracorporeal membrane oxygenation (ECMO)<br>• Duration of ECMO<br>• Organ failure-free days to Day 28 |
| **Safety** | |
| To evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia | • Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0<br>• SARS-CoV-2 viral load over time, as collected by nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if applicable)<br>• Time to reverse-transcriptase polymerase chain reaction (RT-PCR) virus negativity<br>• The proportion of patients with any post-treatment infection (key safety objective)<br>• Change from baseline in targeted clinical laboratory test results |
| **Pharmacodynamic** | |
| To characterize the pharmacodynamic effects of TCZ in patients with COVID-19 pneumonia via longitudinal measures of the following analytes relative to baseline | • Serum concentrations of IL-6, sIL-6R, and CRP at specified timepoints |

***Sample size***

Initially the study planned to enroll 350 patients. However, the protocol and the SAP for Study WA42380 were later updated to Version 3 and Version 2.0 (on 11 June 2020 and on 26 May 2020, respectively) to amend the sample size to 450 patients, in order to increase the power for the primary endpoint to 90%. The estimated sample size was determined for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Week 4 using the Van Elteren test. Table 14 shows the assumed distribution of the ordinal scale in the PBO plus SOC group. Table 15 shows the expected distribution in the TCZ plus SOC group with an odds ratio of 2 (assuming proportional odds). Under these assumptions, the total modified intent to treat (mITT) sample size of 450 with a 2:1 randomization of TCZ to placebo patients was expected to provide approximately 90% power to detect

a difference in distribution between the treatment groups of the ordinal scale at Week 4 using a two-sided Van Elteren test at the 5% significance level.

**Table 14 Distribution of ordinal scale in the placebo group**

| 1 (discharge) | 2 | 3 | 4 | 5 | 6 | 7 (death) |
|---|---|---|---|---|---|---|
| 0.58 | 0.05 | 0.09 | 0.09 | 0.02 | 0.02 | 0.15 |

Assuming proportional odds the expected distribution in the TCZ arm with an odds ratio of 2 would be:

**Table 15 Distribution of ordinal scale in the TCZ group**

| 1 (discharge) | 2 | 3 | 4 | 5 | 6 | 7 (death) |
|---|---|---|---|---|---|---|
| 0.734 | 0.039 | 0.064 | 0.058 | 0.012 | 0.012 | 0.081 |

This sample size was expected to provide approximately 90% power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

***Randomisation***

Patients were randomized at a 2:1 ratio through use of a permuted-block randomization method to receive blinded treatment of either tocilizumab or a matching placebo, respectively. The randomization was stratified by geographic region (North America and Europe) and mechanical ventilation (yes, no) to ensure that the treatment arms were balanced for any differences in regional standard of care across global sites, and for baseline disease severity. The proportion of patients who were supported by mechanical ventilation at the time of randomization was capped at no more than 50% of the overall study population since these patients were expected to be at higher risk for poor outcomes based on limited knowledge at the time of study design.

***Blinding (masking)***

The study was conducted as a double blind trial. Study site personnel and patients were blinded to treatment assignment during the study. The Sponsor and its agents were also be blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfil their job roles during a clinical trial. These roles included the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and Data Monitoring Committee (DMC) members.

***Statistical methods***

*Analysis set & stratification*

Efficacy assessments of the primary and secondary outcomes were planned to be performed in the modified intention-to-treat population, which includes all the patients who had undergone randomization and received a dose of tocilizumab or placebo. The analyses were planned to be stratified according to region and mechanical-ventilation status at randomization.

*Primary endpoint, missing values & estimand*

For the primary outcome of clinical status at day 28, the difference in distributions of the 7-category ordinal scale between TCZ plus SOC and placebo plus SOC were planned to be tested using a non-

parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]).

As an additional analysis, the clinical status according to the 7-category ordinal scale was planned to be compared between the TCZ group and the placebo group at Day 28, using a proportional odds model accounting for stratification factors at randomization in the model (region [North America, Europe] and mechanical ventilation [yes, no]).

For patients who withdraw before Day 28, their last post baseline ordinal category prior to withdrawal was planned to be used in the analysis.

The primary estimand attributes were defined as follows:

- Population: Patients with severe COVID-19 pneumonia as per the inclusion/exclusion criteria specified in the protocol (mITT)
- Primary endpoint: Clinical status at Week 4
- Treatments: Tocilizumab (TCZ) plus SOC versus Placebo (PBO) plus SOC
- Intercurrent events: Events leading to study withdrawal
- Handling of intercurrent events: last observed post-baseline value (except if the patient has been discharged [without re-admittance] or has died up to and including Day 28, then the death or discharge will override the Week 4 value or be imputed for a missing Week 4 value).
- Summary measure: medians (95% CI) PBO plus SOC and TCZ plus SOC

Intercurrent events were those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. For patients who withdrew before Week 4, their last post-baseline ordinal category prior to withdrawal was used in the primary analysis, unless death within the time frame was captured from public records or otherwise; in which case death was used in the analysis.

*Secondary endpoints*

The difference in proportion of patients that have died by Day 28 was planned to be compared using the CMH test as described above. All deaths post discontinuation and discharge were planned to be included in this analysis.

Further secondary endpoints were planned to be analysed descriptively.

*Multiplicity*

The primary endpoint was planned to be tested at a two-sided 5% significance level. If the primary endpoint was statistically significant, then the difference in mortality at Week 4 would have then been tested at 0.05 (two-sided Cochran-Mantel-Haenszel test). No further multiplicity adjustment for the additional secondary endpoints was planned.

This was only specified in the SAP, and not in the study protocol.

*Interim analysis*

Up to three interim analyses for efficacy were planned to be carried out on the data with mortality rate at 28 days (secondary endpoint) evaluated for interim efficacy analyses. The interim looks were planned to occur after roughly 111, 222, and 333 patients are enrolled and followed for 28 days. The first efficacy interim analysis was planned to be conducted when approximately 111 patients (74 TCZ and 37 placebo) have reached the 28-day follow-up time point and will be based on the mortality rate at 28 days (secondary endpoint).

The Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary was planned to be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Interim analyses for efficacy were planned to utilize the Fisher's exact test for difference in proportions for mortality at 28 days and will utilize an O'Brien-Fleming alpha-spending function. The efficacy boundaries for the z-scores at the four looks (three interim looks and final analysis) were planned to be 4.364, 2.986, 2.377, and 2.011.

Interim analyses were not carried out.

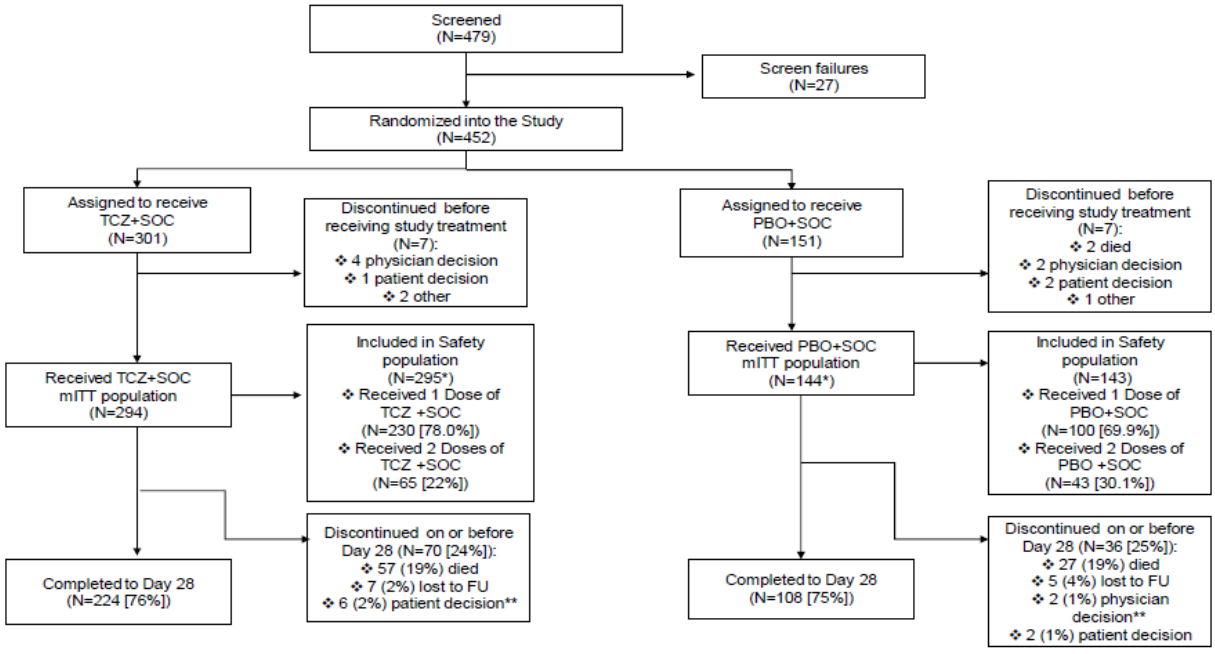
***Results***

***Participant flow***

It was planned to enroll approximately 450 patients. The study randomized 452 patients (301 in the TCZ + SOC arm and 151 in the PBO + SOC arm). 7 patients in each treatment arm randomized into the study did not receive study drug and were excluded from the modified intent-to-treat (mITT) and Safety evaluable populations.

The analysis populations were as follows:

- mITT population: 438 patients
- Safety-evaluable population: 438 patients




*One patient randomly assigned to the placebo arm was treated with tocilizumab; this patient was included in the tocilizumab group for the safety population and in the placebo group for the mITT population; ** One patient in each study arm died after discontinuation and therefore did not hav "death" recorded as the reason for discontinuation.

FU = follow-up; mITT=modified intent-to-treat; PBO=placebo; SOC=standard of care; TCZ=tocilizumab

**Figure 29 WA42380 Summary of patient disposition to Day 28**

***Recruitment***

Patients were enrolled at 62 centers across nine countries and two regions (Europe [Denmark, France, Germany, Italy, Netherlands, Spain, and the United Kingdom] and North America [Canada and the US]). The first patient was enrolled and randomized on 3 April 2020. The last patient was randomized on 28 May 2020.

***Conduct of the study***

This study was 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 (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

***Baseline data***

The demographic characteristics of the mITT population were well balanced across treatment arms with respect to the stratification factors of geographic region at baseline (North America, Europe) and mechanical ventilation (yes, no). Similar proportions of patients between treatment arms in the mITT population were randomized in Europe (40.8% in the TCZ+SOC arm and 41.0% in the PBO+SOC arm) and in North America (59.2% and 59.0%, respectively) and were on mechanical ventilation (37.8% in the TCZ+SOC arm and 37.5% in the PBO+SOC arm).

Based on the 7-category ordinal scale for clinical status, 26.5% and 30.6% were in Category 3, 32.0% and 27.1% were in Category 4, 15.3% and 10.4% were in Category 5, and 23.1% and 27.1% were in Category 6 in the TCZ+SOC and PBO+SOC arms, respectively, at baseline.

The treatment arms were generally balanced with respect to demographic characteristics. In the mITT population, the median age was 63.0 years (range: 25-96 years) in the TCZ + SOC arm and 61.5 years (range: 22-93 years) in the PBO + SOC arm.

The majority of patients were male (69.7% in the TCZ+SOC arm and 70.1% in the PBO+SOC arm, respectively), White (59.9% and 52.8%, respectively) and were not of hispanic or latino ethnicity (61.6% and 59.7%, respectively). The median NEWS2 score was 7.0 in both treatment arms. Notable differences between the two treatment arms included a higher proportion of patients >85 years of age in the TCZ +SOC arm (14 [4.8%]) compared to the PBO+SOC arm (3 [2.1%]) and a lower proportion of Black or African American in the TCZ+SOC arm (40 [13.6%]) compared to PBO+SOC arm (26 [18.1%]). At baseline, lower proportions of patients in the TCZ+SOC arm than the PBO+SOC arm received systemic steroids (57 [19.4%] vs. 41 [28.5%]) and antiviral treatment (71 [24.1%] vs. 42 [29.2 %]). Numerically higher median levels of IL-6 (88.10 ng/L in the TCZ+SOC arm and 71.15 ng/L in the PBO+SOC arm), C-reactive protein (CRP; 157.2 mg/L and 150.30 mg/L, respectively), and ferritin (2.30 pmol/mL and 2.17 pmol/mL, respectively) were observed in the TCZ+SOC arm compared with the PBO+SOC arm.

**Table 16 Demographics at baseline mITT population**

Protocol: WA42380
Snapshot Date: 22JUL2020

| | PBO (N=144) | TCZ 8 mg/kg (N=294) | All Patients (N=438) |
|---|---|---|---|
| Sex | | | |
| n | 144 | 294 | 438 |
| Male | 101 (70.1%) | 205 (69.7%) | 306 (69.9%) |
| Female | 43 (29.9%) | 89 (30.3%) | 132 (30.1%) |
| Age (yr) | | | |
| n | 144 | 294 | 438 |
| Mean (SD) | 60.6 (13.7) | 60.9 (14.6) | 60.8 (14.3) |
| Median | 61.5 | 63.0 | 62.0 |
| Min - Max | 22 - 93 | 25 - 96 | 22 - 96 |
| Age group (yr) | | | |
| n | 144 | 294 | 438 |
| 18-64 | 81 (56.3%) | 163 (55.4%) | 244 (55.7%) |
| 65-84 | 60 (41.7%) | 117 (39.8%) | 177 (40.4%) |
| >=85 | 3 ( 2.1%) | 14 ( 4.8%) | 17 ( 3.9%) |
| Weight (kg) | | | |
| n | 143 | 294 | 437 |
| Mean (SD) | 88.09 (24.31) | 88.90 (23.64) | 88.63 (23.83) |
| Median | 82.00 | 84.60 | 83.00 |
| Min - Max | 37.3 - 185.9 | 43.5 - 186.0 | 37.3 - 186.0 |
| Female Fertility Status | | | |
| n | 43 | 89 | 132 |
| Yes | 9 (20.9%) | 24 (27.0%) | 33 (25.0%) |
| No | 34 (79.1%) | 65 (73.0%) | 99 (75.0%) |
| Post-Menopausal | 32 (74.4%) | 52 (58.4%) | 84 (63.6%) |
| Pre-Menarchal | 0 | 1 ( 1.1%) | 1 ( 0.8%) |
| Surgically Sterile | 1 ( 2.3%) | 12 (13.5%) | 13 ( 9.8%) |
| Ethnicity | | | |
| n | 144 | 294 | 438 |
| Hispanic or Latino | 47 (32.6%) | 94 (32.0%) | 141 (32.2%) |
| Not Hispanic or Latino | 86 (59.7%) | 181 (61.6%) | 267 (61.0%) |
| Not Stated | 6 ( 4.2%) | 12 ( 4.1%) | 18 ( 4.1%) |
| Unknown | 5 ( 3.5%) | 7 ( 2.4%) | 12 ( 2.7%) |
| Race | | | |
| n | 144 | 294 | 438 |
| American Indian or Alaska Native | 5 ( 3.5%) | 8 ( 2.7%) | 13 ( 3.0%) |
| Asian | 10 ( 6.9%) | 28 ( 9.5%) | 38 ( 8.7%) |
| Black or African American | 26 (18.1%) | 40 (13.6%) | 66 (15.1%) |
| Native Hawaiian or other Pacific Islander | 5 ( 3.5%) | 3 ( 1.0%) | 8 ( 1.8%) |
| White | 76 (52.8%) | 176 (59.9%) | 252 (57.5%) |
| Multiple | 1 ( 0.7%) | 0 | 1 ( 0.2%) |
| Unknown | 21 (14.6%) | 39 (13.3%) | 60 (13.7%) |
| Geographic Region (a) | | | |
| n | 144 | 294 | 438 |
| Europe | 59 (41.0%) | 120 (40.8%) | 179 (40.9%) |
| North America | 85 (59.0%) | 174 (59.2%) | 259 (59.1%) |

(a) as listed in IxRS

Program:
root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/TLR_D28CUT/prod/program/t_dm.sas
Output: root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/TLR_D28CUT/prod/output/
t_dm_MITT_D28CUT_42380.out
24JUL2020 1:29 Page
1 of 1

***Numbers analysed***

A total of 330/438 (75.3%) patients received one dose of study treatment, 230/295 (78.0%) in the TCZ+SOC arm and 100/143 (69.9%) in the PBO+SOC arm, and a total of 108/438 (24.7%) patients received two doses of study treatment, 65/295 (22.0%) in the TCZ+SOC arm and 43/143 (30.1%) in the PBO+SOC arm.

The primary analysis population for efficacy (mITT population) comprised 294 patients in the TCZ+SoC arm and 144 patients in the PBO+SoC arm. Similar proportions of patients between treatment arms in

the mITT population were randomized in Europe (40.8% in the TCZ+SoC arm and 41.0% in the PBO+SoC arm) and in North America (59.2% and 59.0%, respectively).

**Outcomes and estimation**

**Primary endpoint**

Clinical status assessed using a 7-category ordinal scale at Day 28

*The primary endpoint was not met*. There was no statistically significant difference in the distribution of clinical status (ordinal scale) at Day 28 between the treatment arms (Van Elteren p-value=0.3600). The difference in medians observed between the two treatment arms was -1.0 (95% CI: -2.5, 0.0). The odds ratio (OR) was 1.19 (95% CI 0.81, 1.76)

**Key Secondary Efficacy Endpoints**

*All p-values for secondary endpoints are nominal because the primary endpoint was not met.*

Difference in Mortality at Week 4 and up to Day 60

No statistical significance was observed for the difference between TCZ+SoC and PBO+SoC in the percentage of patients that died by Day 28 (Week 4); TCZ+SoC= 19.7% and PBO+SoC= 19.4% with a weighted difference of 0.3% (95% CI: −7.6%, 8.2%) and a Cochran-Mantel Haenszel (CMH) p-value of 0.9410. The mortality up to Day 60 (post-hoc analysis) was 24.5% for the TCZ+SoC arm versus 25.0% for the PBO+SoC arm. The weighted difference in mortality between the two treatment arms (TCZ arm – PBO arm) was -0.5% (p-value=0.9045; [95% CI: −9.1%, 8.0%]).

Clinical status assessed using a 7-category ordinal scale at Week 2

No statistically significant difference was observed in the distribution of clinical status on the 7-category Ordinal Scale at Day 14 (Week 2) between TCZ +SoC and PBO +SoC, with medians of TCZ+SoC= 3.0; PBO+SoC= 4.0, a difference in medians = −1.0 [95% CI: −2.0 , 0.5] and a Van Elteren p-value of 0.0548. The OR was 1.42 (95% CI: 0.99, 2.05).

Ventilator-free days at Week 4

No statistical significance was found for the difference in number of ventilator-free days between TCZ+SoC and PBO+SOC at Day 28 (Week 4), with medians of TCZ+SoC = 22.0; PBO+SoC = 16.5, a difference in medians = 5.5 (95%CI: −2.8 , 13.0) and a Van Elteren p-value of 0.3202.

Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status to Week 4

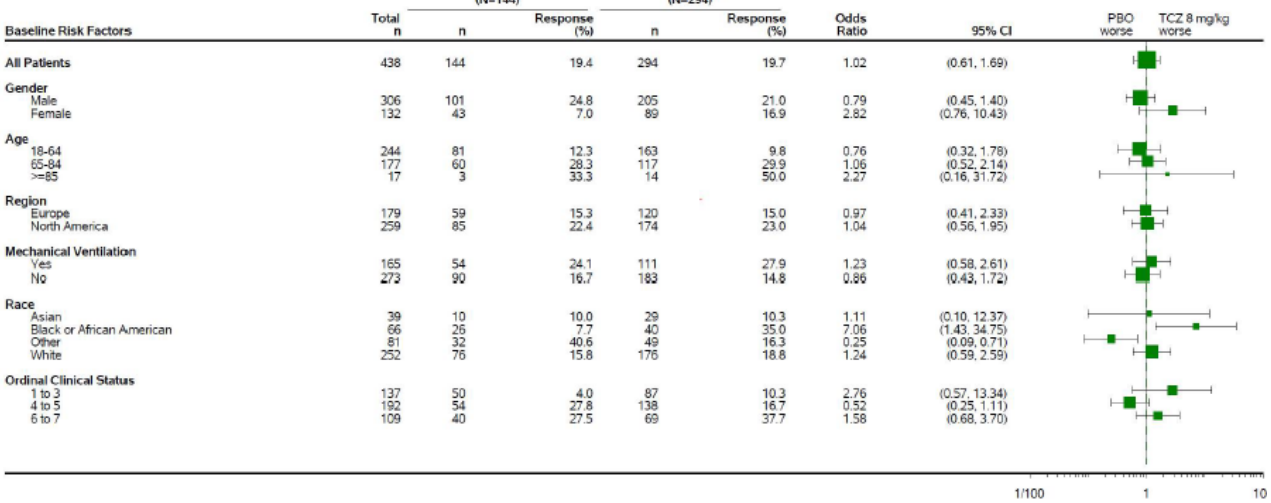
No statistical significance was found for the difference in time to improvement of at least 2 categories relative to baseline, with median times of TCZ+SoC= 14.0 days (95% CI: 12.0, 17.0), PBO+SoC= 18.0 days (95% CI: 15.0, 28.0), a log-rank p-value of 0.0820. The hazard ratio (HR) for time to improvement in the TCZ+SoC arm vs. the PBO+SoC arm was 1.263 (95% CI: 0.97, 1.64).

Time to hospital discharge or "ready for discharge"

Nominal statistical significance was observed for the difference in time to hospital discharge or "ready for discharge", with median times of TCZ+SoC= 20.0 days (95% CI: 17.0 , 27.0), PBO+SoC= 28.0 days (95% CI: 20.0 , not evaluable [NE]), a log-rank p-value of 0.0370. The HR for time to hospital discharge or "ready for discharge" for TCZ+SoC vs. PBO+SoC was 1.35 (95% CI: 1.02, 1.79).

Protocol: WA42380

| Baseline Risk Factors | Total n | PBO (N=144) n | PBO (N=144) Response (%) | TCZ 8 mg/kg (N=294) n | TCZ 8 mg/kg (N=294) Response (%) | Odds Ratio | 95% CI |
|---|---|---|---|---|---|---|---|
| **All Patients** | 438 | 144 | 19.4 | 294 | 19.7 | 1.02 | (0.61, 1.69) |
| **Gender** | | | | | | | |
| Male | 306 | 101 | 24.8 | 205 | 21.0 | 0.79 | (0.45, 1.40) |
| Female | 132 | 43 | 7.0 | 89 | 16.9 | 2.82 | (0.76, 10.43) |
| **Age** | | | | | | | |
| 18-64 | 244 | 81 | 12.3 | 163 | 9.8 | 0.76 | (0.32, 1.78) |
| 65-84 | 177 | 60 | 28.3 | 117 | 29.9 | 1.06 | (0.52, 2.14) |
| >=85 | 17 | 3 | 33.3 | 14 | 50.0 | 2.27 | (0.16, 31.72) |
| **Region** | | | | | | | |
| Europe | 179 | 59 | 15.3 | 120 | 15.0 | 0.97 | (0.41, 2.33) |
| North America | 259 | 85 | 22.4 | 174 | 23.0 | 1.04 | (0.56, 1.95) |
| **Mechanical Ventilation** | | | | | | | |
| Yes | 165 | 54 | 24.1 | 111 | 27.9 | 1.23 | (0.58, 2.61) |
| No | 273 | 90 | 16.7 | 183 | 14.8 | 0.86 | (0.43, 1.72) |
| **Race** | | | | | | | |
| Asian | 39 | 10 | 10.0 | 29 | 10.3 | 1.11 | (0.10, 12.37) |
| Black or African American | 66 | 26 | 7.7 | 40 | 35.0 | 7.06 | (1.43, 34.75) |
| Other | 81 | 32 | 40.6 | 49 | 16.3 | 0.25 | (0.09, 0.71) |
| White | 252 | 76 | 15.8 | 176 | 18.8 | 1.24 | (0.59, 2.59) |
| **Ordinal Clinical Status** | | | | | | | |
| 1 to 3 | 137 | 50 | 4.0 | 87 | 10.3 | 2.76 | (0.57, 13.34) |
| 4 to 5 | 192 | 54 | 27.8 | 138 | 16.7 | 0.52 | (0.25, 1.11) |
| 6 to 7 | 109 | 40 | 27.5 | 69 | 37.7 | 1.58 | (0.68, 3.70) |




Odds Ratios within each subgroup as calculated by Logistic Regression Analysis for Mortality. Each logistic Regression model includes the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]) along with a treatment term, baseline subgroup term (as defined in the table) and a treatment*subgroup interaction. Where the subgroup of interest is a stratification factor, the stratification factor, as well as a stratification*treatment interaction will be fitted. For subgroup analysis of baseline ordinal scale categories, the stratification mechanical ventilation will be dropped from the model. An Odds Ratio < 1 favors TCZ over PBO.
Race category of 'Other' is defined as 'MULTIPLE', 'NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER', 'AMERICAN INDIAN OR ALASKA NATIVE' and 'UNKNOWN'.
95% CIs calculated using Wald method.
Program: root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/FinalCSR/prod/program/g_mort_forest.sas
Output: root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/FinalCSR/prod/output/g_mort_forest_MITT_22SEP2020_42380.pdf 04JAN2021 20:47

**Figure 30 Summary of forest plot of logistic regression analysis of mortality, by subgroup at Day 28 (week 4), mITT population**

### *2.4.2.3. EMPACTA - Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients with Covid-19 Pneumonia*

#### Methods

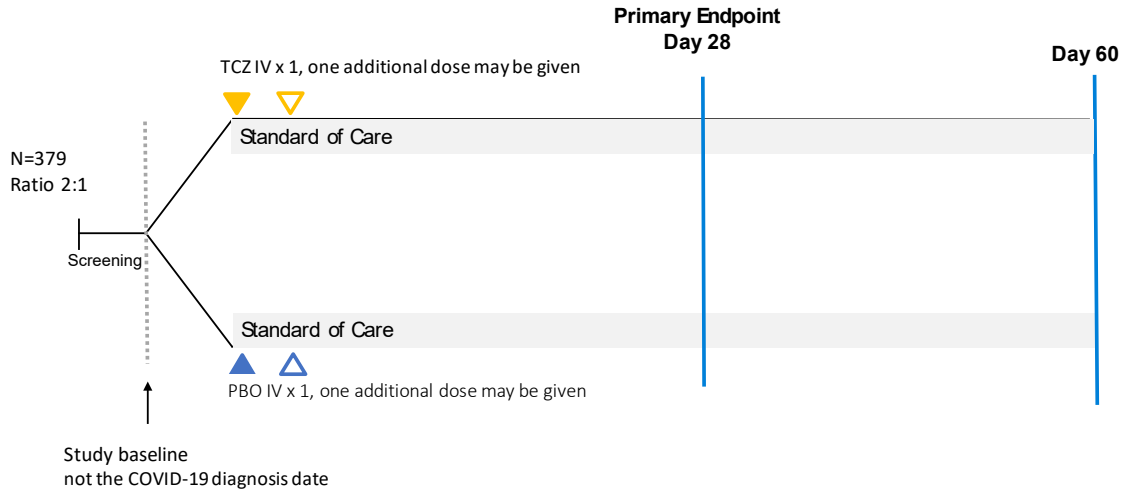
EMPACTA (Evaluating Minority Patients with Actemra) was a global, randomized, double-blind, placebo-controlled, multicenter, Phase III study to evaluate the safety and efficacy of tocilizumab in hospitalized, non-ventilated patients with COVID-19 pneumonia. Study sites were selected to focus on enrolling high-risk minority populations that have been disproportionately affected by the pandemic.

Randomisation was done through permuted-block randomization. Randomization was stratified by country (United States [US], Mexico, Kenya, South Africa, Peru, Brazil) and age (≤60 and >60 years of age). If a patient's clinical signs or symptoms worsened or did not improve, an additional infusion could be administered 8–24 hours after the first.

The study assessments conducted included the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, AEs, concomitant therapies, and clinical laboratory tests.

Patients were followed for a total of 60 days. The primary analysis was performed after the last patient's Day 28 visit.

An overview of the study design is shown in Figure 31.




IV = intravenous; PBO = placebo; TCZ = tocilizumab.

Note: Patients were screened and randomized within 96 hours of hospital admission. Study treatment was given within approximately 4 hours after randomization

**Figure 31 Overview of EMPACTA Study Design**

***Study participants***

A total of 388 patients hospitalized with COVID-19 associated pneumonia were included in this study in 6 countries as follows: 315 patients (81.2%) in the US; 29 patients (7.5%) in Peru; 12 patients (3.1%) in South Africa; 11 patients (2.8%) each in Brazil and Mexico; and 10 patients (2.6%) in Kenya.

***Treatments***

Patients were randomized at a 2:1 ratio to receive blinded treatment of either tocilizumab or placebo, respectively. Patients assigned to the tocilizumab arm (TCZ arm) received one infusion of tocilizumab 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm (PBO arm) received one infusion of placebo, both in addition to SOC. Patients were followed for 60 days after first dose of study medication.

***Objectives/Endpoint***

The primary efficacy objective for this study was to evaluate the efficacy of tocilizumab compared with placebo in combination with SOC for treatment of COVID-19 associated pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

The secondary efficacy objective for this study was to evaluate the efficacy of tocilizumab compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the endpoints shown below.

- Time to hospital discharge or "ready for discharge" (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or <2L supplemental oxygen

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, intensive care unit (ICU) admission, or withdrawal (whichever occurred first)
- Mortality rate by Day 28
- Clinical status on 7-category ordinal scale at Day 28

The exploratory efficacy objective for this study was to evaluate the efficacy of tocilizumab compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (highsensitivity C-reactive protein [hs-CRP], C-reactive protein [CRP], D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) by Day 28

***Sample size***

The estimated sample size of 379 (n=253 randomized to TCZ and n=126 randomized to placebo) was determined based on the time from first dose of study treatment to the first utilization of mechanical ventilation or death by Day 28. It was expected to provide approximately 80% power using a log-rank test to detect a 15% difference between treatment arms in the cumulative proportions of patients with death or mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., alive and not requiring mechanical ventilation) rates of 75% in the TCZ arm and 60% in PBO arm by Day 28, using a two-sided 5% alpha, and 10% dropout rate in each arm.

***Randomisation***

Patients who fulfilled the study entry criteria were planned to be randomized (at a 2:1 ratio) to either tocilizumab (8 mg/kg, maximum 800 mg) plus standard care (TCZ+SoC) or placebo plus standard care (PBO+SoC) through permuted-block randomization. Randomization was planned to be stratified by country (United States [US], Mexico, Kenya, South Africa, Peru, Brazil) and age (≤60 and >60 years of age).

***Blinding (masking)***

This is a double-blinded study.

Study site personnel and patients were planned to be blinded to treatment assignment during the study, with the exception of the study pharmacist. The Sponsor and its agents were also planned to be blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfill their job roles during a clinical trial and members of the IMC. These roles were planned to include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, IMC statistical programming analysts, and IMC members.

Study centers were unblinded after the final study results were reported.

***Statistical methods***

*Analysis set*

All efficacy outcomes were planned to be analyzed in the modified intent-to-treat (mITT) population. The mITT population was defined as all patients randomized in the study who received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

*Primary endpoint and analysis model*

The primary efficacy objective for this study was to evaluate the efficacy of tocilizumab plus SOC compared with placebo plus SOC using the following endpoint: cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

Time to death or the first utilization of mechanical ventilation after Day 1 was planned to be compared between the TCZ arm and the PBO arm using the stratified log-rank test with age group (<=60 years, >60 years) as the stratification factor.

Due to small sample/stratum sizes at ex-US study sites, efficacy analyses were not stratified by country.

*Missing data and censoring*

Any patient, who died prior to requiring invasive mechanical ventilation on or prior to Day 28, was planned to be considered as having an event for the primary endpoint. Time to primary endpoint event was planned to be defined as time from Day 1 to the first occurrence of death or requiring mechanical ventilation by Day 28. Death after day 28 was not planned to be counted as an event.

The following censoring rules were defined in the SAP:

**Table 17 Time to death or requiring mechanical ventilation and censoring status**

| Event | Censor | Date |
|---|---|---|
| Patient with death or requiring mechanical ventilation* recordings on or prior to Day 28 | No | Earlier of date of death and/or first date requiring mechanical ventilation |
| Patient without death and not requiring mechanical ventilation recordings on or prior to Day 28; | | |
| If patient with safety follow-up | Yes | Earlier of the date of Day 28 and the date of last available follow-up** |
| If patient without safety follow-up | Yes | Earlier of the date of Day 28 and the date of last available in-hospital assessment *** |

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO per CRF; ** Follow-up includes (1) safety follow-up per CRF, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

*Multiplicity*

Multiplicity was discussed in the SAP (not in the study protocol as follows):

Along with the primary endpoint (time to death or the first utilization of mechanical ventilation from study medication), key secondary endpoints were planned to be included in the type 1 error control procedure. Following the rejection of null hypothesis of the primary at the alpha=0.05 level, the

family-wise type 1 error was planned to be controlled at alpha=0.05 by means of sequential testing of the key secondary hypotheses in the following order:

- Time to hospital discharge or "ready for discharge" up to Day 28
- Time to improvement in clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status
- Time to clinical failure up to Day 28, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- Mortality rate at Day 28

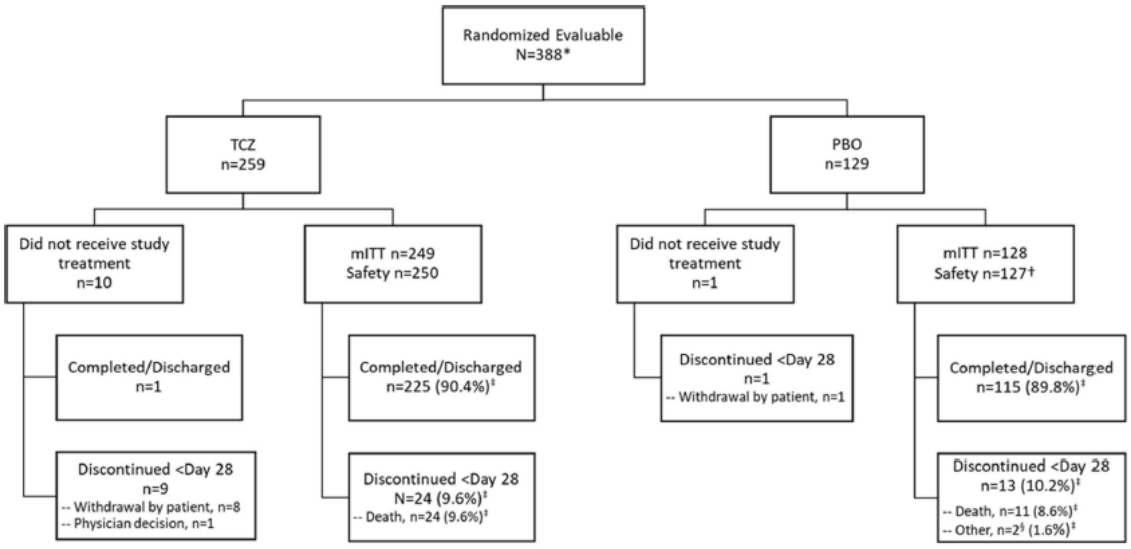
Other secondary endpoint and exploratory efficacy endpoints were planned to be tested at the nominal alpha=0.05 without any multiplicity adjustment.

*Interim analysis*

No interim efficacy analyses were planned.

**Results**

***Participant flow***




mITT=modified-intent-to-treat, which included all randomized patients who received study treatment, PBO=placebo; TCZ=tocilizumab.
*A total of 389 patients were randomized (2:1) to either tocilizumab (8 mg/kg, maximum 800 mg) or placebo plus standard care through permuted-block randomization; one patient was randomized prior to local institutional review board approval of study site. This patient did not receive study drug and no further data was collected for this patient, resulting in 388 evaluable patients.
†One patient randomized to the placebo arm received tocilizumab and was included in the tocilizumab arm in the safety population.
‡Percentages based on mITT population.
§Patients were transferred to other facilities.

**Figure 32 Study ML42528 (EMPACTA) patient disposition at Day 28**

Approximately 80% of the patients were recruited from the United States. One patient was randomized in error and did not receive any study treatment; this patient was considered not evaluable and excluded from all analyses. Of the 388 patients randomized at a 2:1 ratio to the TCZ+SoC arm (259 patients) and the PBO+SoC arm (129 patients), 377 received study treatment.

***Recruitment***

A total of 389 patients hospitalized with COVID-19 associated pneumonia from six countries (United States, Mexico, Kenya, South Africa, Peru, Brazil) were randomized in the study.

***Conduct of the study***

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted.

The original protocol (v 1, 29 April 2020) was amended two times during the study.

***Baseline data***

Baseline demographics were generally balanced between treatment arms (see Table 6). The baseline demographic and disease characteristics were balanced across treatment arms. The majority of patients were male (59.2%) and were enrolled at sites in the US (80.6%), with a median age of 57 years (range 20-95 years). The majority of patients were White (Hispanic and non-Hispanic; 52.8%) and from minority racial and ethnic groups. The largest combined race/ethnic group was Hispanic/Latino (56.0%), followed by Black/African American (14.9%), American Indian/Alaska Native (12.7%), and White (non-Hispanic; 12.7%). Mean body weight and body mass index (BMI) were 89.57 kg and 32.03 kg/m$^2$ respectively, in the TCZ arm, and 94.44 kg and 33.05 kg/m$^2$ respectively, in the PBO arm.

Current or former smokers accounted for 22.9% of patients (57/249) in the TCZ arm and 22.7% of patients (29/128) in the PBO arm. The mean amount of time that patients had smoked was 25.74 years in the TCZ arm (range: 1.0-60.0 years) and 22.94 years in the PBO arm (range: 0.9-60.0 years).

**Table 18 Demographics at baseline (mITT population)**

| | Tocilizumab (N=249) | Placebo (N=128) | All Patients (N=377) |
|---|---|---|---|
| Sex | | | |
| n | 249 | 128 | 377 |
| Male | 150 (60.2%) | 73 (57.0%) | 223 (59.2%) |
| Female | 99 (39.8%) | 55 (43.0%) | 154 (40.8%) |
| Age (yr) | | | |
| n | 249 | 128 | 377 |
| Mean (SD) | 56.0 (14.3) | 55.6 (14.9) | 55.9 (14.4) |
| Median | 57.0 | 56.0 | 57.0 |
| Min, Max | 24, 95 | 20, 89 | 20, 95 |
| Age group 1 | | | |
| n | 249 | 128 | 377 |
| ≤60 | 151 (60.6%) | 76 (59.4%) | 227 (60.2%) |
| >60 | 98 (39.4%) | 52 (40.6%) | 150 (39.8%) |
| Age group 2 | | | |
| n | 249 | 128 | 377 |
| 18 to 64 | 178 (71.5%) | 93 (72.7%) | 271 (71.9%) |
| 65 to 84 | 70 (28.1%) | 33 (25.8%) | 103 (27.3%) |
| ≥85 | 1 (0.4%) | 2 (1.6%) | 3 (0.8%) |

| | Tocilizumab (N=249) | Placebo (N=128) | All Patients (N=377) |
|---|---|---|---|
| Weight (kg) at baseline | | | |
| n | 249 | 128 | 377 |
| Mean (SD) | 89.57 (23.73) | 94.44 (25.95) | 91.22 (24.58) |
| Median | 85.00 | 90.05 | 86.00 |
| Min, Max | 45.4, 171.8 | 44.0, 201.0 | 44.0, 201.0 |
| BMI | | | |
| n | 240 | 122 | 362 |
| Mean (SD) | 32.03 (7.86) | 33.05 (7.18) | 32.38 (7.64) |
| Median | 30.60 | 31.95 | 30.90 |
| Min, Max | 18.4, 66.2 | 17.2, 55.7 | 17.2, 66.2 |
| <30 | 110 (45.8%) | 49 (40.2%) | 159 (43.9%) |
| ≥30 | 130 (54.2%) | 73 (59.8%) | 203 (56.1%) |
| Country group | | | |
| n | 249 | 128 | 377 |
| US | 201 (80.7%) | 103 (80.5%) | 304 (80.6%) |
| ex-US | 48 (19.3%) | 25 (19.5%) | 73 (19.4%) |
| Race | | | |
| n | 249 | 128 | 377 |
| American Indian or Alaska Native | 52 (20.9%) | 25 (19.5%) | 77 (20.4%) |
| Asian | 5 (2.0%) | 1 (0.8%) | 6 (1.6%) |
| Black or African American | 35 (14.1%) | 22 (17.2%) | 57 (15.1%) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (0.8%) | 1 (0.3%) |
| White | 134 (53.8%) | 65 (50.8%) | 199 (52.8%) |
| Multiple | 4 (1.6%) | 2 (1.6%) | 6 (1.6%) |
| Unknown | 19 (7.6%) | 12 (9.4%) | 31 (8.2%) |
| Ethnicity | | | |
| n | 249 | 128 | 377 |
| Hispanic or Latino | 143 (57.4%) | 68 (53.1%) | 211 (56.0%) |
| Not Hispanic or Latino | 106 (42.6%) | 60 (46.9%) | 166 (44.0%) |
| Race/ethnicity combined | | | |
| n | 249 | 128 | 377 |
| Hispanic or Latino | 143 (57.4%) | 68 (53.1%) | 211 (56.0%) |
| American Indian or Alaska Native | 33 (13.3%) | 15 (11.7%) | 48 (12.7%) |
| Black or African American | 35 (14.1%) | 21 (16.4%) | 56 (14.9%) |
| White | 28 (11.2%) | 20 (15.6%) | 48 (12.7%) |
| Other/unknown | 10 (4.0%) | 4 (3.1%) | 14 (3.7%) |

| | Tocilizumab (N=249) | Placebo (N=128) | All Patients (N=377) |
|---|---|---|---|
| Smoking history | | | |
| n | 249 | 128 | 377 |
| Never | 192 (77.1%) | 99 (77.3%) | 291 (77.2%) |
| Current | 16 (6.4%) | 6 (4.7%) | 22 (5.8%) |
| Former | 41 (16.5%) | 23 (18.0%) | 64 (17.0%) |
| Total time smoked (years) | | | |
| n | 37 | 18 | 55 |
| Mean (SD) | 25.74 (18.20) | 22.94 (18.33) | 24.83 (18.13) |
| Median | 20.00 | 20.00 | 20.00 |
| Min, Max | 1.0, 60.0 | 0.9, 60.0 | 0.9, 60.0 |

mITT=modified intent-to-treat; SD=standard deviation.
For Race/Ethnicity combined, other/unknown includes patients who were not of Hispanic or Latino ethnicity and whose race were Asian, Native Hawaiian or other Pacific Islander, multiple, or unknown.

Baseline disease characteristics were balanced between treatment arms (see Table 19). At enrollment, all patients in the mITT population were hospitalized with COVID-19 associated pneumonia and 84.6% of patients were not admitted to an intensive-care unit (ICU) at time of study entry. The mean elapsed time from diagnosis of COVID-19 to baseline was 2.25 days (range: 0-14 days) in the TCZ arm, and 2.13 days (range: 0-12 days) in the PBO arm.

The most frequently reported symptoms at time of diagnosis were Shortness of breath (TCZ arm 74.3%; PBO arm 77.3%), Cough (TCZ arm 72.3%; PBO arm 79.7%), and Fever (TCZ arm 60.6%; PBO arm 67.2%). The mean time from onset of symptoms to study baseline was 7.82 days (range: 0.0-31.0 days) in the TCZ arm, and 8.55 days (range: 0.0-36.0 days) in the PBO arm.

Clinical status was assessed using the 7-category ordinal scale. In the TCZ arm, 24 (9.6%) did not require supplemental oxygen (category 2), 161 (64.7%) required supplemental oxygen (category 3) and, 64 (25.7%) required non-invasive ventilation or high-flow oxygen (category 4). In the PBO arm, 11 (8.6%) did not require supplemental oxygen (category 2), 81 (63.3%) required supplemental oxygen (category 3) and, 36 (28.1%) required non-invasive ventilation or high-flow oxygen (category 4).

Across treatment arms, the majority of patients reported steroid use (72.7%) and antiviral treatment (77.2%) within 7 days of Day 1.

Baseline levels of inflammatory markers (hs-CRP/CRP, D-dimer, ferritin) were elevated in most patients in the TCZ and PBO arms.

- At baseline, 81.9% of patients in the TCZ arm and 86.7% in the PBO arm had elevated concentrations of CRP (defined as CRP >50 mg/L or hs-CRP >3 mg/L).
- Median CRP levels were 124.50 mg/L (range: 2.5-2099.0 mg/L) in the TCZ arm, and 143.40 mg/L (range: 9.0-3776.0 mg/L) in the PBO arm.
- The baseline median D-dimer level (fibrinogen equivalent units [FEU]) was 1.60 yg/mL (range: 0.2-8873.0 yg/mL) in the TCZ arm, versus 1.21 yg/mL (range: 0.2-10384.0 yg/mL) in the PBO arm.
- Median ferritin levels at baseline were 1401.34 pmol/L (range:29.2-38482.1 pmol/L) in the TCZ arm, and 1353.14 pmol/L (range:110.1-122328.9 pmol/L) in the PBO arm.

**Table 19 Disease characteristics at baseline (mITT population)**

| | Tocilizumab (N=249) | Placebo (N=128) | All Patients (N=377) |
|---|---|---|---|
| Ordinal scale for clinical status at Day 1 | | | |
| n | 249 | 128 | 377 |
| 2 | 24 (9.6%) | 11 (8.6%) | 35 (9.3%) |
| 3 | 161 (64.7%) | 81 (63.3%) | 242 (64.2%) |
| 4 | 64 (25.7%) | 36 (28.1%) | 100 (26.5%) |
| Elevated CRP | | | |
| n | 227 | 120 | 347 |
| Yes | 186 (81.9%) | 104 (86.7%) | 290 (83.6%) |
| No | 41 (18.1%) | 16 (13.3%) | 57 (16.4%) |
| CRP levels (mg/L) | | | |
| n | 186 | 99 | 285 |
| Mean (SD) | 149.03 (171.05) | 202.80 (404.92) | 167.71 (276.21) |
| Median | 124.50 | 143.40 | 136.10 |
| Min, Max | 2.5, 2099.0 | 9.0, 3776.0 | 2.5, 3776.0 |
| hs-CRP levels (mg/L) | | | |
| n | 41 | 21 | 62 |
| Mean (SD) | 98.23 (111.36) | 88.46 (75.01) | 94.92 (100.00) |
| Median | 68.25 | 76.40 | 70.85 |
| Min, Max | 0.1, 494.7 | 2.0, 290.7 | 0.1, 494.7 |
| D-dimer (µg/mL FEU) | | | |
| n | 219 | 114 | 333 |
| Mean (SD) | 430.18 (1103.92) | 467.52 (1400.65) | 442.97 (1211.71) |
| Median | 1.60 | 1.21 | 1.50 |
| Min, Max | 0.2, 8873.0 | 0.2, 10384.0 | 0.2, 10384.0 |

| | | | |
|---|---|---|---|
| Ferritin levels (pmol/L) | | | |
| n | 212 | 109 | 321 |
| Mean (SD) | 2309.56 (3446.50) | 3624.50 (12646.06) | 2756.06 (7886.39) |
| Median | 1401.34 | 1353.14 | 1395.39 |
| Min, Max | 29.2, 38482.1 | 110.1, 122328.9 | 29.2, 122328.9 |
| Symptoms at time of COVID-19 diagnosis | | | |
| n | 249 | 128 | 377 |
| Chest pain | 41 (16.5%) | 20 (15.6%) | 61 (16.2%) |
| Chills | 69 (27.7%) | 33 (25.8%) | 102 (27.1%) |
| Confusion or inability to arouse | 7 (2.8%) | 2 (1.6%) | 9 (2.4%) |
| Cough | 180 (72.3%) | 102 (79.7%) | 282 (74.8%) |
| Fatigue | 60 (24.1%) | 31 (24.2%) | 91 (24.1%) |
| Fever | 151 (60.6%) | 86 (67.2%) | 237 (62.9%) |
| GI symptoms | 78 (31.3%) | 44 (34.4%) | 122 (32.4%) |
| Headache | 57 (22.9%) | 36 (28.1%) | 93 (24.7%) |
| Loss of taste or smell | 30 (12.0%) | 16 (12.5%) | 46 (12.2%) |
| Muscle pain | 51 (20.5%) | 24 (18.8%) | 75 (19.9%) |
| Repeated shaking with chills | 10 (4.0%) | 7 (5.5%) | 17 (4.5%) |
| Shortness of breath | 185 (74.3%) | 99 (77.3%) | 284 (75.3%) |
| Sore throat | 33 (13.3%) | 15 (11.7%) | 48 (12.7%) |
| Other | 84 (33.7%) | 38 (29.7%) | 122 (32.4%) |
| Days from first COVID-19 symptom at baseline | | | |
| n | 248 | 127 | 375 |
| Mean (SD) | 7.82 (4.36) | 8.55 (6.07) | 8.07 (5.01) |
| Median | 8.00 | 8.00 | 8.00 |
| Min, Max | 0.0, 31.0 | 0.0, 36.0 | 0.0, 36.0 |
| COVID-19 diagnosis based on PCR of specimen type | | | |
| n | 249 | 128 | 377 |
| Nasopharyngeal swab | 242 (97.2%) | 125 (97.7%) | 367 (97.3%) |
| Nasopharyngeal wash | 7 (2.8%) | 2 (1.6%) | 9 (2.4%) |
| Other bodily fluid | 0 | 1 (0.8%) | 1 (0.3%) |
| Days from COVID-19 diagnosis | | | |
| n | 249 | 128 | 377 |
| Mean (SD) | 2.25 (2.44) | 2.13 (2.24) | 2.21 (2.37) |
| Median | 1.00 | 2.00 | 2.00 |
| Min, Max | 0.0, 14.0 | 0.0, 12.0 | 0.0, 14.0 |

| | | | |
|---|---|---|---|
| PCR result at screening | | | |
| n | 249 | 128 | 377 |
| Positive | 249 (100%) | 128 (100%) | 377 (100%) |
| Negative | 0 | 0 | 0 |
| ICU admission status at baseline | | | |
| n | 249 | 128 | 377 |
| Yes | 36 (14.5%) | 22 (17.2%) | 58 (15.4%) |
| No | 213 (85.5%) | 106 (82.8%) | 319 (84.6%) |
| Steroid use (within 7 days of Day 1 or concomitant) | | | |
| n | 249 | 128 | 377 |
| Yes | 200 (80.3%) | 112 (87.5%) | 312 (82.8%) |
| No | 49 (19.7%) | 16 (12.5%) | 65 (17.2%) |
| Steroid use (within 7 days of Day 1) | | | |
| n | 249 | 128 | 377 |
| Yes | 183 (73.5%) | 91 (71.1%) | 274 (72.7%) |
| No | 66 (26.5%) | 37 (28.9%) | 103 (27.3%) |
| Anti-viral treatment use (within 7 days of Day 1 or concomitant) | | | |
| n | 249 | 128 | 377 |
| Yes | 196 (78.7%) | 101 (78.9%) | 297 (78.8%) |
| No | 53 (21.3%) | 27 (21.1%) | 80 (21.2%) |
| Anti-viral treatment use (within 7 days of Day 1) | | | |
| n | 249 | 128 | 377 |
| Yes | 192 (77.1%) | 99 (77.3%) | 291 (77.2%) |
| No | 57 (22.9%) | 29 (22.7%) | 86 (22.8%) |

CRP=C-reactive protein; ECMO=extracorporeal membrane oxygenation; FEU=fibrinogen equivalent units; ICU=intensive care unit; mITT=modified intent-to-treat; PCR=polymerase chain reaction; SD=standard deviation.

Ordinal scale for clinical status: 1=Discharged (or ready for discharge); 2=Non-ICU hospital ward (or ready for hospital ward) not requiring supplemental oxygen; 3=Non-ICU hospital ward (or ready for hospital ward) requiring supplemental oxygen; 4=ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5=ICU, requiring intubation and mechanical ventilation; 6=ICU, requiring ECMO or mechanical ventilation and additional organ support; 7=Death. Elevated CRP levels are patients with CRP >50 mg/L or hs-CRP >3 mg/L at baseline. Steroid use refers to systemic steroids.

***Numbers analysed***

The analysis populations were as follows:

- Modified intent-to treat (mITT) population: 377 patients (249 in TCZ arm and 128 in PBO arm)
- Safety-evaluable population: 377 patients (250 in TCZ arm and 127 in PBO arm). One patient in the PBO arm received tocilizumab and was included in the TCZ.

***Outcomes and estimation***

**Primary Efficacy Endpoint**

Time to Death or Mechanical Ventilation

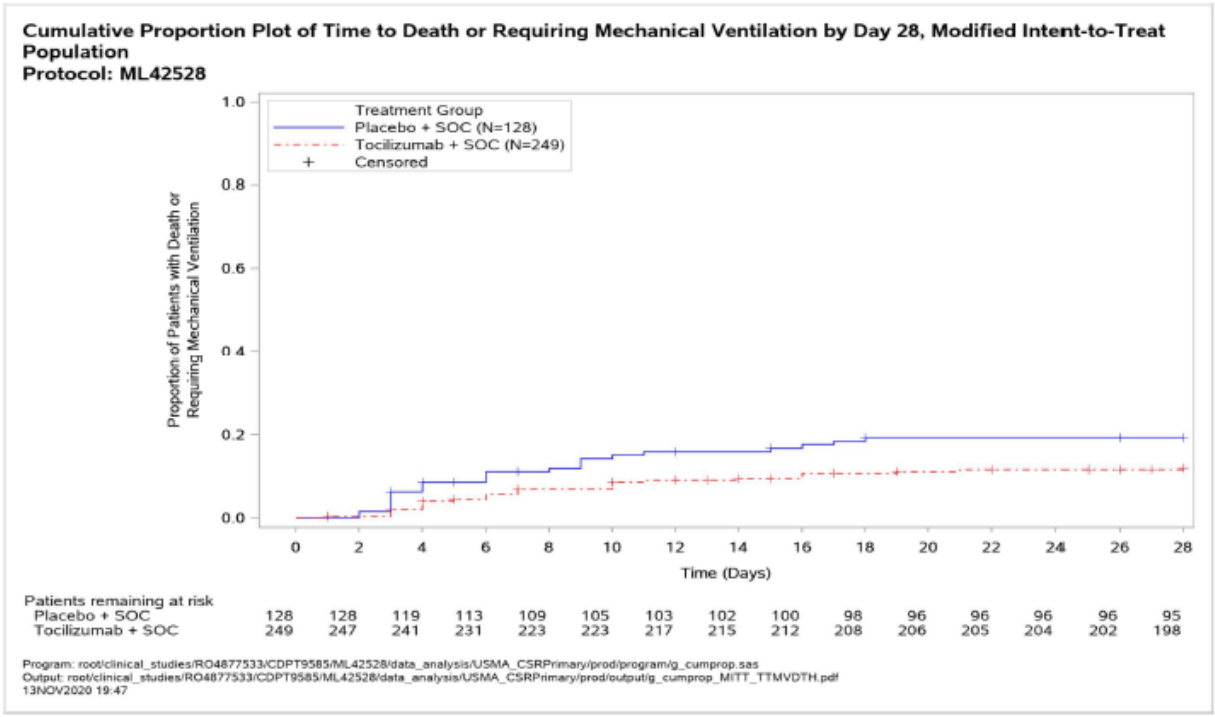
The primary efficacy endpoint was met; patients with COVID-19 associated pneumonia who received TCZ+SoC were 44% less likely to progress to mechanical ventilation or death compared to patients who received PBO+SoC (log-rank p value=0.0360; HR [95% CI] = 0.56 [0.33, 0.97]). The cumulative proportion of patients who required mechanical ventilation or died by Day 28 estimated by the Kaplan-

Meier method was 12.0% (95% CI: 8.52% to 16.86%) for TCZ+SoC and 19.3% (95% CI: 13.34% to 27.36%) for PBO+SoC.

**Table 20 Analysis of time to death or requiring mechanical ventilation by Day 28 (mITT population)**

| | Tocilizumab (N=249) | Placebo (N=128) |
|---|---|---|
| Patients without event (%) | 220 (88.4%) | 104 (81.3%) |
| Patients with event (%) | 29 (11.6%) | 24 (18.8%) |
| Earliest contributing event | | |
| Death (%) | 9 (3.6%) | 8 (6.3%) |
| Mechanical ventilation (%) | 20 (8.0%) | 16 (12.5%) |
| Time to event (days) | | |
| Median | NE | NE |
| 95% CI | NE | NE |
| Stratified analysis | | |
| p-value (log-rank) | 0.0360 | |
| Hazard ratio (ref=PBO) | 0.56 | |
| 95% CI | (0.33, 0.97) | |
| 7 days | | |
| Cumulative proportion of event | 6.94% | 11.04% |
| 95% CI | (4.37, 10.92) | (6.69, 17.93) |
| 14 days | | |
| Cumulative proportion of event | 9.45% | 15.94% |
| 95% CI | (6.38, 13.88) | (10.59, 23.61) |
| 21 days | | |
| Cumulative proportion of event | 11.59% | 19.26% |
| 95% CI | (8.15, 16.35) | (13.34, 27.36) |
| 28 days | | |
| Cumulative proportion of event | 12.04% | 19.26% |
| 95% CI | (8.52, 16.86) | (13.34, 27.36) |

CI=confidence interval; K-M=Kaplan-Meier; mITT=modified intent-to-treat; PBO=placebo.
Time to event is defined as the time (in days) from Day 1 till the date of first documented death or requiring mechanical ventilation due to any cause on or prior to Day 28, whichever occurs first. Patients without any events on or prior to Day 28 are censored at the earlier date of Day 28 and date of last available follow-up. Median time to event is estimated by the K-M method; 95% CI for median is computed using Brookmeyer and Crowley method. Stratified log-rank test and Cox proportional hazards model includes stratification factor at randomization (age [≤60 years, >60 years]). Hazard ratio <1 favors tocilizumab over placebo.




mITT=modified intent to treat; SOC=standard of care.

**Figure 33 Cumulative proportion plot of time to death or requiring mechanical ventilation by Day 28 (mITT population)**

**Key Secondary Efficacy Endpoints**

Four secondary endpoints were compared between the TCZ+SoC and the placebo+SOC arms in the pre-specified hierarchical testing order. Time to discharge/ready for discharge, the first secondary endpoint in the pre-defined hierarchical testing order, was not statistically significantly different between the treatment arms; therefore, all p values for other secondary endpoints are nominal.

Time to Hospital Discharge or "ready for discharge"

Median (95% CI) time to hospital discharge/ready for discharge to Day 28 was 6.0 days (6.0 to 7.0) for TCZ+SoC and 7.5 days (7.0 to 9.0) for PBO+SoC (log-rank p value=0.2417; HR=1.16 [95% CI: 0.91 to 1.48]).

Time to Improvement in Clinical Ordinal Status

Median (95% CI) time to improvement in ordinal clinical status to Day 28 relative to baseline was 6.0 days (6.0 to 7.0) for TCZ+SoC and 7.0 days (6.0 to 9.0) for PBO+SoC (log-rank p value=0.2547; HR=1.15 [95% CI: 0.90 to 1.48]).

Time to Clinical Failure

Median (95% CI) time to clinical failure to Day 28 was not evaluable in either group (log-rank p value=0.0223; HR = 0.55 [95% CI: 0.33 to 0.93]).

Mortality Rate at Day 28 and Day 60

Mortality rate by Day 28 was 10.4% (95% CI: 7.2%, 14.9%) in the TCZ+SoC arm compared with 8.6% (95% CI: 4.9%, 14.7%) in the PBO+SoC arm. The weighted difference in mortality between the two treatment arms (TCZ arm – PBO arm) was 2.0% (p-value=0.5146; [95% CI: –5.2%, 7.8%]).

The mortality rate up to Day 60 (post-hoc analysis) was 11.2% for the TCZ+SoC arm versus 10.9% for the PBO+SoC arm (t_ef_inc_cmh_d60_MITT). The weighted difference in mortality between the two treatment arms (TCZ arm – PBO arm) was 0.5% (p-value=0.8789; [95% CI: –6.9%, 6.8%]).

**Subgroup Analyses by Baseline Standard of Care Treatment**

Post-hoc subgroup analyses of time to mechanical ventilation (MV) or death and time to hospital discharge/ready for discharge by baseline SoC treatment were conducted to estimate hazard ratios and their associated 95% CIs.

Baseline treatment with systemic corticosteroids (defined as treatment any time from Day -7 through Day 1) was associated with a lower hazard ratio for time to MV or death up to Day 28 for TCZ compared to PBO (HR=0.79 [95% CI: 0.42, 1.48]).

Baseline treatment with systemic corticosteroids was not associated with a difference in treatment effect of TCZ compared to PBO for time to hospital discharge/ready for discharge up to Day 28. Subgroup analyses showed a HR close to 1 for time to hospital discharge/ready for discharge at Day 28 in patients treated with systemic corticosteroids at baseline (HR=1.15 [95% CI: 0.86, 1.53]) and at baseline.

### *2.4.2.4. REMDACTA - Phase III, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir plus Tocilizumab Compared With Remdesivir plus Placebo in Hospitalized Patients With Severe COVID-19 Pneumonia.*

#### Methods

REMDACTA was a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with RDV compared with matching placebo in combination with RDV in hospitalized adult patients with severe COVID-19 pneumonia.

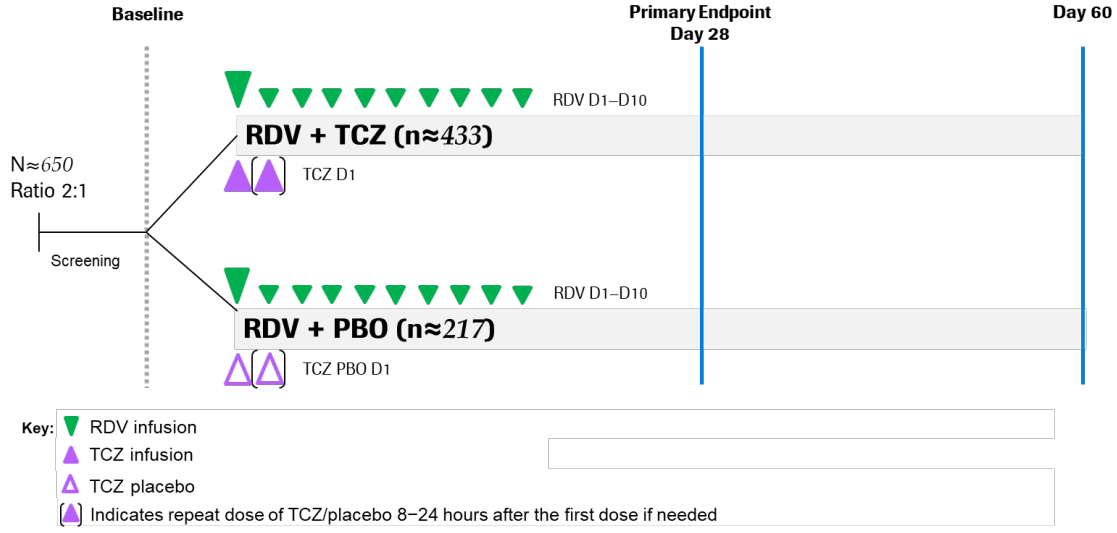



**Figure 34 Study design REMDACTA**

***Study participants***

Patients (≥ 12 years of age) with confirmed SARS-CoV-2 (COVID-19*)* infection based on a positive PCR result of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and pneumonia confirmed by radiography were enrolled. At the time of enrollment, patients required > 6 L/min

supplemental oxygen to maintain oxygen saturation ($SpO_2$) > 93% despite being on SoC, which could include, low dose steroids, and supportive care. Patients with severe renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min) were excluded from the study. Patients were also excluded if progression to death was imminent and inevitable within 24 hours as determined by the treating physician or they had any suspected active bacterial, fungal, or viral infection other than COVID-19.

***Treatments***

Patients who fulfilled the study entry criteria were randomized at a 2:1 ratio to receive blinded treatment of either tocilizumab plus remdesivir (TCZ + RDV) or a matching placebo plus remedesivir (PBO+ RDV), respectively. Study treatment was given in combination with standard supportive care.

For both arms, if the patient had a sustained fever or clinically significant worsening of signs or symptoms, one additional infusion of blinded TCZ/PBO could be given 8-24 hours after the first TCZ/PBO infusion. The second dose of blinded TCZ/PBO was not given if the patient developed an adverse event or laboratory abnormalities that warranted discontinuation of TCZ/PBO. Patients assigned to the TCZ+RDV arm received RDV as a 200 mg IV loading dose followed by one infusion of TCZ 8 mg/kg (maximum dose of 800 mg) on Day 1. Patients were subsequently administered a 100 mg once daily IV maintenance dose of RDV from Days 2-10. RDV was discontinued at the time of hospital discharge even if 10 days of RDV dosing had not been completed.

Patients assigned to the PBO+RDV arm received RDV as a 200 mg IV loading dose followed by one infusion of PBO on Day 1. Patients were subsequently administered a 100 mg once daily IV maintenance dose of RDV from Days 2-10. RDV was discontinued at the time of hospital discharge even if 10 days of RDV dosing had not been completed.

***Objectives/Outcomes/endpoints***

**Table 21 Objectives REMDACTA**

| Objectives | Endpoints | Statistical Test |
|---|---|---|
| **Primary Efficacy Objectives** | | |
| To evaluate the efficacy of the TCZ+RDV arm compared with the PBO+RDV arm for the treatment of severe COVID 19 pneumonia | Time from randomization to hospital discharge or "ready for discharge" up to Day 28<br>Hospital discharge or "ready for discharge" is defined as a score of 1 on the 7-category ordinal scale. | Stratified log-rank test |
| **Secondary Efficacy Objectives** | | |
| To evaluate the efficacy of the TCZ+RDV arm compared with the PBO+RDV arm for the treatment of severe COVID 19 pneumonia | Time to mechanical ventilation or death up to Day 28, defined as time from randomization to first occurrence of mechanical ventilation or death (whichever occurs first) | Stratified log-rank test |
| | Time to improvement of at least 2 categories relative to baseline, on a 7-category ordinal scale of clinical status up to Day 28 | Stratified log-rank test |
| | Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Days 7, 14, 21, 28, and 60 as follow-up | Ordinal logistic regression analysis |
| | Proportion of patients requiring initiation of mechanical ventilation post-baseline up to Day 28 and Day 60 (patients who do not require mechanical ventilation at baseline) | Cochran-Mantel-Haenszel test |
| | Proportion of patients who are alive and free of respiratory failure at Day 28 and Day 60 (patients who require mechanical ventilation at baseline) | Cochran-Mantel-Haenszel test |
| | Duration of mechanical ventilation (patients who require mechanical ventilation at baseline) up to Day 28 | Linear regression analysis with Huber White sandwich estimates for the standard errors |
| | Time to death up to Day 28 and Day 60 | Stratified log-rank test |
| | Mortality on Days 14, 28, and 60 (proportions at specified time points) | Cochran-Mantel-Haenszel test |
| | Time to recovery up to Day 28, defined as time from randomization to the time when a category of 2 on the 7-category ordinal scale, non ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen, or better is observed | Stratified log-rank test |
| | Proportion of patients discharged or "ready to discharge" up to Day 28 | Cochran-Mantel-Haenszel test |
| | Proportion of patients who require initiation of mechanical ventilation post-baseline or die up to Day 28 | Cochran-Mantel-Haenszel test |

***Sample size***

The primary endpoint, time to discharge or "ready for discharge", was event driven. Based on the severe cohort receiving 10 days of RDV in Gilead's SIMPLE trial (Study GS US 540-5773), the median time to discharge or "ready for discharge" was 11 days. Assuming a median time to discharge or "ready for discharge" of 11 days in the PBO+RDV arm, a hazard ratio of 1.3 or an approximately 2.5-day reduction in median time for TC+RDV vs PBO+RDV, and a 2:1 randomization to TCZ+RDV or PBO+RDV, it was planned that approximately 650 patients were needed to accrue approximately 520 events to achieve approximately 80% power. It was planned, that while the study was being conducted, further sample size adjustments could be considered based on external information, and the sample size could be increased up to a maximum of approximately 800 randomized patients if fewer events than expected were observed or further shifts in SOC warranted reassessing sample size assumptions. Initially, n=450 patients were planned to be recruited. This was increased two times, first to 500 patients in protocol version 4, then to 650 patients in protocol version 6. These changes were motivated by results from COVACTA, and by considerations on clinical relevance of the effect.

***Randomisation***

Patients were planned to be randomly assigned via IxRS, an Interactive Web Response System, using a permuted block randomization method to one of two treatment arms at a 2:1 ratio. The randomization was planned to be stratified by geographic region (North America, Europe, and other) and a 2-level severity factor based on the 7-category ordinal scale of clinical status at screening (categories 4–5 and category 6). The proportion of patients in category 6 of the ordinal scale (mechanical ventilation and additional organ support or ECMO) was planned to be capped at 25% of the overall study population.

***Blinding (masking)***

Study site personnel and patients were planned to be blinded to TCZ/PBO treatment assignment during the study as were the Sponsor and its agents, with the exception of individuals who required access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles included the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, unblinded pharmacist (if required), IxRS service provider, and DMC members and support staff as specified in the DMC Charter who could be Roche employees but independent of the study team.

***Statistical methods***

*Analysis set & stratification*

All efficacy analyses were planned to be based on the mITT population, if not otherwise specified. The mITT population was defined as all patients randomized in the study who received any amount of TCZ or PBO, with patients grouped according to the treatment assignment at randomization (TCZ+RDV or PBO+RDV).

*Primary endpoint & analysis model*

The primary efficacy objective for this study was to evaluate the efficacy of the TCZ+RDV arm compared with the PBO+RDV arm for the treatment of severe COVID-19 pneumonia on the basis of the endpoint: "Time from randomization to hospital discharge or "ready for discharge" up to Day 28." It was planned, that Patients met the endpoint at the time of discharge or the time that they achieved

category 1 of the 7-category ordinal scale, provided that they did not have any further ordinal scale assessments > category 1 on or prior to Day 28, they were not rehospitalized on or prior to Day 28, and they did not die on or prior to Day 28.

In the SAP it was later specified, that Patients who did not meet the event at the point of discharge or category 1 due to rehospitalization or ordinal scale assessments > category 1 were planned to be still eligible to meet the event at a later time provided the above conditions were met.

Furthermore, Patients who died by Day 28, regardless of discharge and ordinal scale category prior to death, and patients who remained hospitalized at Day 28 with an ordinal scale category > 1 were planned to be not considered as having met the endpoint.

The estimand attributes were discussed in the SAP (not in the protocol) as follows:

- Population: Patients with severe COVID-19 pneumonia as per the inclusion/exclusion criteria specified in the protocol (mITT)
- Intercurrent events: Events that led to study withdrawal or loss to follow-up. Strategy to address intercurrent events: Hypothetical strategy, i.e., patients were censored at time of their last ordinal scale assessment, unless they died on or prior to Day 28.
- Summary measures:

  a) The hazard ratio (95% confidence interval [CI])

  b) Kaplan-Meier plot

  c) Cumulative incidence function, i.e., the cumulative probability of being discharged or "ready to discharge" over the 28 day follow-up period. The CIF of the competing event of death prior to discharge was also summarized.

  d) Median event time in each treatment arm (95% CI)

Intercurrent events, such as events leading to loss to follow-up or discontinuation for any reason prior to achieving the event or patients who do not have the event, were planned according to the SAP to be accounted for through rules, as described in the SAP:

**Table 22 Time to hospital discharge or "ready for discharge" censoring rules**

| Event | Censor | Date and Time |
|---|---|---|
| Death | Yes | Day 28 |
| Withdrawal or lost to follow-up for any reason prior to discharge or "ready for discharge" criterion met (no event or death recorded including post-withdrawal or lost to follow-up) | Yes | last recorded ordinal scale assessment |
| Not discharged or "ready for discharge" | Yes | Day 28 |

In the study protocol it was planned to compare the distribution of time from randomization to hospital discharge (or "ready for discharge") of the remdesivir plus tocilizumab arm with the remdesivir plus placebo arm up to Day 28 "using an appropriate method for comparing censored event distributions such as the Cox model". Patients discharged after Day 28 were planned to be administratively censored. Furthermore it was planned to present Kaplan-Meier and cumulative incidence plots as well as median time to discharge (or "ready for discharge"), with 95% confidence intervals for the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm.

In the SAP this was later further specified in terms of using the stratified log-rank test at a two-sided 5% significance level with region (North America, Europe, Other) and baseline ordinal score (4-5, 6)

included as the stratification factors. Additionally, it was further specified in the SAP, that the treatment groups were planned to be compared descriptively using a Cox proportional hazards model adjusted for the stratification factors of baseline ordinal score (4-5 or 6) and region (North America, Europe or Other).

*Multiplicity*

Multiplicity was discussed in the SAP (not in the study protocol) as follows:

The following key secondary endpoints were planned to be tested in a simple gated hierarchy starting with the primary endpoint. The hierarchy was:

- Time from randomization to hospital discharge or "ready for discharge" up to Day 28
- Time to mechanical ventilation or death up to Day 28
- Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 14
- Time to death up to Day 28

Each endpoint was planned to be tested with a fixed two-sided 0.05 error rate if the previous endpoint reached significance, starting with the primary.

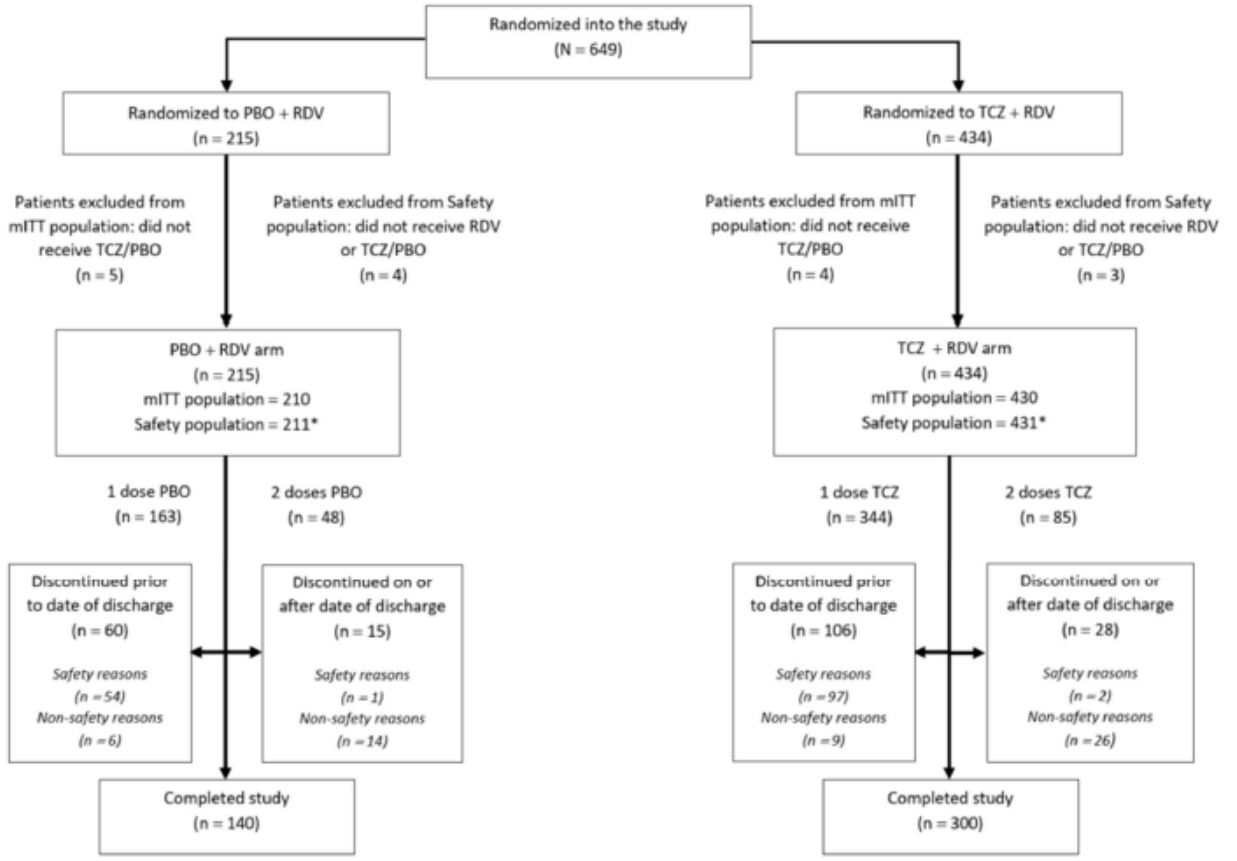
Other secondary endpoint and exploratory efficacy endpoints were planned to be tested at the nominal alpha=0.05 without any multiplicity adjustment.

*Interim analysis*

It was originally planned that there will be up to three optional interim analyses. The first interim analysis was planned to occur after approximately one-third to one-half of the patients would have been assessed for the primary endpoint on Day 28, depending on enrolment rate. It was planned that there will be up to two additional unplanned interim analyses in case of major changes to the study design following the first interim analysis. It was planned that questions to be addressed at the interim analysis might include futility as well as potential efficacy. Later in the SAP it was stated that no interim analysis for efficacy have been conducted during the course of the trial.

## Results

### *Participant flow*




*Patients grouped as randomized. Two patients randomized to the TCZ+RDV arm were included in the PBO+RDV arm for safety analysis: one patient only received RDV, while the other patient received PBO in error (RDV was given). The safety-evaluable analysis population, grouped by treatment received, was thus comprised of 213 patients in the PBO+RDV arm and 429 patients in the TCZ+RDV arm

**Figure 35 WA42511 Summary of patients disposition**

Of the 649 patients randomized at a 2:1 ratio to the TCZ+RDV arm (434 patients) and the PBO+RDV arm (215 patients), 640 received both RDV and TCZ/PBO. A total of 336 patients (77.4%) in the TCZ + RDV arm and 160 patients (74.4%) in the PBO+RDV arm completed the study to the Day 28 timepoint. The most common reason for discontinuation was death (78 [18.0%] in the TCZ+RDV arm and 42 patients [19.5%] in the PBO+RDV arm).

### *Recruitment*

A total of 649 patients were enrolled at 53 centers across four countries (United States, Russian Federation, Brazil and Spain). Approximately 67% of the patients were recruited from the United States.

***Conduct of the study***

Version 1.0 of the protocol was approved on 27 April 2020. It was amended to Version 2.0 on 21 May 2020, to include the main following changes:

- Add description of the EUA permitting use of RDV as treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease
- Amending the protocol throughout to include only the TCZ+RDV and the PBO+RDV arms
- Adjustment of inclusion criteria to include patients aged 12 years and older along with reference to an assent form
- Update of inclusion criteria for patients receiving supplemental oxygen
- Amendment of exclusion criteria to remove prolonged mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or evidence of MOF, and to add low body weight
- Addition of lopinavir/ritonavir to the list of prohibited therapies
- Addition of coagulation samples to the list of samples for laboratory analysis

Version 3.0, approved on 1 July 2020, introduced the main following changes:

- Clarification that patients previously treated with RDV for COVID-19 were ineligible for the study

Version 4 of the protocol was approved on 21 September 2020 to include the main following changes:

- The primary efficacy endpoint of the study was changed on the basis of results from Study WA42380 (COVACTA) to "Time from randomization to hospital discharge or ready for discharge," which previously was a secondary study endpoint. The previous primary endpoint "Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 28" was made a secondary endpoint.
- The sample size of the study was changed from "450 patients up to 800 patients'' to "500 patients up to 800 patients.'' To accommodate the change in sample size, the total length of the study was increased by 2 months.
- An exclusion criterion was updated to allow patients who had received up to two doses of RDV prior to enrollment. Patients who received RDV prior to randomization will not exceed 10 days of dosing and will only receive the maintenance dose.

Version 5.0 of the protocol was approved on 10 December 2020. Updates included the main following changes:

- The wording of the primary endpoint was changed from "time from randomization" to "time from administration of TCZ", as this aligns better with the definition of the mITT population (all patients who received TCZ/PBO) used for the efficacy analyses. The definition of hospital discharge or "ready for discharge" was added for clarification.

Version 6.0 of the protocol was approved on 22 February 2021 in response to health authority feedback. These changes were related to the planned data analyses and did not affect the Schedule of Activities or data collected in the study. Main updates included the following:

- The derivation of the primary endpoint was updated
- Two additional secondary endpoints were added

- Proportion of patients discharged or "ready for discharge" up to Day 28
- Proportion of patients who require initiation of mechanical ventilation post-baseline or die up to Day 28 and up to Day 60
- The definition of the mITT population was clarified as all patients randomized in the study who received any amount of TCZ/PBO
- Time to event endpoints were changed from "time from administration of TCZ/placebo" to "time from randomization"
- Analysis timepoints were defined for all efficacy endpoints
- It was clarified that SARS-CoV-2 viral load is not limited to respiratory samples and will also be analyzed in serum samples

***Baseline data***

The treatment arms were generally balanced with respect to demographic characteristics in the mITT population. The median age was 61.0 years (range: 20–93 years) in the TCZ+RDV arm and 59.0 years (range: 21–86 years) in the PBO+RDV arm. The majority of patients were male (61.9% in the TCZ+RDV arm and 66.2% in the PBO+RDV arm, respectively) and White (64.9% and 71.4%, respectively). Of note, there were minor imbalances in ethnicity between the treatment arms: 58.1% of patients in the PBO+RDV arm were Hispanic or Latino versus 48.4% in the TCZ+RDV arm.

The baseline disease characteristics were generally comparable across treatment arms in the mITT population. A slightly higher proportion of patients were on mechanical ventilation at baseline in the TCZ+RDV arm compared with the PBO+RDV arm (13.7% and 10.5%, respectively). At baseline, similar proportions of patients in the mITT population were in ordinal scale category 3 (required supplemental low flow oxygen; 6.7% in TCZ+RDV arm and 6.2% in the PBO+RDV arm), and category 6 (on invasive mechanical ventilation and additional organ support) 6.0% and 6.2%, respectively. The proportion of patients in category 4 was slightly lower in the TCZ+RDV arm compared with the PBO+RDV arm (required high-flow oxygen or non-invasive ventilation; 78.1% and 83.3%, respectively), while the proportion of patients in category 5 was slightly higher (on invasive mechanical ventilation without additional organ support; 9.1% and 4.3%, respectively).

The median NEWS2 score was 7.0 in the TCZ+RDV arm and 6.0 in the PBO+RDV arm. The median time from first COVID-19 symptom to baseline on Day 1 was 8.0 days in both arms. Median ferritin levels were 2.09 pmol/mL in the TCZ+SoC arm and 2.27 pmol/mL in the PBO+SoC arm. C-reactive protein (CRP) levels per the central laboratory were also similar at baseline: mean levels of 113.78 mg/L in the TCZ+RDV arm and 115.9 mg/L in the PBO+RDV arm.

At baseline, 83.3% patients in the TCZ+RDV arm and 86.2% patients in the PBO+RDV arm received systemic corticosteroids. As per protocol, patients could have received up to 2 doses of RDV prior to randomization. Nineteen point three percent (19.3%) of patients in the TCZ+RDV arm and 19.0% of patients in the PBO+RDV arm had been treated with RDV prior to randomization. For the patients previously treated with RDV, the median number of days of treatment prior to randomization was 1.00 (range: 0–2.0 days) in the TCZ+RDV arm and 2.00 (range: 0–2.0 days) in the PBO+RDV arm.

The majority of patients in the mITT population reported at least one pre-existing comorbidity at baseline (80.9% in the TCZ+RDV arm and 79.5% in the PBO+RDV arm), with the most common comorbidities being hypertension (TCZ+RDV: 62.1% and PBO+RDV: 61.0%), diabetes (TCZ+RDV: 40.0% and PBO+RDV: 38.6%), obesity (TCZ+RDV: 26.5% and PBO+RDV: 28.1%), and cardiovascular impairment (TCZ+RDV: 23.5% and PBO+RDV: 20.5%).

**Table 23 Demographics at baseline, mITT population**

Demographics at Baseline, Modified Intent-to-Treat Population
Protocol: WA42511
CCOD: 1FEB2021 , SNAPSHOT :1MARCH2021

| | PBO + RDV (N=210) | TCZ + RDV (N=430) | All Patients (N=640) |
|---|---|---|---|
| **Sex** | | | |
| n | 210 | 430 | 640 |
| Male | 139 (66.2%) | 266 (61.9%) | 405 (63.3%) |
| Female | 71 (33.8%) | 164 (38.1%) | 235 (36.7%) |
| **Age (yr)** | | | |
| n | 210 | 430 | 640 |
| Mean (SD) | 58.2 (13.3) | 60.1 (13.3) | 59.4 (13.3) |
| Median | 59.0 | 61.0 | 60.0 |
| Min - Max | 21 - 86 | 20 - 93 | 20 - 93 |
| **Age group (yr)** | | | |
| n | 210 | 430 | 640 |
| 18-64 | 138 (65.7%) | 257 (59.8%) | 395 (61.7%) |
| 65-84 | 70 (33.3%) | 165 (38.4%) | 235 (36.7%) |
| >=85 | 2 ( 1.0%) | 8 ( 1.9%) | 10 ( 1.6%) |
| **Ethnicity** | | | |
| n | 210 | 430 | 640 |
| Hispanic or Latino | 122 (58.1%) | 208 (48.4%) | 330 (51.6%) |
| Not Hispanic or Latino | 86 (41.0%) | 207 (48.1%) | 293 (45.8%) |
| Not Stated | 1 ( 0.5%) | 10 ( 2.3%) | 11 ( 1.7%) |
| Unknown | 1 ( 0.5%) | 5 ( 1.2%) | 6 ( 0.9%) |
| **Race** | | | |
| n | 210 | 430 | 640 |
| American Indian or Alaska Native | 4 ( 1.9%) | 4 ( 0.9%) | 8 ( 1.3%) |
| Asian | 5 ( 2.4%) | 17 ( 4.0%) | 22 ( 3.4%) |
| Black or African American | 19 ( 9.0%) | 51 (11.9%) | 70 (10.9%) |
| Native Hawaiian or other Pacific Islander | 3 ( 1.4%) | 7 ( 1.6%) | 10 ( 1.6%) |
| White | 150 (71.4%) | 279 (64.9%) | 429 (67.0%) |
| Multiple | 2 ( 1.0%) | 9 ( 2.1%) | 11 ( 1.7%) |
| Unknown | 27 (12.9%) | 63 (14.7%) | 90 (14.1%) |
| **Geographic Region (a)** | | | |
| n | 210 | 430 | 640 |
| Europe | 4 ( 1.9%) | 9 ( 2.1%) | 13 ( 2.0%) |
| North America | 138 (65.7%) | 288 (67.0%) | 426 (66.6%) |
| Other | 68 (32.4%) | 133 (30.9%) | 201 (31.4%) |

(a) as listed in IxRS. "Europe" includes Spain, "North America" includes United States of America, "Other" includes Russia and Brazil.

Program: root/clinical_studies/RO4877533/CDT30169/WA42511/data_analysis/SREP_CCOD/prod/program/t_dm.sas
Output: root/clinical_studies/RO4877533/CDT30169/WA42511/data_analysis/SREP_CCOD/prod/output/t_dm_MITT_01FEB2021_42511.out

**Table 24 Disease characteristics at baseline, mITT population**

| Baseline Characteristics | PBO+RDV (n=210) | TCZ+RDV (n=430) | All Patients (n=640) |
|---|---|---|---|
| Baseline Weight (kg) | | | |
| n | 210 | 430 | 640 |
| Mean (SD) | 96.38 (25.27) | 94.42 (26.45) | 95.06 (26.06) |
| Median | 90.0 | 90.0 | 90.0 |
| Min–Max | 50.0–206.0 | 46.7–279.9 | 46.7–279.9 |
| Smoking History | | | |
| n | 210 | 427 | 637 |
| Current | 8 (3.8%) | 15 (3.5%) | 23 (3.6%) |
| Former | 39 (18.6%) | 95 (22.2%) | 134 (21.0%) |
| Never | 163 (77.6%) | 317 (74.2%) | 480 (75.4%) |
| NEWS2 Score [a] | | | |
| n | 202 | 417 | 619 |
| Mean (SD) | 6.28 (2.40) | 6.47 (2.32) | 6.41 (2.35) |
| Median | 6.00 | 6.00 | 6.00 |
| Min–Max | 2.0–15.0 | 0.0–13.0 | 0.0–15.0 |
| NEWS2 Score (complete assessments) [b] | | | |
| n | 196 | 405 | 601 |
| Mean (SD) | 6.40 (2.44) | 6.54 (2.29) | 6.49 (2.34) |
| Median | 6.00 | 7.00 | 6.00 |
| Min–Max | 2.0–15.0 | 2.0–13.0 | 2.0–15.0 |
| Ordinal Scale for Clinical Status [c] | | | |
| n | 210 | 430 | 640 |
| 1 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 |
| 3 | 13 (6.2%) | 29 (6.7%) | 42 (6.6%) |
| 4 | 175 (83.3%) | 336 (78.1%) | 511 (79.8%) |
| 5 | 9 (4.3%) | 39 (9.1%) | 48 (7.5%) |
| 6 | 13 (6.2%) | 26 (6.0%) | 39 (6.1%) |
| 7 | 0 | 0 | 0 |
| Ferritin Levels (Central labs; pmol/mL)* | | | |
| n | 210 | 422 | 632 |

| | | | |
|---|---|---|---|
| Mean (SD) | 2.85 (2.22) | 2.84 (2.63) | 2.84 (2.50) |
| Median | 2.27 | 2.09 | 2.13 |
| Min–Max | 0.1–13.7 | 0.2–30.8 | 0.1–30.8 |
| Days on Mechanical Ventilation Prior to Randomization** | | | |
| n | 22 | 63 | 85 |
| Mean (SD) | 1.45 (1.14) | 2.11 (3.43) | 1.94 (3.01) |
| Median | 1.00 | 1.00 | 1.00 |
| Min–Max | 0.0–5.0 | 0.0–23.0 | 0.0–23.0 |
| Mechanical Ventilation [d] | | | |
| n | 210 | 430 | 640 |
| Yes | 22 (10.5%) | 59 (13.7%) | 81 (12.7%) |
| No | 188 (89.5%) | 371 (86.3%) | 559 (87.3%) |
| Steroid Use [e] | | | |
| n | 210 | 430 | 640 |
| Yes | 181 (86.2%) | 358 (83.3%) | 539 (84.2%) |
| No | 29 (13.8%) | 72 (16.7%) | 101 (15.8%) |
| Diabetes [f] | | | |
| n | 210 | 430 | 640 |
| Yes | 81 (38.6%) | 172 (40.0%) | 253 (39.5%) |
| No | 129 (61.4%) | 258 (60.0%) | 387 (60.5%) |
| Heart Disease [f] | | | |
| n | 210 | 430 | 640 |
| Yes | 45 (21.4%) | 105 (24.4%) | 150 (23.4%) |
| No | 165 (78.6%) | 325 (75.6%) | 490 (76.6%) |
| Hypertension [f] | | | |
| n | 210 | 430 | 640 |
| Yes | 128 (61.0%) | 267 (62.1%) | 395 (61.7%) |
| No | 82 (39.0%) | 163 (37.9%) | 245 (38.3%) |
| RDV prior to Randomization | | | |
| n | 210 | 430 | 640 |
| Yes | 40 (19.0%) | 83 (19.3%) | 123 (19.2%) |
| No | 170 (81.0%) | 347 (80.7%) | 517 (80.8%) |
| RDV Days Prior to Randomization (g) | | | |
| n | 40 | 83 | 123 |
| Mean (SD) | 1.48 (0.60) | 1.29 (0.69) | 1.35 (0.67) |
| Median | 2.00 | 1.00 | 1.00 |

| | | | |
|---|---|---|---|
| Min–Max | 0.0–2.0 | 0.0–2.0 | 0.0–2.0 |
| Symptoms at time of COVID-19 diagnosis | | | |
| n | 210 | 430 | 640 |
| Fever | 142 (67.6%) | 279 (64.9%) | 421 (65.8%) |
| Cough | 158 (75.2%) | 313 (72.8%) | 471 (73.6%) |
| Shortness of Breath | 174 (82.9%) | 348 (80.9%) | 522 (81.6%) |
| GI Symptoms [h] | 62 (29.5%) | 139 (32.3%) | 201 (31.4%) |
| Headache | 34 (16.2%) | 84 (19.5%) | 118 (18.4%) |
| Fatigue | 79 (37.6%) | 178 (41.4%) | 257 (40.2%) |
| Other | 77 (36.7%) | 159 (37.0%) | 236 (36.9%) |
| Anosmia | 26 (12.4%) | 62 (14.4%) | 88 (13.8%) |
| Days from first COVID-19 symptom at baseline | | | |
| n | 209 | 427 | 636 |
| Mean (SD) | 8.92 (4.65) | 8.83 (4.77) | 8.86 (4.73) |
| Median | 8.00 | 8.00 | 8.00 |
| Min–Max | 0.0–35.0 | 0.0–43.0 | 0.0–43.0 |
| COVID-19 Diagnosis Based on PCR of Specimen Type | | | |
| n | 210 | 430 | 640 |
| Nasopharyngeal swab | 208 (99.0%) | 418 (97.2%) | 626 (97.8%) |
| Nasopharyngeal wash | 1 (0.5%) | 1 (0.2%) | 2 (0.3%) |
| Nasal aspirate | 0 | 2 (0.5%) | 2 (0.3%) |
| Tracheal aspirate | 0 | 2 (0.5%) | 2 (0.3%) |
| Bronchoalveolar lavage | 0 | 1 (0.2%) | 1 (0.2%) |
| Blood | 1 (0.5%) | 4 (0.9%) | 5 (0.8%) |
| Sputum | 0 | 1 (0.2%) | 1 (0.2%) |
| Other bodily fluid | 0 | 1 (0.2%) | 1 (0.2%) |
| Days from most recent positive PCR | | | |
| n | 210 | 430 | 640 |
| Mean (SD) | 2.35 (2.12) | 2.47 (2.11) | 2.43 (2.11) |
| Median | 2.00 | 2.00 | 2.00 |
| Min–Max | 0.0–15.0 | 0.0–13.0 | 0.0–15.0 |
| IL-6 Level (ng/L) *** | | | |
| n | 210 | 422 | 632 |
| Mean (SD) | 61.85 (143.46) | 90.91 (220.26) | 81.25 (198.43) |
| Median | 22.05 | 30.2 | 28.15 |

| | | | |
|---|---|---|---|
| Min–Max | 5.0–1624.0 | 5.0–2198.0 | 5.0–2198.0 |
| D-Dimer Levels (ug/mL FEU)**** | | | |
| n | 171 | 360 | 531 |
| Mean (SD) | 2.25 (4.76) | 2.05 (3.98) | 2.11 (4.24) |
| Median | 0.93 | 0.99 | 0.98 |
| Min–Max | 0.0–40.0 | 0.0–43.0 | 0.0–43.0 |
| CRP Levels (mg/L) | | | |
| n | 210 | 422 | 632 |
| Mean (SD) | 115.90 (84.98) | 113.78 (85.52) | 114.48 (85.28) |
| Median | 100.05 | 97.15 | 98.20 |
| Min–Max | 8.2–388.5 | 1.3–418.3 | 1.3–418.3 |

ECMO=extracorporeal membrane oxygenation; FEU=fibrinogen equivalent units; GI=gastrointestinal; ICU=intensive care unit; IL-6=interleukin-6; LLOQ=lower limit of quantitation; PBO=placebo; PT=Preferred Term; RDV=remdesivir; SD=standard deviation; TCZ=tocilizumab;

(a) The NEWS2 score was calculated even if one or more of the NEWS2 components was missing.

(b) If one or more of the components of the NEWS2 score was missing, then the NEWS2 score was not calculated.

(c) Ordinal Scale for Clinical Status 1. Discharged (or "ready for discharge") 2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring ECMO or mechanical ventilation and additional organ support 7. Death

(d) One patient had a missing baseline mechanical ventilation record so their baseline ordinal scale category (category 3 - Non-ICU hospital ward or "ready for hospital ward" requiring supplemental oxygen) was used to impute their baseline mechanical ventilation status (not on mechanical ventilation).

(e) Between Day -7 and Day 1. Systemic steroid treatments limited to corticosteroids excluding fludrocortisone or those reported as being topical, inhalants or dermatological, or with reported dose units of OTHER, %, AMPULE, or UNKNOWN.

(f) Diabetes is defined by the PTs: Diabetes mellitus; Type 2 Diabetes Mellitus; Diabetic nephropathy; Diabetic neuropathy; Diabetic vascular disorder; Diabetic retinopathy; and Diabetic ketoacidosis. Heart disease is defined by the System Organ Class: Cardiac disorders. Hypertension is defined by the PTs: Hypertension; and Essential hypertension

(g) RDV days prior to randomization calculated as (randomization date – earliest concomitant RDV date)

(h) Gastrointestinal symptoms include, but not limited to, diarrhea, nausea, loss of appetite

For the ordinal scale and each of the biomarkers, baseline is the patient's last pre-treatment assessment on or prior to Day 1 and where baseline data is not available, the first available assessment (up to Day 2) is used as baseline.

***Numbers analysed***

The primary analysis population for efficacy (mITT population) comprised 430 patients in the TCZ+RDV arm and 210 patients in the PBO+RDV arm. The Safety-evaluable population comprised 429 and 213 patients in the TCZ+RDV and PBO+RDV arms, respectively. Two patients received RDV but did not receive TCZ or PBO so were not included in the mITT population but were included in the Safety-Evaluable population in the PBO+RDV arm and one patient randomized to the TCZ+RDV arm received PBO+RDV in error so was included in the TCZ+RDV arm in the mITT population but the PBO+RDV arm in the Safety-Evaluable population.

Four hundred and thirty (430) patients (99.1%) and 263 patients (60.6%) in the TCZ+RDV arm completed TCZ and RDV treatment, respectively. In comparison, 210 patients (97.7%) and 120 patients (55.8%) in the PBO+RDV arm completed PBO and RDV treatment, respectively.

***Outcomes and estimation***

**Primary Efficacy Endpoint**

*The primary endpoint was not met*; there was no statistically significant difference between treatment arms in time to hospital discharge or "ready for discharge" up to Day 28 (log-rank p-value = 0.7414). The median time to hospital discharge or "ready for discharge" was 14.0 days in both treatment arms (95% CI: [12.0, 15.0] in the TCZ+RDV arm and [11.0, 16.0] in the PBO+RDV arm). The HR for time to hospital discharge or "ready for discharge" for TCZ+RDV vs PBO+RDV was 0.965 (95% CI: 0.78, 1.19).

**Table 25 Overview of key efficacy endpoints, mITT population**

| | TCZ + RDV (N=430) | PBO + RDV (N=210) |
|---|---|---|
| **Primary Efficacy Endpoint** | | |
| Time to hospital discharge or "ready for discharge" up to Day 28 [a, b] | | |
| Patients included in analysis | 430 | 210 |
| Patients with event (%) | 284 (66.0%) | 141 (67.1%) |
| Patients without event (%) | 146 (34.0%) | 69 (32.9%) |
| Time to Event (days) | | |
| Median (95% CI) | 14.0 (12.0, 15.0) | 14.0 (11.0, 16.0) |
| p-value (log-rank) | 0.7414 | |
| HR (95% CI) | 0.965 (0.78, 1.19) | |

A Kaplan-Meier plot for time to hospital discharge or "ready for discharge" up to Day 28 is provided in Figure 35. A cumulative incidence function plot of time to hospital discharge or "ready for discharge" and mortality up to Day 28 is provided in Figure 36.

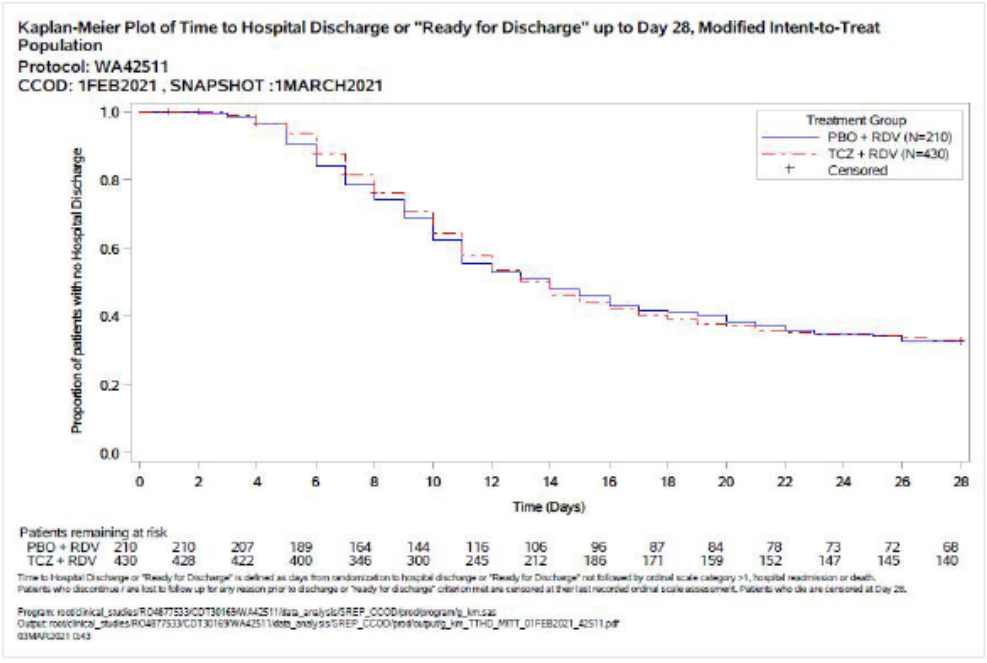



**Figure 36 Kaplan-Meier plot of time to hospital discharge or "ready for discharge" up to Day 28, mITT population**

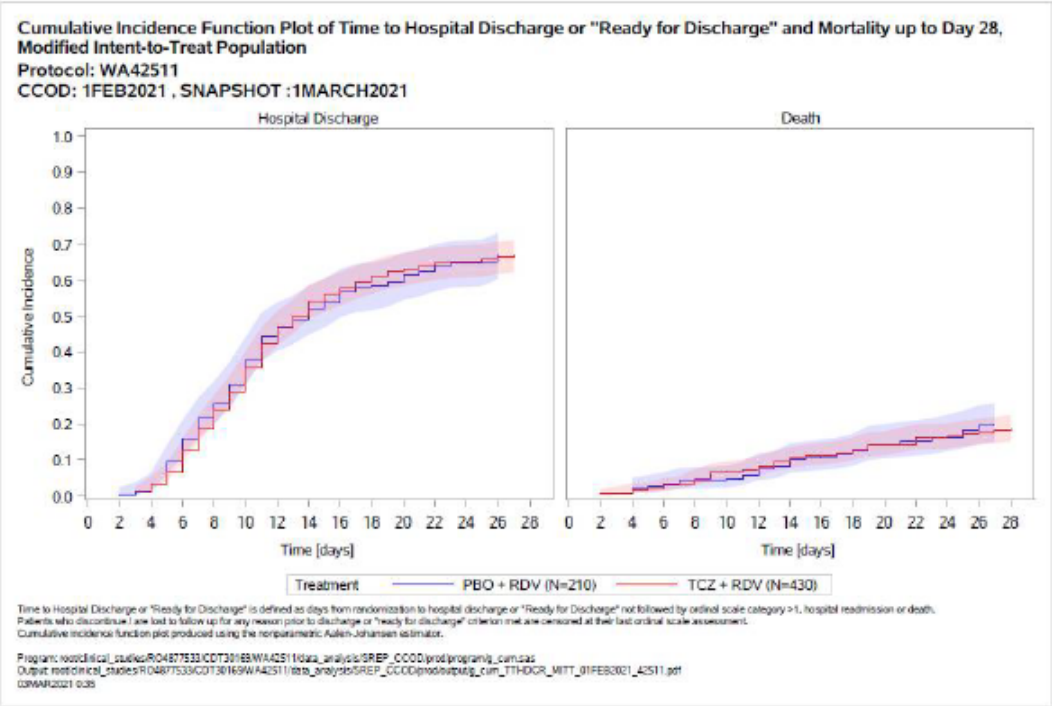



**Figure 37 Cumulative incidence function plot of time to hospital discharge or "ready for discharge" and death up to day 28, mITT population**

## Key Secondary Efficacy Endpoints

*As the primary endpoint was not met, all p-values presented for the key secondary endpoints are nominal.*

Time to Mechanical Ventilation or Death up to Day 28

*There was no statistically significant difference* between treatment arms in time to mechanical ventilation or death up to Day 28 (log-rank p-value = 0.8993). The median time to mechanical ventilation or death was not estimable (NE) in both arms. The HR for time to mechanical ventilation or death for TCZ+RDV vs PBO+RDV was 0.980 (95% CI: 0.72, 1.34).

Clinical Status (Assessed using a 7-Category Ordinal Scale) at Day 14

*There was no statistically significant difference* in the distribution of clinical status at Day 14 between patients in the TCZ+RDV arm and the PBO+RDV arm (OR=1.05 [95% CI: 0.77, 1.44]; p=0.7648). The mean value for the 7-category ordinal scale clinical status at Day 14 was 2.8 in the TCZ+RDV arm (95% CI: 2.6, 3.0) and 2.9 in the PBO+RDV arm (95% CI: 2.6, 3.2), with a difference in means between the two treatment arms of −.0652 (95% CI: −0.42, 0.29).

Time to Death up to Day 28

*There was no statistically significant difference* in time from randomization to death up to Day 28 between treatment arms (log-rank p-value = 0.7867). The median time to death was not estimable in both arms. The HR for time to death for TCZ+RDV versus PBO+RDV was 0.948 (95% CI: 0.65, 1.39).

**Additional Mortality-related Secondary Endpoint**

Mortality at Day 28 and Day 60

Mortality at Day 28 was 18.1% (95% CI: 14.5%, 21.8%) in the TCZ+RDV arm and 19.5% (95% CI: 14.2%, 24.9%) in the PBO+RDV arm. The weighted difference in mortality between the two treatment arms was −1.3% at Day 28 (95% CI: −7.8%, 5.2%). Mortality at Day 60 was 22.6% (95% CI: 18.6%, 26.5%) in the TCZ+RDV arm and 25.7% (95% CI: 19.8%, 31.6%) in the PBO+RDV arm. The weighted difference in mortality between the two treatment arms was −3.0% at Day 60 (95% CI: −10.1%, 4.0%.

**Subgroup Analyses by Baseline Standard of Care Treatment**

Post-hoc subgroup analyses of time to death up to Day 28, time to hospital discharge/ready for discharge up to Day 28 and time to MV or death up to Day 28 by baseline SoC treatment were conducted. Hazard ratios were estimated using a Cox proportional hazards model (unstratified) together with the associated 95% CIs.

Baseline treatment with systemic corticosteroids was associated with a hazard ratio <1 for time to death up to Day 28 for TCZ compared to PBO (HR=0.89 [95% CI: 0.60, 1.33]) and for time to MV or death up to Day 28 (HR=0.90 [95% CI: 0.65, 1.25]).

Among patients who were treated with systemic corticosteroids at baseline, the hazard ratio for time to hospital discharge or "ready for discharge" up to Day 28 for TCZ compared with PBO was 1.01 (95% CI: 0.81, 1.28).

Among patients who were treated with systemic corticosteroids at baseline (between Day -7 and Day 1), the hazard ratio for time to hospital discharge or "ready for discharge" up to Day 28 for TCZ□RDV compared with PBO□RDV was 1.01 (95% CI: 0.81, 1.28). Among patients who were not treated with systemic corticosteroids at baseline, the hazard ratio for TCZ compared with placebo was 0.76 (95% CI: 0.45, 1.26).

## Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 26 Summary of efficacy for RECOVERY trial**

| **Title: Randomised Evaluation of COVID-19 Therapy (RECOVERY)** | | | | |
|---|---|---|---|---|
| Study identifier | ISRCTN (50189673) and clinicaltrials.gov (NCT04381936) | | | |
| Design | Randomized, controlled, open-label, multicenter platform trial in adult patients (≥18 years) hospitalized in the UK with severe COVID-19 | | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | Within 28 days after randomization<br>Not applicable<br>Up to 6 months after randomization | |
| Hypothesis | Superiority | | | |
| Treatments groups | Tocilizumab (TCZ)+Usual Care arm | | 400 – 800 mg TCZ for patients >40 kg (max. 800 mg) or 8 mg/kg for patients ≤40 kg IV on Day 1.<br>One additional infusion of TCZ could be given 12-24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>N=2022 | |
| | Usual Care arm | | Usual standard of care<br>n=2094 | |
| Endpoints and definitions | Primary endpoint | 28-day mortality | All-cause mortality within 28 days of randomization (time-to-event analysis) | |
| | Secondary endpoint | Time to discharge alive from hospital | Time to discharge from hospital alive within 28 days | |
| | Secondary endpoint | Use of invasive mechanical ventilation (including ECMO) or death | Use of invasive mechanical ventilation (including Extra Corporeal Membrane Oxygenation [ECMO]) or death within 28 days in patients not receiving invasive mechanical ventilation or ECMO at randomization | |
| Database lock | 29 March 2021 | | | |
| **Results and Analysis** | | | | |
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | Intention to Treat Population - defined as all patients randomized, grouped according to the treatment assignment at randomization, irrespective of treatment received<br>Time point: 28 days after randomization | | | |
| Descriptive statistics and estimate variability | **Treatment group** | | **TCZ+Usual Care** | **Usual Care** |
| | Number of subjects | | 2022 | 2094 |
| | 28-day mortality (Number (%) of patients) | | 621 (31%) | 729 (35%) |
| Effect estimate per comparison | Primary endpoint – 28-day mortality | Comparison groups | | TCZ+Usual Care and Usual Care |
| | | Hazard Ratio (using log-rank 'observed minus | | 0.85 |

| | | | |
|---|---|---|---|
| | | expected' statistic and its variance) | |
| | | 95% CI | (0.76, 0.94) |
| | | P-value (log-rank) | 0.0028 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Intention to Treat Population<br>Time point: 28 days after randomization | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+Usual Care** | **Usual Care** |
| | Number of subjects | 2022 | 2094 |
| | Time to discharge alive from hospital<br><br>(Number (%) of patients)<br><br>(Median (days)) | <br><br>1150 (57%)<br><br>19 | <br><br>1044 (50%)<br><br>>28 |
| Effect estimate per comparison | Secondary endpoint - Time to discharge alive from hospital | Comparison groups | TCZ+Usual Care and Usual Care |
| | | Hazard Ratio (using log-rank 'observed minus expected' statistic and its variance) | 1.22 |
| | | 95% CI | (1.12, 1.33) |
| | | P-value (log-rank) | <0·0001 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Subgroup of patients not receiving invasive mechanical ventilation or ECMO at randomization in the Intention to Treat Population<br>Time point: 28 days after randomization | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+Usual Care** | **Usual Care** |
| | Number of subjects | 1754 | 1800 |
| | Use of invasive mechanical ventilation (including ECMO) or death (Number (%) of patients) | 619 (35%) | 754 (42%) |
| Effect estimate per comparison | Secondary endpoint - Use of invasive mechanical ventilation (including ECMO) or death | Comparison groups | TCZ+Usual Care and Usual Care |
| | | Risk Ratio | 0.84 |
| | | 95% CI | (0.77, 0.92) |
| | | P-value | <0.0001 |
| Notes | 1964/2022 (97%) patients of those allocated to TCZ+Usual Care and 2049/2094 (98%) of those allocated to Usual Care had a completed follow−up form at time of analysis. Among those patients who completed the follow-up form, 16% (317/1964) patients in the TCZ+Usual Care arm did not receive TCZ and 4% (77/2049) patients in the Usual Care arm received at least one dose of TCZ (or sarilumab, another IL-6 antagonist); these patients were included per treatment allocation in the Intention to Treat population for efficacy analyses. | | |

**Table 27 Summary of efficacy for Study WA42380 (COVACTA)**

| **Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia** | | | |
|---|---|---|---|
| Study identifier | WA42380, EudraCT (2020-001154-22) and clinicaltrials.gov (NCT04320615) | | |
| Design | Randomized, double-blind, placebo-controlled, multicenter study in hospitalized adult (≥18 years) patients with severe COVID-19 pneumonia | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 60 days after randomization<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Tocilizumab + Standard of care (TCZ+SoC) | | 8 mg/kg TCZ (max. 800 mg) IV on Day 1.<br>One additional infusion of TCZ could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=301 |
| | Placebo + Standard of Care (PBO+SoC) | | TCZ PBO IV on Day 1<br>One additional infusion of blinded TCZ PBO could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=151 |
| Endpoints and definitions | Primary endpoint | Clinical status assessed using a 7-category ordinal scale at Day 28 | Clinical status assessed using a 7-category ordinal scale at Day 28<br>(1, discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); 2, non–ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen; 3, non–ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death) |
| | Secondary endpoint | Mortality at Day 28 | Difference in mortality at Day 28 |
| | Secondary endpoint | Time to hospital discharge or "ready for discharge" | Defined as the days from the first dose of study drug to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen) up to Day 28 |

| | | | |
|---|---|---|---|
| | Secondary endpoint | Incidence of mechanical ventilation (patients not on mechanical ventilation at baseline) | Incidence of mechanical ventilation (including invasive mechanical ventilation or ECMO) by Day 28 in patients not on mechanical ventilation at baseline |
| Database lock | 22 September 2020 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Modified Intent to Treat Population: defined as all patients randomized in the study that received any amount of study medication, grouped according to the treatment assignment at randomization.<br>Time point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 294 | 144 |
| | Clinical status assessed using a 7-category ordinal scale at Day 28 (Median) | 1.0 | 2.0 |
| | 95% CI | (1.0, 1.0) | (1.0, 4.0) |
| Effect estimate per comparison | Primary endpoint - Clinical status assessed using a 7-category ordinal scale at Day 28 | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Difference in Medians (TCZ-PBO) | -1.0 |
| | | 95% CI | (-2.5, 0.0) |
| | | P-value (Van Elteren test) ** | 0.3600 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Modified Intent to Treat Population<br>Time point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 294 | 144 |
| | Mortality at Day 28 (Number (%) of patients) | 58 (19.7%) | 28 (19.4%) |
| | 95% CI | (15.2%, 24.3%) | (13.0%, 25.9%) |
| Effect estimate per comparison | Secondary endpoint - Mortality at Day 28 | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Weighted difference (TCZ-PBO) in % * | 0.3% |
| | | 95% CI | (–7.6%, 8.2%) |
| | | P-value (Cochran-Mantel-Haenszel test) §§§ | 0.9410 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Modified Intent to Treat Population<br>Time point: Day 28 | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 294 | 144 |
| | Time to hospital discharge or "ready for discharge" (Median (days) ‡) | 20.0 | 28.0 |
| | 95% CI | (17.0, 27.0) | (20.0, NE) |
| Effect estimate per comparison | Secondary endpoint - Time to hospital discharge or "ready for discharge" | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Hazard Ratio (using cox proportional hazards model) ††† | 1.35 |
| | | 95% CI | (1.02, 1.79) |
| | | P-value (stratified log-rank test) ** | 0.037 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Subgroup of patients not receiving mechanical ventilation at baseline in the Modified Intent to Treat Population<br>Time point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 183 | 90 |
| | Incidence of mechanical ventilation (patients not on mechanical ventilation at baseline)<br>(Number (%) of patients) | 51 (27.9%) | 33 (36.7%) |
| | 95% CI | (21.4%, 34.4%) | (26.7%, 46.6%) |
| Effect estimate per comparison | Secondary endpoint - Incidence of mechanical ventilation (patients not on mechanical ventilation at baseline) | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Weighted difference (TCZ-PBO) in % ‡‡ | -8.9% |
| | | 95% CI | (-20.7%, 3.0%) |
| | | P-value (Cochran-Mantel-Haenszel test) ^^^ | 0.1355 |
| Notes | Missing data were minimal for the primary endpoint of clinical status for the mITT population (3.7% TCZ+SoC arm, 2.1% PBO+SoC arm). | | |

**Test stratified by region [North America, Europe] and mechanical ventilation [yes, no].

* Calculated using the Cochran- Mantel-Haenszel test stratified by region [North America, Europe] and mechanical ventilation [yes, no].

§§§ Test adjusted by region [North America, Europe] and mechanical ventilation [yes, no].

‡ Estimated from the Kaplan-Meier curve.

†††Model includes stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]).

‡‡ Weighted difference in proportions as calculated using the Cochran-Mantel- Haenszel test stratified by region [North America, Europe].

^^^ Test adjusted by region [North America, Europe].

**Table 28 Summary of efficacy for Study ML42528 (EMPACTA)**

| **Title: A Randomized, Double-Blind Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients with COVID-19 Pneumonia** | | | |
|---|---|---|---|
| Study identifier | ML42528 and clinicaltrials.gov (NCT04372186) | | |
| Design | Randomized, double-blind, placebo-controlled, multicenter study in hospitalized adult (≥18 years) patients with COVID-19 pneumonia. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 60 days after randomization<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Tocilizumab + Standard of care (TCZ+SoC) | | 8 mg/kg TCZ (max. 800 mg) IV on Day 1.<br>One additional infusion of TCZ could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=259 |
| | Placebo + Standard of Care (PBO+SoC) | | TCZ PBO IV on Day 1<br>One additional infusion of blinded TCZ PBO could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=129 |
| Endpoints and definitions | Primary endpoint | Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28 | The primary endpoint was the cumulative proportion of patients with death or requiring mechanical ventilation (mechanical invasive ventilation or ECMO) by Day 28. Time to death or requiring mechanical ventilation was defined as the time from Day 1 to the first occurrence of death or requiring mechanical ventilation by Day 28. |
| | Secondary endpoint | Mortality rate by Day 28 | Difference in proportion of patients who have died by Day 28 |
| | Secondary endpoint | Time to hospital discharge or "ready for discharge" up to Day 28 | Defined as the time from Day 1 to hospital discharge or "ready for discharge" (defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen based on the 7-category ordinal scale) up to Day 28. |

| | | | |
|---|---|---|---|
| Database lock | 30 September 2020 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Modified intent to treat: defined as all randomized patients who received any amount of study medication, with patients grouped according to the treatment assigned at randomization.<br>Time point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 249 | 128 |
| | Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28 | 12.04% | 19.26% |
| | 95% CI | (8.52, 16.86) | (13.34, 27.36) |
| Effect estimate per comparison | Primary endpoint – Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28 | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Hazard ratio (using Cox proportional hazards model) †† | 0.56 |
| | | 95% CI | (0.33, 0.97) |
| | | P-value (stratified log-rank test)† | 0.0360 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Modified Intent to Treat Population<br>Time point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 249 | 128 |
| | Mortality rate by Day 28 (Number (%) of patients) | 26 (10.4%) | 11 (8.6%) |
| | 95% CI | (7.2%, 14.9%) | (4.9%, 14.7%) |
| Effect estimate per comparison | Secondary endpoint - Mortality rate by Day 28 | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Weighted difference (TCZ-PBO) in % * | 2.0% |
| | | 95% CI | (-5.2%, 7.8%) |
| | | P-value (Cochran-Mantel-Haenszel test) § | 0.5146 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Modified Intent to Treat<br>Time point: Day 28 | | |
| | **Treatment group** | **TCZ+SoC** | **PBO+SoC** |
| | Number of subjects | 249 | 128 |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Time to hospital discharge or "ready for discharge" up to Day 28 (Median (days)**) | 6 | 7.5 |
| | 95% CI | (6.0, 7.0) | (7.0, 9.0) |
| Effect estimate per comparison | Secondary endpoint - Time to hospital discharge or "ready for discharge" up to Day 28 | Comparison groups | TCZ+SoC and PBO+SoC |
| | | Hazard Ratio (using Cox proportional hazards model) †† | 1.16 |
| | | 95% CI | (0.91, 1.48) |
| | | P-value (stratified log-rank test) † | 0.2417 |

** Estimated using the Kaplan-Meier method.

†Test stratified by age group (≤60, >60 years).

* Calculated using the Cochran- Mantel-Haenszel weighting approach with stratification factor of age group (≤60, >60 years).

††Model includes stratification factor at randomization (age group [≤60, >60 years]).

§ Test adjusted by age group (≤60, >60 years).

**Table 29 Summary of efficacy for Study WA42511 (REMDACTA)**

| **Title: A Phase III, Randomized, Double-Blind Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir plus Tocilizumab Compared with Remdesivir plus Placebo in Hospitalized Patients with Severe COVID-19 Pneumonia** | | |
|---|---|---|
| Study identifier | WA42511, EudraCT (2020-002275-34) and clinicaltrials.gov (NCT04409262) | |
| Design | Randomized, double-blind, placebo-controlled, multicenter study in hospitalized patients (≥12 years) with severe COVID-19 pneumonia | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 60 days after randomization<br>not applicable<br>not applicable |
| Hypothesis | Superiority | |
| Treatments groups | Tocilizumab (TCZ) + Remdesivir (RDV) | RDV 200 mg IV loading dose + 8 mg/kg TCZ (max. 800 mg) IV on Day 1 followed by RDV 100 mg IV qd on Days 2-10 [a]<br>One additional infusion of TCZ could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=434 |
| | Placebo (PBO) + Remdesivir (RDV) | RDV 200 mg IV loading dose + TCZ PBO IV on Day 1 followed by RDV 100 mg IV qd on Days 2-10 [a]<br>One additional infusion of blinded TCZ PBO could be given 8–24 hours after the initial infusion if the clinical signs or symptoms worsened or did not improve.<br>n=215 |

| | | | |
|---|---|---|---|
| Endpoints and definitions | Primary | Time to hospital discharge or "ready for discharge" up to Day 28 | Defined as days from randomization to hospital discharge or "ready for discharge" (hospital discharge or "ready for discharge" is defined as a score of 1 on the 7-category ordinal scale‖) not followed by ordinal scale category >1, hospital readmission or death up to Day 28 |
| | Secondary | Mortality by Day 28 | Difference in mortality at Day 28 |
| | Secondary | Proportion of patients requiring initiation of mechanical ventilation post-baseline up to Day 28 | Proportion of patients requiring initiation of mechanical ventilation post-baseline up to Day 28 in patients who do not require mechanical ventilation at baseline |
| Database lock | 23 April 2020 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Modified Intent to Treat Population: defined as all patients randomized in the study that received any amount of TCZ or PBO, grouped according to the treatment assignment at randomization.<br>Time Point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+RDV** | **PBO+RDV** |
| | Number of subjects | 430 | 210 |
| | Time to hospital discharge or "ready for discharge" up to Day 28 (Median (days) ‡) | 14.0 | 14.0 |
| | 95% CI | (12.0, 15.0) | (11.0, 16.0) |
| Effect estimate per comparison | Primary endpoint - Time to hospital discharge or "ready for discharge" up to Day 28 | Comparison groups | TCZ+RDV and PBO+RDV |
| | | Hazard Ratio (using Cox proportional hazards model) †† | 0.965 |
| | | 95% CI | (0.78, 1.19) |
| | | P-value (stratified log-rank test) ††† | 0.7414 |

| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
|---|---|---|---|
| Analysis population and time point description | Modified Intent to Treat Population<br>Time Point: Day 28 | | |
| | **Treatment group** | **TCZ+RDV** | **PBO+RDV** |
| | Number of subjects | 430 | 210 |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Mortality by Day 28 (Number (%) of patients) | 78 (18.1%) | 41 (19.5%) |
| | 95% CI | (14.5%, 21.8%) | (14.2%, 24.9%) |
| Effect estimate per comparison | Secondary endpoint - Mortality by Day 28 | Comparison groups | TCZ+RDV and PBO+RDV |
| | | Weighted difference (TCZ-PBO) in % * | -1.3% |
| | | 95% CI | -7.8%, 5.2% |
| | | P-value (Cochran-Mantel-Haenszel test) §§§ | 0.6944 |
| **Analysis description** | **Secondary Analysis (pre-specified)** | | |
| Analysis population and time point description | Subgroup of patients who were not on mechanical ventilation at baseline in the Modified Intent to Treat Population<br>Time Point: Day 28 | | |
| Descriptive statistics and estimate variability | **Treatment group** | **TCZ+RDV** | **PBO+RDV** |
| | Number of subjects | 371 | 188 |
| | Proportion of patients requiring initiation of mechanical ventilation post-baseline up to Day 28 (Number (%) of patients) | 102 (27.5%) | 56 (29.8%) |
| | 95% CI | (23.0%, 32.0%) | (23.3%, 36.3%) |
| Effect estimate per comparison | Secondary endpoint - Proportion of patients requiring initiation of mechanical ventilation post-baseline up to Day 28 | Comparison groups | TCZ+RDV and PBO+RDV |
| | | Weighted difference (TCZ-PBO) in % * | -2.2% |
| | | 95% CI | (-10.2%, 5.9%) |
| | | P-value (Cochran-Mantel-Haenszel test) §§§ | 0.5915 |

a Patients could have up to 2 doses of RDV prior to randomization. Remdesivir dosing was adjusted for patients that entered the study having received prior RDV such that total RDV dosing did not exceed 10 days (including RDV received prior to the study and during the study). In both arms, study treatment was given in combination with standard supportive care.

‖7-category ordinal scale: 1, discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); 2, non–ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen; 3, non–ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

‡ Estimated from the Kaplan-Meier curve.

††Model includes stratification factors at randomization (region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]).

†††Test stratified by region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

* Calculated using the Cochran-Mantel-Haenszel test stratified by region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

§§§ Test adjusted by stratification factors at randomization (region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]).

#### *2.4.2.5. Analysis performed across trials (Side-by-Side Comparison of RECOVERY, COVACTA, EMPACTA, and REMDACTA)*

**Patient population across studies**

The primary analysis population for efficacy (intent-to-treat [ITT] population) in RECOVERY included all 2022 patients in the TCZ+Usual Care arm and 2094 patients in the Usual Care arm. However, among those patients who completed the follow-up form for RECOVERY, 317 patients in the TCZ+Usual Care arm did not receive TCZ (RECOVERY Collaborative Group 2021).

A total of 1489 patients (TCZ: 994 and PBO: 495) were randomized in COVACTA, EMPACTA and REMDACTA. Of these, 1455 patients were included in the meta-analysis population for efficacy (mITT population; 973 patients in the TCZ arm and 482 patients in the PBO arm) (**Table 30**). A total of 21 patients randomized to the TCZ arm and 13 patients randomized to the placebo arm did not receive TCZ or PBO and were excluded from the mITT population.

**Table 30 Summary of Analysis Populations (COVACTA, EMPACTA, REMDACTA, and RECOVERY) – All Patients**

| | COVACTA | | EMPACTA | | REMDACTA | | Pooled Roche Studies | | RECOVERY (TCZ Cohort) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TCZ | PBO | TCZ | PBO | TCZ | PBO | TCZ | PBO | TCZ + Usual Care | Usual Care |
| Randomized patients | 301 | 151 | 259 | 129 | 434 | 215 | 994 | 495 | 2022 | 2094 |
| ITT population | | | | | | | | | 2022 | 2094 |
| mITT population | 294 | 144 | 249 | 128 | 430 | 210 | 973 | 482 | | |
| Did not receive study drug [ł] | 7 | 7 | 10 | 1 | 4 | 5 | 21 | 13 | | |
| Safety-Evaluable Population | 294 | 144 | 249 | 128 | 431 | 211 | 974 | 483 | | |
| Did not receive study drug [ǂ] | 7 | 7 | 10 | 1 | 3 | 4 | 20 | 12 | | |

[ł] Study drug only includes TCZ or PBO in REMDACTA

[ǂ] Study drug includes TCZ, PBO or RDV in REMDACTA

**Patient Demographics**

A side-by-side comparison of key baseline demographics of patients enrolled in the four studies (RECOVERY, COVACTA, EMPACTA and REMDACTA) is presented in Table 31.

In all four studies the majority of patients were male and the mean age ranged between 56 and 64 years. The proportion of patients aged ≥ 65 years was higher in COVACTA compared to REMDACTA and EMPACTA. A total of 34% of patients in the TCZ arm and 35% patients in the Usual Care arm in RECOVERY, which reported the age categories differently, were aged ≥70 years.

A higher proportion of White patients were recruited in RECOVERY compared with the other three studies. The proportion of patients from racial and ethnic minorities was highest in EMPACTA compared to COVACTA, REMDACTA and RECOVERY (Table 31); this was expected given EMPACTA's emphasis on enrolling high-risk minority populations.

The demographic characteristics of the pooled meta-analysis population of Roche-sponsored studies were balanced between the treatment arms. The majority of patients were male (TCZ: 63.8% and PBO: 64.9%), White (60.6% and 60.4%) and enrolled at US sites (66.9% and 67.0%). The median age was 60.0 years (range 20 to 96 years) in the TCZ arm and 59.0 years (range 20 to 93 years) in the PBO arm.

**Table 31 Comparison of Key Baseline Demographics from COVACTA (mITT), EMPACTA (mITT), REMDACTA (mITT), Pooled Roche Studies (mITT) and RECOVERY (ITT)**

| | COVACTA (mITT) | | EMPACTA (mITT) | | REMDACTA (mITT) | | Pooled Roche Studies (mITT) | | RECOVERY (ITT) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TCZ N=294 | PBO N=144 | TCZ N=249 | PBO N=128 | TCZ N=430 | PBO N=210 | TCZ N=973 | PBO N=482 | TCZ N=2022 | Usual Care N=2094 |
| **Male, n (%)** | 205 (69.7%) | 101 (70.1%) | 150 (60.2%) | 73 (57.0%) | 266 (61.9%) | 139 (66.2%) | 621 (63.8%) | 313 (64.9%) | 1337 (66.1%) | 1437 (68.6%) |
| **Age (Years)** | | | | | | | | | | |
| Mean (SD) | 60.9 (14.6) | 60.6 (13.7) | 56.0 (14.3) | 55.6 (14.9) | 60.1 (13.3) | 58.2 (13.3) | 59.3 (14.1) | 58.2 (13.9) | 63.3 (13.7) | 63.9 (13.6) |
| Median | 63.0 | 61.5 | 57.0 | 56.0 | 61.0 | 59.0 | 60.0 | 59.0 | - | - |
| Min- Max | 25 - 96 | 22 - 93 | 24 – 95 | 20 - 89 | 20 - 93 | 21 - 86 | 20 - 96 | 20 - 93 | - | - |
| **Age category, years, n (%)** | | | | | | | | | | |
| 18-64 | 163 (55.4%) | 81 (56.3%) | 178 (71.5%) | 93 (72.7%) | 257 (59.8%) | 138 (65.7%) | 598 (61.5%) | 312 (64.7%) | - | - |
| 65-84 | 117 (39.8%) | 60 (41.7%) | 70 (28.1%) | 33 (25.8%) | 165 (38.4%) | 70 (33.3%) | 352 (36.2%) | 163 (33.8%) | - | - |
| ≥85 | 14 (4.8%) | 3 (2.1%) | 1 (0.4%) | 2 (1.6%) | 8 (1.9%) | 2 (1.0%) | 23 (2.4%) | 7 (1.5%) | - | - |
| ≥18-<70 | - | - | - | - | - | - | 739 (76.0%) | 370 (76.8%) | 1331(65.8%) | 1355 (64.7%) |
| ≥70-<80 | - | - | - | - | - | - | 170 (17.5%) | 93 (19.3%) | 478 (23.6%) | 480 (22.9%) |
| ≥80 | - | - | - | - | - | - | 64 (6.6%) | 19 (3.9%) | 213 (10.5%) | 259 (12.4%) |
| **Weight, kg.** | n=294 | n=143 | n=249 | n=128 | n=430 | n=210 | n=973 | n=481 | | |
| Mean (SD) | 88.90 (23.64) | 88.09 (24.31) | 89.57 (23.73) | 94.44 (25.95) | 94.42 (26.45) | 96.38 (25.27) | 91.51 (25.05) | 93.40 (25.37) | - | - |
| Median | 84.60 | 82.00 | 85.00 | 90.05 | 90.00 | 90.00 | 87.00 | 88.00 | - | - |
| Min- Max | 43.5 - 186.0 | 37.3 - 185.9 | 45.4 – 171.8 | 44.0 – 201.0 | 46.7 - 279.9 | 50.0 - 206.0 | 43.5 – 279.9 | 37.3 – 206.0 | - | - |
| **Ethnicity Hispanic or Latino** | 94 (32.0%) | 47 (32.6%) | 143 (57.4%) | 68 (53.1%) | 208 (48.4%) | 122 (58.1%) | 445 (45.7%) | 238 (49.4%) | - | - |
| **Race, n (%)** | | | | | | | | | | |
| Asian / Asian British | 28 (9.5%) | 10 (6.9%) | 5 (2.0%) | 1 (0.8%) | 17 (4.0%) | 5 (2.4%) | 51 (5.2%) | 16 (3.3%) | 225 (11.1%) | 228 (10.9%) |
| Black/African American/Black British | 40 (13.6%) | 26 (18.1%) | 35 (14.1%) | 22 (17.2%) | 51 (11.9%) | 19 (9.0%) | 126 (12.9%) | 67 (13.9%) | 64 (3.2%) | 73 (3.5%) |
| White | 176 (59.9%) | 76 (52.8%) | 134 (53.8%) | 65 (50.8%) | 279 (64.9%) | 150 (71.4%) | 590 (60.6%) | 291 (60.4%) | 1530 (75.7%) | 1597 (76.3%) |
| Multiple/Mixed | 0 | 1 (0.7%) | 4 (1.6%) | 2 (1.6%) | 9 (2.1%) | 2 (1.0%) | 13 (1.3%) | 5 (1.0%) | 24 (1.2%) | 21 (1.0%) |
| Other ethnic groups [a] | 11 (3.7%) | 10 (6.9%)- | 52 (20.9%) | 26 (20.3%) | 11 (2.6%) | 7 (3.3%) | 74 (7.6%) | 43 (8.9%) | 41 (2.0%) | 56 (2.7%) |
| Unknown | 39 (13.3%) | 21 (14.6%) | 19 (7.6%) | 12 (9.4%) | 63 (14.7%) | 27 (12.9%) | 119 (12.2%) | 60 (12.4%) | 138 (6.8%) | 119 (5.7%) |
| **Region, n (%)** | | | | | | | | | | |
| North America or US[b] | 174 (59.2%) | 85 (59.0%) | 201 (80.7%) | 103 (80.5%) | 288 (67.0%) | 138 (65.7%) | 663 (68.1%) | 326 (67.6%) | - | - |
| Europe or ex-US[b] | 120 (40.8%) | 59 (41.0%) | 48 (19.3%) | 25 (19.5%) | 142 (33.0%) | 72 (34.3%) | 263 (27.0%) | 138 (28.6%) | - | - |
| UK[b] | - | - | - | - | - | - | 47 (4.8%) | 18 (3.7%) | 2022 (100%) | 2094 (100%) |

ITT=intention-to-treat population; mITT=modified intention-to-treat population; PBO=placebo; SD=standard deviation; TCZ=tocilizumab; UK=United Kingdom; US=United States of America.

[a] For COVACTA, EMPACTA and REMDACTA this category combines American Indian/Alaska Native and Native Hawaiian/other Pacific Islander.

[b] COVACTA recruited from sites in North America and Europe; EMPACTA in US, Mexico, Brazil, Peru, South Africa and Kenya; REMDACTA in US, Brazil, Spain and Russia; RECOVERY in the United Kingdom.

Note: Individual study data were derived from the study CSRs; pooled Roche study data were based on the final Day 60 datasets. As a result of updates to the data between the clinical cut-off for the CSRs and cut-off for the final Day 60 analysis, the sum of the total number of patients derived from each individual study may differ from the total number of patients included in the pooled meta-analysis patient population.

## Baseline Disease Characteristics

COVACTA enrolled patients across a broader range of disease severity and higher proportions of patients on mechanical ventilation alone or requiring additional organ support compared to the other three studies:

- At baseline, approximately 38% of patients from each arm in COVACTA were on invasive mechanical ventilation (ordinal scale categories 5 and 6). A total of 26.5% of TCZ and 30.6%

of PBO patients were on low flow oxygen (category 3) and 32.0% TCZ and 27.1% PBO patients on high flow oxygen/non-invasive ventilation (category 4).

- The majority of patients in REMDACTA were on high flow oxygen/non-invasive ventilation (category 4; TCZ: 78.1% and PBO: 83.3%). The remaining patients were on low flow oxygen (category 3: TCZ: 6.7% and PBO: 6.2%), on invasive mechanical ventilation without additional organ support (category 5: TCZ: 9.1% and PBO: 4.3%) or on invasive mechanical ventilation and additional organ support (category 6: TCZ: 6.0% and PBO: 6.2%).
- In comparison, EMPACTA excluded patients who required non-invasive or invasive mechanical ventilation (but allowed patients on high-flow oxygen), with the majority of patients on low flow oxygen (category 3, TCZ: 64.7% and PBO: 63.3%).
- Similar to COVACTA, the TCZ cohort of RECOVERY recruited hospitalized patients across a broader range of respiratory support; however, compared with COVACTA, the proportion of patients on invasive mechanical ventilation was much lower (TCZ: 13% and Usual Care: 14%), while the proportions of patients on low-flow oxygen (TCZ: 46% and Usual Care: 45%) and high-flow oxygen/non-invasive ventilation (41% in both arms) were higher. Compared to the EMPACTA study, RECOVERY enrolled a higher proportion of patients on high-flow oxygen/non-invasive ventilation and a lower proportion of patients on low-flow oxygen.

In all four studies, very few patients did not require any supplemental oxygen.

The median time from first COVID-19 symptom to baseline was longer in COVACTA (TCZ: 11.0 days and PBO: 10.0 days) compared with EMPACTA and REMDACTA (8.0 days in both arms) and RECOVERY (TCZ: 9.0 days and Usual Care: 10.0 days), consistent with higher average disease severity in COVACTA.

The baseline median CRP levels were similar in COVACTA, EMPACTA and RECOVERY and higher compared to those in REMDACTA. Of note, all patients enrolled in RECOVERY had baseline CRP value of ≥75 mg/L as this was one of the entry criteria in the study.

The release of positive results from the RECOVERY dexamethasone cohort in June 2020 had a major impact on systemic corticosteroids usage (as part of SoC) for severe COVID-19 globally (Horby et al. 2021). This may explain why the proportion of patients on systemic corticosteroids at baseline was lowest in COVACTA (19.4% in TCZ and 28.5% in PBO) considering that the last patient in the study was randomized on 28 May 2020. In contrast, 73.5% TCZ patients and 71.1% PBO patients in EMPACTA, 83.3% TCZ patients and 86.2% PBO patients in REMDACTA and 82% patients in each arm in RECOVERY were on systemic steroids at baseline.

The use of RDV at baseline (defined as use of medication between Day -7 and Day 1) was also much lower in COVACTA (TCZ: 6.5% and PBO: 4.2%) compared to EMPACTA (TCZ: 46.6% and PBO: 50.0%). This difference also most likely reflects the evolving standard of care following the US EUA and EU conditional approval of RDV after the end of the enrollment for COVACTA (28 May 2020). Information regarding baseline RDV use in RECOVERY was available for 1712 TCZ and 1790 Usual Care patients; the use of baseline RDV in RECOVERY was lower (TCZ: 31.8% and Usual Care: 32.0%) than in EMPACTA, reflecting more limited availability of RDV in the UK. All patients in REMDACTA received RDV during the study as per protocol.

The baseline disease characteristics of the pooled mITT meta-analysis population were generally well balanced between the treatment arms. At baseline, a slightly lower proportion of patients in the TCZ arm than the PBO arm received systemic corticosteroids (61.4% vs 64.9%), whereas the proportion of patients who received RDV at baseline was the same in both treatment arms (58.1% in both arms).

Consistently across the four studies, the majority of the patients enrolled had at least one of the pre-existing conditions that were considered as risk factors for hospitalized COVID-19. The most common comorbidity in COVACTA, EMPACTA and REMDACTA was hypertension (TCZ: 60.5% and PBO: 65.3% in COVACTA; TCZ: 47.6% and PBO: 49.6% in EMPACTA; and TCZ: 62.1% and PBO: 61.0% in REMDACTA). In RECOVERY, diabetes was the most common comorbidity amongst the comorbidities assessed (TCZ: 28% and Usual Care: 29%).

**Side-by-Side Comparison of RECOVERY, COVACTA, EMPACTA, and REMDACTA**

A side-by-side comparison of results for the following key efficacy endpoints in RECOVERY, COVACTA, EMPACTA, and REMDACTA is presented in Table 32 including:

- Mortality by Day 28
- Time to hospital discharge or ready for discharge
- Incidence of mechanical ventilation/ time to mechanical ventilation or death/ use of invasive mechanical ventilation (including ECMO) or death

These endpoints were selected on the basis of their clinical meaningfulness in the context of the natural history of severe COVID-19. Reducing mortality, decreasing the need for mechanical ventilation and ICU level care, and shortening time to hospital discharge are of great individual and public health importance and may significantly reduce the burden on strained healthcare resources in the context of the ongoing global pandemic.

**Table 32 Side-by-Side Comparison of Key Efficacy Outcomes from RECOVERY (ITT), COVACTA (mITT), EMPACTA (mITT) and REMDACTA (mITT)**

| | COVACTA (mITT) | | EMPACTA (mITT) | | REMDACTA (mITT) | | RECOVERY (ITT) | |
|---|---|---|---|---|---|---|---|---|
| | TCZ N=294 | PBO N=144 | TCZ N=249 | PBO N=128 | TCZ N=430 | PBO N=210 | TCZ N=2022 | Usual Care N=2094 |
| **Mortality by Day 28** | | | | | | | | |
| Mortality (%) by Day 28 | TCZ: 19.7%, PBO: 19.4% | | TCZ: 10.4%, PBO: 8.6% | | TCZ: 18.1%, PBO: 19.5% | | TCZ: 31%,Usual Care: 35% | |
| (Weighted) difference (TCZ-PBO) in % (95% CI) | 0.3% (–7.6%, 8.2%)* | | 2.0% (-5.2%, 7.8%)* | | –1.3% (–7.8%, 5.2%)* | | -4.1% (-7.0%, -1.3%)[β] | |
| Hazard Ratio (TCZ/PBO)(95% CI) | 1.07 (0.68, 1.67) ^ | | 1.20 (0.61, 2.38) ^ | | 0.94 (0.64, 1.37) ^ | | 0.85 (0.76 to 0.94)^ | |
| p-value | 0.9410[§§§] | | 0.5146[#§] | | 0.6944[§§§] | | 0.0028^ | |
| **Time to Hospital discharge or ready for discharge[a]** | | | | | | | | |
| Proportion of patients at Day 28 | TCZ: 56.8%, PBO: 50.0% | | TCZ: 87.1%, PBO: 82.8% | | TCZ: 66.0%, PBO: 67.1% | | TCZ: 57%, Usual Care: 50% | |
| Median time (days) | TCZ: 20, PBO: 28[‡] | | TCZ: 6, PBO: 7.5[‡] | | TCZ: 14.0, PBO: 14.0[‡] | | TCZ: 19, Usual Care: >28 | |
| Hazard ratio (TCZ/PBO) (95% CI) | 1.35 (1.02, 1.79)[†††] | | 1.16 (0.91, 1.48)[†] | | 0.965 (0.78, 1.19)[†††] | | 1.22 (1.12 to 1.33)^ | |
| p-value | 0.037[†††] | | 0.2417[†§] | | 0.7414[†††] | | <0·0001^ | |
| **Incidence of MV/ Time to MV or Death/ Use of invasive MV (including ECMO) or Death[b]** | | | | | | | | |
| | n=183 | n=90 | | | n=371 | n=188 | n=1754 | n=1800 |
| Cumulative proportion** of patients at Day 28 | - | | TCZ: 12.0%, PBO: 19.3% | | - | | - | |
| Proportion of patients by Day 28 | TCZ: 27.9%, PBO: 36.7%^^ | | TCZ: 11.6%, PBO: 18.8% | | TCZ: 27.5%, PBO: 29.8% | | TCZ: 35%, Usual Care: 42%*** | |
| Weighted difference (TCZ-PBO) in % (95% CI) | -8.9% (-20.7%, 3.0%)[‡‡] | | - | | –2.2% (–10.2%, 5.9%)[‡‡] | | - | |
| Hazard ratio (TCZ/PBO) (95% CI) | - | | 0.56 (0.33, 0.97)[†] | | - | | - | |
| Risk Ratio (TCZ/PBO) (95% CI) | - | | - | | - | | 0.84 (0.77 to 0.92) | |
| p value | 0.1355^^^ | | 0.0360[†§] | | 0.5915^^^ | | <0.0001 | |

ICU=intensive care unit; ITT=intention-to-treat population; mITT=modified intention-to-treat population, MV=mechanical ventilation.

[a] Defined as days from randomization to hospital discharge or "Ready for Discharge" not followed by ordinal scale category >1, hospital readmission or death for REMDACTA.

[b] COVACTA and REMDACTA results include incidence of mechanical ventilation by Day 28 in patients not on mechanical ventilation at baseline in the mITT Population. Time to mechanical ventilation or death by Day 28 was reported in EMPACTA mITT. RECOVERY reported use of invasive mechanical ventilation (including ECMO) or death among patients not on invasive mechanical ventilation at baseline in ITT population.

* Mortality included all cause up to Day 28. The Cochran- Mantel-Haenszel weighting approach was used to calculate the weighted difference with stratification factors (two stratification factors (region [North America, Europe] and mechanical ventilation [yes, no]) for COVACTA, one stratification factor (age group [≤60, >60 years]) for EMPACTA, two stratification factors (region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]) for REMDACTA). The Newcombe method was used to estimate the 95% CI for the weighted difference.

[β] Mortality included all cause up to Day 28. In RECOVERY, mortality difference (TCZ-PBO) at Day 28 estimated by the Kaplan−Meier approach (using Zee and Xie 2018 method) on time to death endpoint.

^ The log-rank 'observed minus expected' statistic (and its variance) was used (Peto et al 1977). The log-rank test driven rate ratios and its 95% CI are identical to unstratified Cox hazard ratio and its 95% CIs.

§§§ P value based on extended Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

[‖] P value for this EMPACTA endpoint was calculated with the stratified Cochran-Mantel-Haenszel test with age group (≤ 60, >60 years) as a stratification factor.

[†††]Cox Proportional Hazards model includes stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]

[†]Hazard ratios and associated 95% CIs were estimated for EMPACTA with stratified Cox proportional hazard model with age group (≤60, >60 years) as a stratification factor.

[†††]P value based on log-rank test stratified by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

[†]P values for EMPACTA were calculated with the stratified Log-rank test with age group (≤60, >60 years) as a stratification factor.

[§]Significance testing for EMPACTA was performed hierarchically to control for study-wide Type I error rate at a two-sided 5% significance level. Nominal P values are presented for secondary endpoints because first secondary endpoint failed to reach significance.

^^ For this analysis, COVACTA and REMDACTA patients who withdrew prior to discharge or died prior to Day 28 were assumed to have required mechanical ventilation by Day 28.

** Mortality included all cause up to Day 28. For EMPACTA, cumulative proportion of patients and associated 95% CI were estimated using the Kaplan-Meier method.

‡‡ Weighted difference in proportions as calculated using the Cochran-Mantel- Haenszel test stratified by stratification factor at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

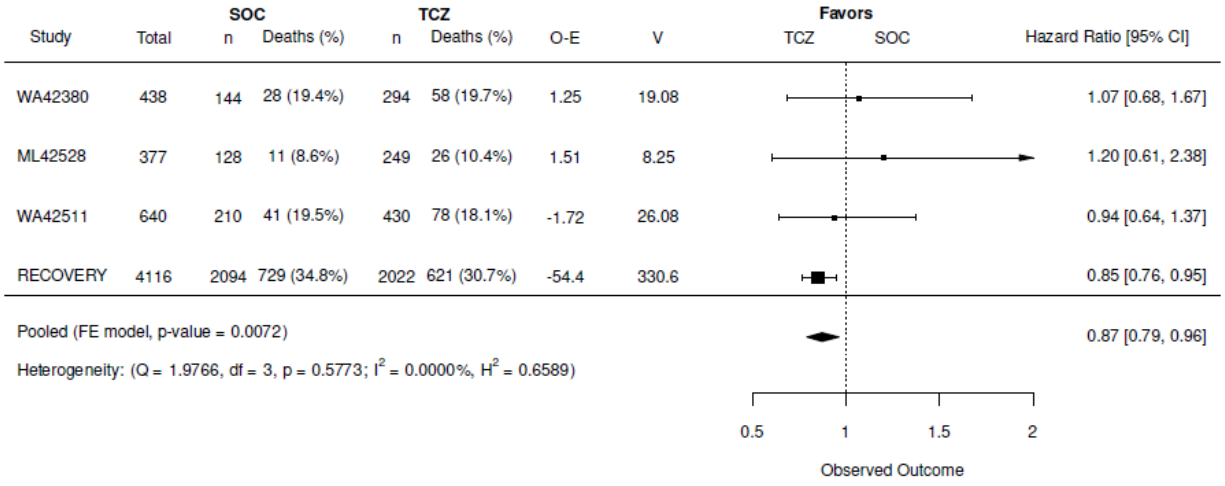
***Analyses include only those patients on no ventilator support or non-invasive ventilation at baseline (1754 patients in TCZ+Usual Care arm and 1800 in Usual Care arm).

^^^ P value based on extended Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].

‡ Median time-to-event were estimated using the Kaplan-Meier method.

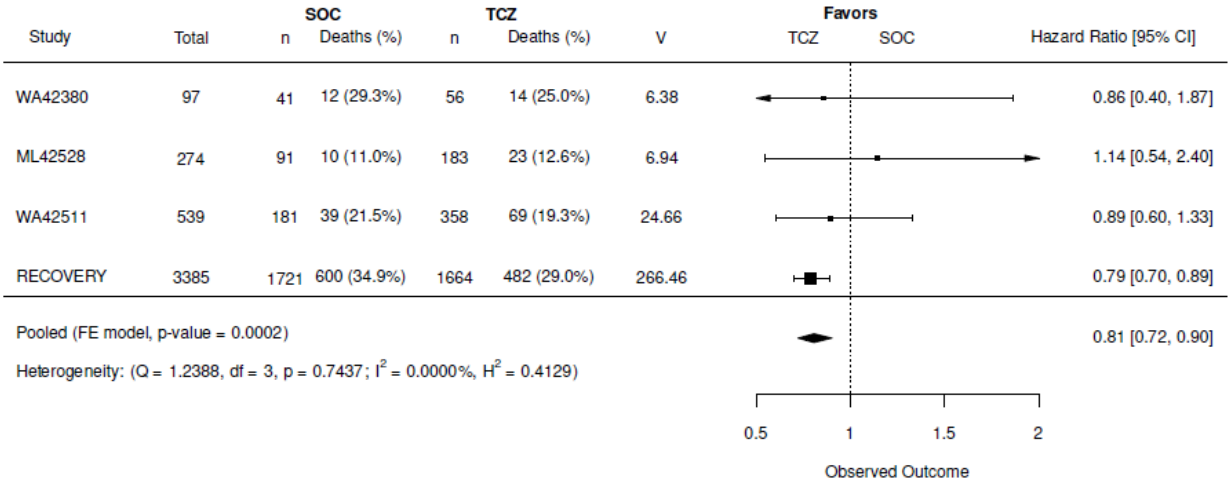
The MAH was asked to present further insight into the mortality data that seems to be slightly higher in the tocilizumab arm of study COVACTA compared to the placebo arm. The applicant stated, as shown in Figure 38, the hazard ratio (HR) and 95% confidence interval (CI) for time to death up to Day 28 estimated by the log-rank approach for RECOVERY are contained within the 95% CIs for

COVACTA and the other MAH-sponsored studies, indicating that the results from COVACTA and the other Roche-sponsored studies are not statistically inconsistent with the RECOVERY results. Furthermore, in the subgroup of patients in the Roche-sponsored studies who were receiving systemic corticosteroids at baseline, more consistent mortality benefits were seen (Figure 39).




Log-rank O-E for RECOVERY and Roche Trials. The hazard ratio (HR) is calculated by taking ln(HR) to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse variance weighted averages of the ln(HR) values. This is fitted by a fixed effects model with ln(HR) as the response and V as the weights to get the pooled effect.
Roche Data Sources:
root/clinical_studies/RO4877533/share/pool_COVID19/prod/outdata_vad

**Figure 38 Fixed Effects Meta-analysis based on combining study-level log death rate ratio up to Day 28 estimated by log-rank approach**




Cox hazard ratio (HR) for Roche Trials. Log-rank O-E for RECOVERY
where HR calculated by taking ln(HR) to be (O-E)/V with normal variance 1/V.
A fixed effects model with ln(HR) as response and V as the weights to get the pooled effect.
Roche Data Source:
root/clinical_studies/RO4877533/share/pool_COVID19/prod/outdata_vad

**Figure 39 Fixed effects meta-analysis based on combining study-level log death rate ratio up to Day 28 estimated by log-rank approach in Patients Receiving Systemic Corticosteroids at Baseline**

**Mortality in females and Black/African American patients**

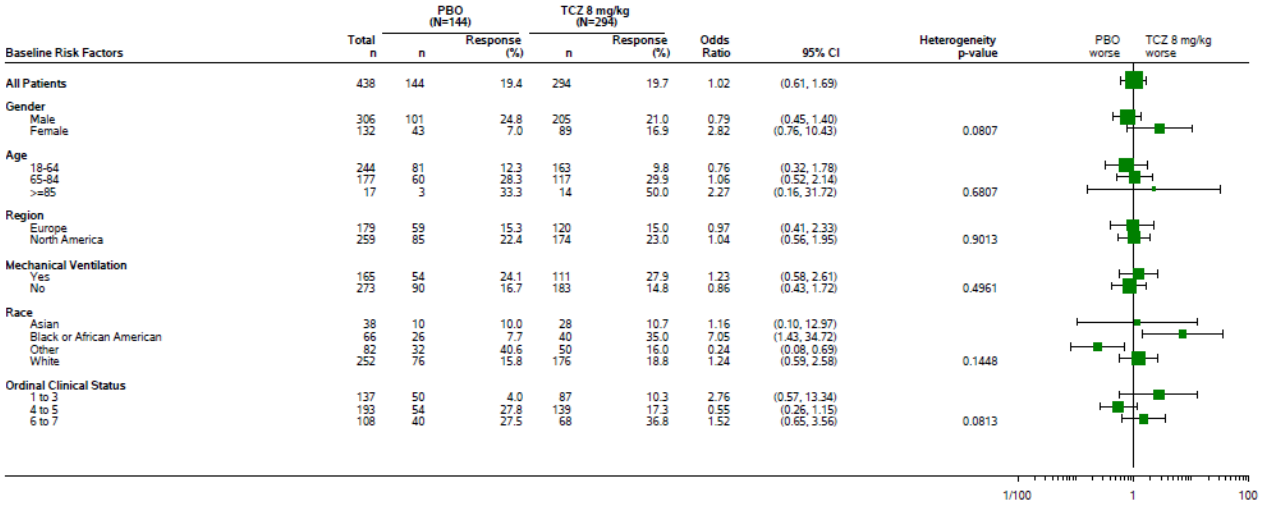
The MAH was also requested to provide further analyses on Mortality in females and Black/African American patients. According to the MAH, the subgroup analyses by gender and race in COVACTA suggesting that tocilizumab might be less effective in females and Black/African Americans must be interpreted with caution, given the relatively small numbers in these subgroups. As indicated in Figure 40 below, additional heterogeneity test p-values were provided for each set of subgroup analyses; these suggest that there were no statistically significant differences in the odds ratios (OR) for mortality between genders and between races.

Furthermore, a logistic regression analysis of Day 28 mortality combining all patients from Roche-sponsored trials (COVACTA, EMPACTA and REMDACTA) showed that the differences in gender and race are less apparent compared to those observed in COVACTA alone: OR of 1.20 (95% CI: 0.69–2.09) in females and 0.90 (95% CI: 0.63–1.29) in males with overlapping CIs. The OR for the Black/African American patient subgroup was 2.08 (95% CI: 0.83–5.21); information regarding other variables analyzed is presented in Figure 41.

A logistic regression analysis of Day 28 mortality from all Roche-sponsored trials (COVACTA, EMPACTA, and REMDACTA) in the subgroup of patients receiving systemic corticosteroids at baseline (the indicated patient population) suggested treatment benefits with TCZ in both genders (females: OR=0.83 [95% CI: 0.44–1.55] and males: OR=0.88 [0.56–1.38]) and in Black/African Americans (OR=0.85 [95% CI: 0.28–2.60]) (

Figure 42).

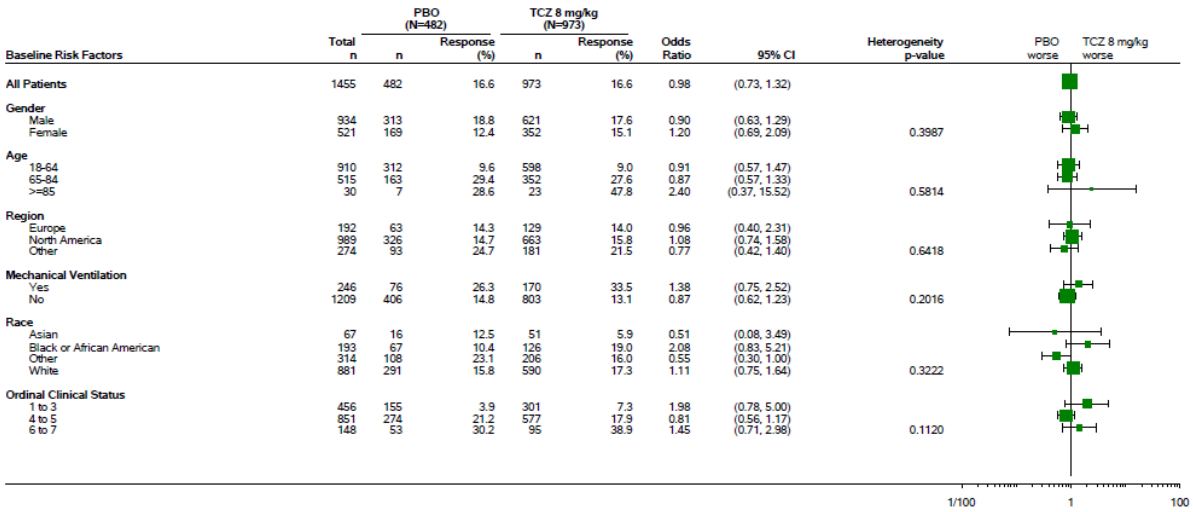
**Protocol: WA42380**
**Snapshot Date: 22JUL2020**




Odds Ratios within each subgroup as calculated by Logistic Regression Analysis for Mortality. Each logistic Regression model includes the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]) along with a treatment term, baseline subgroup term (as defined in the table) and a treatment*subgroup interaction. Where the subgroup of interest is a stratification factor, the stratification factor, as well as a stratification*treatment interaction will be fitted. For subgroup analysis of baseline ordinal scale categories, the stratification mechanical ventilation will be dropped from the model. An Odds Ratio < 1 favors TCZ over PBO.
Race category of 'Other' is defined as 'MULTIPLE', 'NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER', 'AMERICAN INDIAN OR ALASKA NATIVE' and 'UNKNOWN'.
95% CIs calculated using Wald method.
Program: root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/TLR_D28CUT/prod/program/g_mort_forest_ema.sas
Output: root/clinical_studies/RO4877533/CDT30169/WA42380/data_analysis/TLR_D28CUT/prod/output/g_mort_forest_ema_MITT_D28CUT_42380.pdf 19OCT2021 17:48

**Figure 40 Summary Forest Plot of Logistic Regression Analysis of Mortality, by Subgroup at Day 28 (Week 4), Modified Intent-to-Treat Population (Study WA42380)**

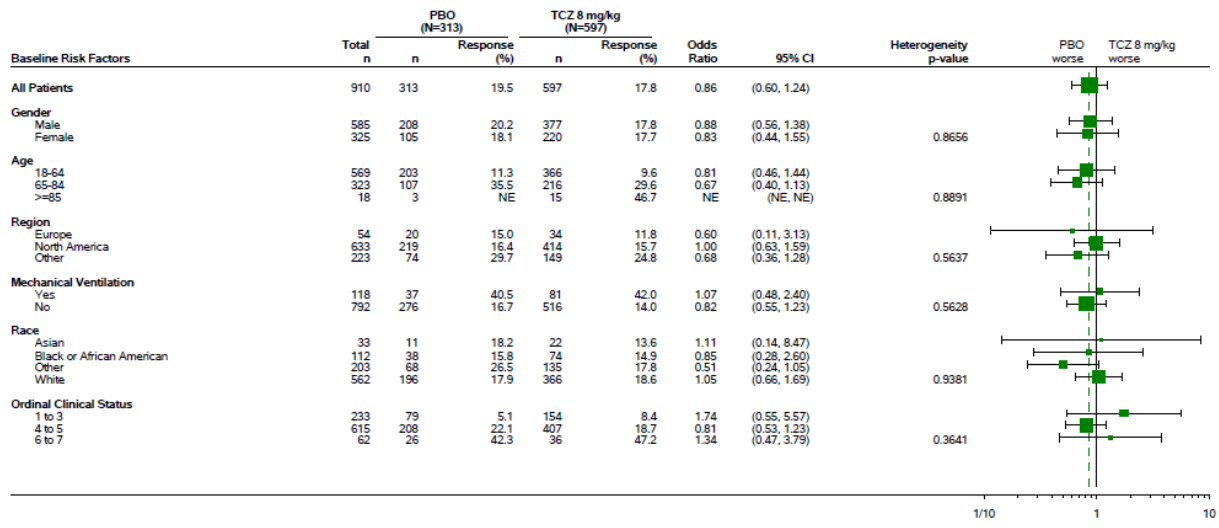
Protocol: WA42511, WA42380, ML42528




Odds Ratios within each subgroup as calculated by Logistic Regression Analysis for Mortality. Each logistic regression model is stratified by study and includes the covariates of region [North America, Europe, Other] and baseline mechanical ventilation [yes, no] along with a treatment term, baseline subgroup term (as defined in the table) and a treatment*subgroup interaction. Where the subgroup of interest is the covariate of region or baseline mechanical ventilation, the covariate, as well as a covariate*treatment interaction will be fitted. For subgroup analysis of baseline ordinal scale categories, mechanical ventilation will be dropped from the model. An Odds Ratio < 1 favors TCZ over PBO.
Race category of 'Other' is defined as 'MULTIPLE', 'NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER', 'AMERICAN INDIAN OR ALASKA NATIVE' and 'UNKNOWN'.
95% CIs calculated using Wald method.
Program: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/program/g_mort_forest_ema.sas
Output: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/g_mort_forest_ema_MITT.pdf 19OCT2021 16:26

**Figure 41 Summary Forest Plot of Logistic Regression Analysis of Mortality, by Subgroup at Day 28 (Week 4), Pooled Modified Intent-to-Treat Population**

Protocol: WA42511, WA42380, ML42528




Odds Ratios within each subgroup as calculated by Logistic Regression Analysis for Mortality. Each logistic regression model is stratified by study and includes the covariates of region [North America, Europe, Other] and baseline mechanical ventilation [yes, no] along with a treatment term, baseline subgroup term (as defined in the table) and a treatment*subgroup interaction. Where the subgroup of interest is the covariate of region or baseline mechanical ventilation, the covariate, as well as a covariate*treatment interaction will be fitted. For subgroup analysis of baseline ordinal scale categories, mechanical ventilation will be dropped from the model. An Odds Ratio < 1 favors TCZ over PBO.
Race category of 'Other' is defined as 'MULTIPLE', 'NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER', 'AMERICAN INDIAN OR ALASKA NATIVE' and 'UNKNOWN'.
95% CIs calculated using Wald method.
Program: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/program/g_mort_forest_bstrd_ema.sas
Output: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/g_mort_forest_bstrd_ema_MITT.pdf 19OCT2021 16:55

**Figure 42 Summary Forest Plot of Logistic Regression Analysis of Mortality, by Subgroup at Day 28 (Week 4) in Patients with Baseline Steroid Use, Pooled Modified Intent-to-Treat Population**

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

Evaluation of **MARIPOSA** regarding dose response and PK/PD data can be found in the PK/PD part of this AR (see Section 2.3.2). Exploratory efficacy outcomes were evaluated at Day 28 and patients were followed for a total of 60 days. All efficacy assessments were exploratory. The mortality rate at Day 28 was similar in both treatment groups. Results presented are acceptable to suggest 8mg/kg as the optimal dose for patients with COVID-19 pneumonia. Further conclusions on efficacy cannot be drawn from this study.

**RECOVERY** (Randomized Evaluation of COVID-19 Therapy) is an investigator-initiated, randomized, controlled, open-label, platform trial to evaluate the effects of potential treatments in patients hospitalized with COVID-19 in the UK.

The study enrolled patients with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L). The chosen patient population is representative for the COVID-19 disease with a more pronounced severity and this population has a high unmet medical need for effective therapy. The proposed dosing regimen of a single infusion of TCZ 8 mg/kg (with an additional infusion 8-24 hours later if the clinical signs or symptoms do not improve) is considered to be appropriate.

The chosen primary endpoint of 28-day mortality allows a robust evaluation of efficacy. The list of secondary endpoints (time to discharge from hospital, receipt of invasive mechanical ventilation, or death, use of non-invasive respiratory support, time to successful cessation of invasive mechanical ventilation, and use of renal dialysis or hemofiltration) is conclusive and allow further insight into efficacy of tocilizumab in COVID-19 treatment.

The adaptive study design allowed quick recruiting of patient into different treatment arms to facilitate a timely evaluation of various treatment options. Evaluation of such complex and adaptive study settings might be confounded by these protocol amendments, interim analysis, and unblinding of data from single study arms. As this study enrolled patients in a worldwide pandemic situation, this was considered acceptable by the CHMP, but respective uncertainties warrant further discussion (see below).

All eligible patients received usual care and underwent an initial (main) randomization. Eligible patients for the trial had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization to receive either intravenous tocilizumab or usual care alone.

Patients were randomized in a factorial design to combinations of numerous experimental treatments, and were eligible for enrolment into the tocilizumab cohort upon deterioration within 21 days from the initial randomization. Eligible patients were randomized to either tocilizumab or no additional treatment on top of standard care and previously allocated treatments. Adaptations to the design, such as opening or stopping randomization to other experimental treatment options that might have been given in addition, add uncertainty. On the other hand, the factorial design is considered a strength, as it allows further investigation of potential drug-drug interactions, which is of particular interest for corticosteroids. The MAH explained that after 16 June 2020, i.e. after discontinuation of part A randomization to dexamethasone on 8 June 2020 and subsequent recommendations, 97% of the patients received corticosteroids. This is considered reassuring by the CHMP.

The randomization was simple randomization, using a 1:1 allocation ratio for the tocilizumab comparison. Simple randomization may not be optimal in light of expected differences across study sites (e.g. with regard to standard care and availability of therapies). However, the methods are acceptable to the CHMP.

Randomization was not stratified by study site. The reason behind the decision not to stratify by trial site was that in an open-label trial there would have been the risk that an investigator could guess the next allocation before randomizing a patient, and therefore introduce bias into the randomized comparison. This is understood by the CHMP. The results of the Cox modelling adjusted for trial site showed no difference in hazard ratio compared to the unadjusted results.

No estimand has been defined. However, it seems clear that the primary analysis of 28-day mortality targets a treatment policy estimand, and this would be the estimand of primary interest.

The analysis set, consisting of all subjects randomized in the second randomization, is endorsed by the CHMP. Adherence to the intent-to-treat principle is endorsed.

The CHMP endorsed that the protocol stated that for any pairwise comparison, only concurrent controls would be analysed.

The primary outcome of 28-day mortality was planned to be analysed by means of a log-rank test. The analyses were not adjusted for baseline covariates. The methods are acceptable to the CHMP.

The degree of pre specification is low. No sample size was prespecified in the study protocol. However, the MAH refers to a contract signed in April 2020 between Roche and the RECOVERY sponsor specifying the delivery of tocilizumab to be able to treat 2000 patients. The presented sample size calculation that sufficient patients should be enrolled to each comparison to provide at least 90% power at two-sided p=0.01 to detect a proportional reduction in 28-day mortality of one-fifth is comprehensible. The independent data monitoring committee was tasked to repeatedly evaluate accumulating data for efficacy on 28-day mortality, at intervals of approximately 2-4 weeks.

At the CHMP's request, the MAH discussed type I error control: The MAH clarified that a significance level of 0.05 was specified in the SAP (but not in the study protocol). Further the MAH explained that there were 16 interim reviews of efficacy in the tocilizumab cohort by the DMC before the recommendation to stop enrolment was issued in the 17th review. There were additional DMC reviews that assessed baseline data. The MAH provided considerations on how this might have affected type I error control, assuming a version of the Haybittle-Peto stopping rule being adopted. In short, the MAH states that the significance level to be used in the "final" analysis would have been reduced from 0.05 to 0.044 (or 0.049, assuming different stopping rules). The CHMP noted that no such adjustment of the significance level was planned or performed, and the above considerations would consequently translate into an inflation of type I error. Further, the stopping rule "benefit on total mortality of at least 3 to 3.5 standard errors" is somewhat imprecise and not necessarily in line with the sample size considerations aiming at a mortality reduction of one fifth. However, the CHMP agreed that a benefit of at least 3 to 3.5 standard errors can be regarded statistically persuasive. Despite uncertainty, it seems that the overall type I error inflation on the primary endpoint is rather small. There was not multiplicity adjustment for secondary outcomes. There was no multiplicity adjustment for different treatment comparisons. RECOVERY is a platform study including a range of treatments. The fact that the same individuals might have been included in more than one analysis (e.g. in the tocilizumab analysis and in the dexamethasone analysis) adds complexity and increases uncertainty because results are likely correlated. The MAH's justification was considered acceptable to the CHMP.

**COVACTA** was a randomized double-blind study comparing tocilizumab against placebo on top of standard of care in severely ill Covid-19 pneumonia patients. The outline of the study and the primary

endpoint of clinical status using a 7 point ordinal scale at day 28 are appropriate to evaluate efficacy and safety. Overall mortality was evaluated as secondary endpoint.

In study COVACTA, the treatment arms were generally balanced with respect to demographic and baseline disease characteristics. The only differences of clinical interest between the two treatment arms include a higher proportion of patients >85 years of age in the TCZ +SOC arm (14 [4.8%]) compared to the PBO+SOC arm (3 [2.1%]), and a lower proportion of patients in the TCZ+SOC arm than the PBO+SOC arm that received systemic steroids (57 [19.4%] vs. 41 [28.5%]) and antiviral treatment (71 [24.1%] vs. 42 [29.2 %]). This might have an influence on the efficacy results.

The study design of the **EMPACTA** study is a classical double-blind randomized placebo controlled study applying tocilizumab as add on to standard of care. The design is appropriate to evaluate efficacy and safety of tocilizumab in hospitalized, non-ventilated patients with COVID-19 pneumonia.

The primary endpoint of the EMPACTA study is cumulative proportion of patients with death or requiring mechanical ventilation by Day 28. This is an acceptable and clinically meaningful endpoint. Together with the comprehensive set of secondary and exploratory endpoints, an evaluation of the effect of addition of tocilizumab to standard of care is possible with this design. Especially the secondary endpoint of mortality at day 28 is of interest.

EMPACTA randomized 388 evaluable patients. Of the 388 patients randomized at a 2:1 ratio to the TCZ+SoC arm (259 patients) and the PBO+SoC arm (129 patients), 377 received study treatment. The study conduct followed all applicable regulations and guidelines.

Study design of **REMDACTA** was a classical phase III, randomized, double-blind, multicenter design to evaluate the efficacy and safety of Remdesivir plus Tocilizumab compared with Remdesivir plus placebo in hospitalized patients with severe COVID-19 pneumonia. The defined patient population is representative for COVID-19 pneumonia already treated with standard of care including low dose steroids.

The primary endpoint "time to discharge or ready for discharge up to day 28" together with a comprehensive set of secondary and exploratory endpoints is appropriate and will allow assessment of efficacy in the proposed patient population in comparison to Remdesivir. REMDACTA randomized 649 patients in a 2:1 ratio to the TCZ+RDV arm (434 patients) and the PBO+RDV arm (215 patients), 640 received both RDV and TCZ/PBO.

## Efficacy data and additional analyses

In RECOVERY 4116 patients were randomized. One thousand four hundred and eight nine (1489) patients (TCZ: 994 and PBO: 495) were randomized in COVACTA, EMPACTA and REMDACTA. With regard to patient demographics, the majority were male and the mean age ranged between 56 and 64 years. The proportion of patients aged ≥ 65 years was higher in COVACTA compared to REMDACTA and EMPACTA. Thirty four percent (34%) of patients in the TCZ arm and 35% patients in the Usual Care arm in RECOVERY, which reported the age categories differently, were aged ≥70 years. COVACTA enrolled patients across wide range of disease severity and higher rate of patients on mechanical ventilation compared to the other three studies whereas EMPACTA excluded patients who required non-invasive or invasive mechanical ventilation. The tocilizumab arm of RECOVERY recruited hospitalized patients across a broader range of respiratory support.

In **RECOVERY** efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomized with 2022 patients in the tocilizumab + usual care arm and 2094 patients in the usual care alone arm.

The baseline demographic and disease characteristics of the ITT population were well balanced across treatment arms: The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White (76%). The median (range) level of CRP was 143 mg/L (75-982). At baseline, 0.2% (n=9) of patients were not on supplemental oxygen, 45% of patients required low flow oxygen, 41% of patients required non-invasive ventilation or high-flow oxygen and 14% of patients required invasive mechanical ventilation; 82% were reported receiving systemic corticosteroids. The most common comorbidities were diabetes (28.4%), heart disease (22.6%) and chronic lung disease (23.3%).

Among those patients who completed the follow-up form for RECOVERY, 317 patients in the TCZ+Usual Care arm (16%) did not receive TCZ. At the CHMP's request, the MAH presented an evaluation of baseline characteristics of patients allocated to receive tocilizumab and those who actually received it, versus those allocated to tocilizumab but did not receive it for unknown reasons. The baseline and disease characteristics of the two groups are very balanced. Therefore, it was concluded that a bias was not introduced.

At the CHMP's request, the MAH provided the confirmation that for all patients not withdrawing from the study, either a follow up form or registry data to identify deaths were used. With regard to drop outs/missing values, the data are 99% complete which was considered re assuring to the CHMP.

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

Furthermore, allocation to tocilizumab was associated with a greater probability of discharge from hospital within 28 days (57% vs 50%). The median time to hospital discharge was 19 days in the tocilizumab+ usual care arm and >28 days in the usual care arm (hazard ratio [95% CI] = 1.22 [1.12 to 1.33]). There is some uncertainty on the correct estimation of the effect on time to discharge, as there is an observed difference in deaths between the treatment groups. However, such uncertainty is only of little relevance in light of an observed reduction in mortality.

Furthermore, the need for application of invasive mechanical ventilation (including ECMO) was reduced for patients on tocilizumab compared to SOC only (15% versus 19%, p 0,0019).

These results are of clinical relevance and are regarded as supportive for the primary endpoint.

The CHMP questioned that eligibility/inclusion criteria and baseline criteria after the first randomisation may have an impact on the ultimately studied population. The MAH provided an overview of the randomisation process and the underlying eligibility criteria showing that criteria for the first randomisation were very broad and so a selection of more than 20000 patients was possible. The criteria for the second randomisation were also quite broad, as up to 21 days after the first randomization and regardless of treatment allocation, adult patients with clinical evidence of 'progressive COVID-19' (defined as patients who met both criteria of hypoxia [oxygen saturation <92% on air or receipt of oxygen] and inflammation [CRP ≥75 mg/L]) were eligible for the second randomization. This analysis indicates that randomized patients were overall similar to non-randomized patients, but had a relatively worse respiratory status. Reasons for the decision not to randomize a patient to tocilizumab were e.g. bacterial sepsis. The CHMP concluded that the presented comparison

of baseline characteristics of patients eligible for randomization to tocilizumab that were actually randomized versus those that were not randomized does not show differences that would allow a better characterization of the studied population.

At the CHMP's request, the MAH provided a more detailed insight with regard to the timing of the two randomization steps. The median time between first and second randomization was 0.3 hours (interquartile range [IQR] 0.1–25.3 hours), so these patients could not have progressed, but were in danger of progressing. The maximum duration between the two randomizations was up to 21 days, with 90% patients up to 5.0 days between the randomizations (5.0 days for TCZ arm and 6.0 days for usual care) and 95% patients up to 8.0 days between the randomizations (8.0 days for TCZ arm and 9.0 days for usual care). These time periods are regarded as comprehensive by the CHMP.

The CHMP also questioned whether baseline CRP levels have a major influence on the efficacy of tocilizumab. The MAH presented two Cox regression models. Results from the two statistical evaluations showed no significant impact of CRP levels (≥ 75 mg/L) on the tocilizumab treatment effect for 28-day mortality over usual care. It has to be kept in mind that CRP levels <75 mg/L were not included in this evaluation as these patients were excluded from the second randomization. Further subgroup analysis from the MAH sponsored trials as well as from the WHO meta-analysis (Association between administration of interleukin-6 antagonists and mortality among hospitalized patients with COVID-19: a meta-analysis' by Shankar-Hari M, Vale C, J Sterne et al in JAMA) on the influence of different CRP levels on the efficacy of tocilizumab also showed no correlation. However, since patients with CRP levels <75 mg/L were not included in RECOVERY, it is uncertain whether the treatment effect can be extrapolated to patients with CRP levels <75 mg/L. Therefore, a corresponding warning statement was included into section 4.4 of the SmPC.

In study **COVACTA**, the primary endpoint of <Clinical status assessed using a 7-category ordinal scale at Day 28> was not met. There was no statistically significant difference in the distribution of clinical status (ordinal scale) at Day 28 between the treatment arms tocilizumab +SOC and placebo+SOC. Therefore, all secondary endpoints failed as well due to the hierarchical statistical program. Not even a nominal statistical significance could be seen in the secondary endpoints <mortality at Week 4 and up to Day 60>, <Clinical status assessed using a 7-category ordinal scale at Week 2>, <Ventilator-free days at Week 4>, and >Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status to Week 4>.

The results with regard to mortality were seen as rather critical as the tocilizumab arm had a slightly higher mortality compared to the placebo arm. In the rapidly evolving treatment setting and the pandemic situation, this might be a chance finding, but it was still of concern. The MAH responded that this study was insufficiently powered to evaluate mortality and that only the RECOVERY study was sufficiently powered. They further expand that the hazard ratio (HR) and 95% confidence interval (CI) for time to death up to Day 28 estimated by the log-rank approach for RECOVERY are contained within the 95% CIs for COVACTA and the other MAH-sponsored studies, indicating that the results from COVACTA and the other MAH-sponsored studies are not statistically inconsistent with the RECOVERY results. The MAH argued that the results are more compelling in the patient cohort receiving corticosteroids as seen in the RECOVERY results. This is endorsed by the CHMP; see below for use with corticosteroids.

Only for the secondary endpoint <Time to hospital discharge or "ready for discharge"> a nominal statistical significance was observed. The median time to hospital discharge was 20 days for the tocilizumab group compared to 28 days for the control group. This time difference could be regarded as of medical importance for the CHMP.

In study **EMPACTA**, the baseline demographics were overall balanced between treatment arms. More than 80% were in a minority race/ethnic group, more than 75% had at least one coexisting condition,

and more than 25% of the patients were older than 65 years of age. The majority of patients were White (Hispanic and non-Hispanic; 52.8%) and from minority racial and ethnic groups. The largest combined race/ethnic group was Hispanic/Latino (56.0%), followed by Black/African American (14.9%), American Indian/Alaska Native (12.7%), and White (non-Hispanic; 12.7%).

Also, baseline disease characteristics (including symptoms at diagnosis, clinical status, use of supplemental oxygen, use of steroid or antiviral treatments, and levels of inflammatory markers), baseline prior and concurrent diseases, and use of previous and concomitant medications, were mostly well balanced between treatment arms.

Study EMPACTA met the primary endpoint of cumulative proportion of patients with death or requiring mechanical ventilation by Day 28. The cumulative proportion of patients who required mechanical ventilation or died by Day 28 estimated by the Kaplan-Meier method was 12.0% (95% CI: 8.52% to 16.86%) for TCZ+SoC and 19.3% (95% CI: 13.34% to 27.36%) for PBO+SoC. This difference of 7.3% points was statistically significant with a p-Value of 0.0360. Although this combined endpoint of mechanical ventilation or death is not optimal, both parts are of clinical relevance. The results clearly show that the both events of death and progress to mechanical ventilation contribute equally to the superiority of tocilizumab.

The secondary endpoints are not supportive for this finding. The four secondary endpoints comparing efficacy between the TCZ+SoC and the placebo+SOC arms were evaluated in a pre-specified hierarchical testing order. Time to discharge/ready for discharge was the first secondary endpoint in this order and here, no statistical significance in the different between the treatment arms could be shown. Therefore, all other p values for other secondary endpoints are only nominal.

Time to Improvement in Clinical Ordinal Status did not show any significant difference between tocilizumab and placebo.

Time to Clinical Failure to Day 28 was not evaluable in either group.

The secondary endpoint with the highest clinical relevance, mortality rate at Day 28 and Day 60 was 10.4% (95% CI: 7.2%, 14.9%) in the TCZ+SoC arm compared with 8.6% (95% CI: 4.9%, 14.7%) in the PBO+SoC arm and not statistically significant. Also, for the day 60 evaluation, no difference in mortality between tocilizumab and placebo arms was seen. These findings do not support a strong evidence of efficacy for the addition of tocilizumab to SOC.

The treatment arms of **REMDACTA** study were generally balanced with respect to demographic characteristics and age. The majority of patients were male (61.9% in the TCZ+RDV arm and 66.2% in the PBO+RDV arm, respectively) and White (64.9% and 71.4%, respectively). Some differences in ethnicity ca be seen between the treatment arms: 58.1% of patients in the PBO+RDV arm were Hispanic or Latino versus only 48.4% in the TCZ+RDV arm. These imbalances are not regarded as of any importance for the efficacy evaluation.

Also, the baseline disease characteristics were more or less comparable across treatment arms in the study population. With regard to mechanical ventilation a little difference can be seen as a higher proportion of patients in the TCZ+RDV arm were on mechanical ventilation (13.7%) at baseline compared with the PBO+RDV arm (10.5%). No other meaningful differences are observed with regard to all other evaluated baseline and disease characteristic factors.

The primary endpoint of study was not met; there was no statistically significant difference between treatment arms in time to hospital discharge or "ready for discharge" up to Day 28 (log-rank p-value = 0.7414). The median time to hospital discharge or "ready for discharge" was 14.0 days in both treatment arms (95% CI: [12.0, 15.0] in the TCZ+RDV arm and [11.0, 16.0] in the PBO+RDV arm). Therefore, study REMDACTA could not show superiority against Remdesivir.

As the primary endpoint was not met, evaluations of the key secondary endpoints are only nominal.

The secondary endpoints (Time to Mechanical Ventilation or Death up to Day 28, Clinical Status (Assessed using a 7-Category Ordinal Scale) at Day 14, Time to Death up to Day 28) were not able to even show a nominal superiority of tocilizumab treatment compared to placebo + SOC. There was also no difference between the treatment arms regarding mortality at day 28 or day 60.

At the CHMP's request, a thorough discussion was also provided by the MAH with the focus on the observed inconsistency regarding D28 mortality across the different trials. According to the MAH, the main reason for the inconsistent efficacy results among the different randomized controlled studies is seen in the challenges of designing an adequately powered study during the pandemic situation and the lack of knowledge of optimal treatment and the disease at the beginning of the pandemic. Only the RECOVERY study was appropriately powered to detect differences in mortality. The MAH points out that meta-analysis e.g. by the WHO also point in the same direction as the results of RECOVERY and showed that that tocilizumab reduces all-cause mortality at Day 28 compared to usual care/placebo. The CHMP considered that the response was acceptable. Considering that the demonstration of the efficacy is based on the data from the RECOVERY study, only this information is included in Section 5.1 of the SmPC.

Relevant heterogeneity of the treatment effect was observed with corticosteroid use. In RECOVERY, in those patients who did not receive corticosteroid treatment at baseline, the point estimate for the effect of tocilizumab on 28-day mortality was negative (risk ratio: RR: 1.16, 95%-CI: (0.91; 1.48)) suggesting a potential detriment. This heterogeneity is of clinically relevant size, is significant (interaction p-value =0.01) and is replicated through a pooled mITT analysis of the three MAH-sponsored studies (hazard ratio: 1.34 (0.79; 2.26)).

At the CHMP's request, the MAH discussed the role of corticosteroid treatment in the significant efficacy results throughout the main and the supportive studies and the CHMP concluded that the benefit seen in the tocilizumab arms was attributable to tocilizumab. This is further substantiated by the findings of the WHO prospective meta-analysis.

The CHMP concluded that tocilizumab has benefit on top of corticosteroids but not without corticosteroids. Consequently, the CHMP recommended that tocilizumab should not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup. This is adequately reflected in the indication "*RoActemra is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation*" and a corresponding warning has been included in the Section 4.4 of the SmPC at the CHMP's request. Section 5.1 of the SmPC also states that "*The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).*"

The CHMP concluded that tocilizumab reduces mortality at Day 28 compared to usual care/placebo among patients also receiving treatment with a systemic corticosteroid at baseline. The proposed indication was considered acceptable except for the word "hospitalized" which the MAH agreed to delete at the CHMP's request.

## 2.4.4. Conclusions on the clinical efficacy

The tocilizumab arm of RECOVERY met its primary endpoint and shows that administration of tocilizumab was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone. Furthermore, allocation to tocilizumab was associated with a greater

probability of discharge from hospital within 28 days (57% vs 50%). These results are considered clinically relevant.

Study EMPACTA met the primary endpoint. The proportion of patients who required mechanical ventilation or died by Day 28 was 12.0% for TCZ-SoC and 19.3%. This difference of 7.3% points was statistically significant with a p-Value of 0.0360. However, the secondary endpoints are not supportive for this finding. The secondary endpoint with the highest clinical relevance, mortality rate at Day 28 and Day 60 was not statistically significant between the treatment arms. Also, for the day 60 evaluation, no difference in mortality between tocilizumab and placebo arms was seen.

The studies COVACTA and REMDACTA did not meet the primary endpoints and could not show statistical significant benefit of addition of tocilizumab to SOC or a superiority against Remdesivir. The secondary endpoints of these studies do not provide further supportive evidence. However, the CHMP recognised that the situation of rapidly evolving standard of care treatment, ongoing and fluently changing pandemic situation with different virus variants emerging in different parts of the world hinder a clear and straight forward study conduct and efficacy evaluation.

A thorough discussion was provided by the MAH with the focus on the observed inconsistency regarding D28 mortality across the different trials. Only the RECOVERY study was appropriately powered to detect differences in mortality. Meta-analysis e.g. by the WHO also point in the same direction as the results of RECOVERY and showed that that tocilizumab reduces all-cause mortality at Day 28 compared to usual care/placebo. This was considered acceptable to the CHMP.

Tocilizumab should not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup.

The CHMP considered that the efficacy was demonstrated in the indication: "*treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation*."

## *2.5. Clinical safety*

### *Patient exposure*

**RECOVERY**

Four thousand one hundred sixteen (4116) adults of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, (2022 TCZ and 2094 SOC) including 3385 (82%) patients receiving systemic corticosteroids: 1664 (82%) in TCZ arm and 1721 (82%) in SOC arm.

At randomisation, 562/4116 (14%) patients were receiving invasive mechanical ventilation, 1686/4116 (41%) were receiving non-invasive respiratory support (including high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation), and 1868/4116 (45%) were receiving no respiratory support other than simple oxygen therapy.

The RECOVERY trial has presented limited safety data and is not presented in the SmPC.

**COVACTA (WA42380)**

Of the 452 patients randomized, 234 (224 (74.4%) in the TCZ + SOC arm and 108 (71.5%) in the PBO+SOC arm) completed the study to the Day 28 follow-up time point.

A total of 77 patients (25.6%) in the TCZ+SOC arm and 43 patients (28.5%) in the PBO+SOC arm discontinued the study on or prior to Day 28. The most common reason for study discontinuation was

death (57 patients [18.9%] in the TCZ+SOC arm and 29 patients [19.2%] in the PBO+SOC arm), followed by lost to follow-up (7 [2.3%] and 5 [3.3%] patients, respectively), withdrawal by subject (7 [2.3%] and 4 [2.6%] patients, respectively).

Safety-evaluable population in COVACTA: 438 patients (295 in TCZ arm and 143 in PBO arm).

Duration

Patients were followed for 60 days after first dose of study medication. A total of 190 patients (63.1%) in the TCZ+SOC arm and 96 patients (63.6%) in the PBO+SOC arm completed the study to Day 60.

Exposure to study treatment: A total of 330/438 (75.3%) patients received one dose of study treatment, 230/295 (78.0%) in the TCZ+SOC arm and 100/143 (69.9%) in the PBO+SOC arm, and a total of 108/438 (24.7%) patients received two doses of study treatment, 65/295 (22.0%) in the TCZ + SOC arm and 43/143 (30.1%) in the PBO + SOC arm. The median total cumulative dose of tocilizumab was 731.2 mg (range 189.3 - 1600.0 mg).

At baseline, 56.8% (167/294) of patients in the TCZ+SOC arm and 55.6% (80/144) of patients in the PBO+SOC arm were in the ICU. At baseline, a total of 165 patients were on mechanical ventilation: 111 patients (37.7%) in the TCZ+SOC arm and 54 patients (37.5%) in the PBO+SOC arm

Baseline corticosteroids were used in 57/294 (19.3%) in the TCZ+SOC arm and 41/ 144 (28.4%) in the PBO+SOC arm

**EMAPACTA (ML42528)**

Safety-evaluable population: 377 patients (250 in TCZ arm and 127 in PBO arm). One patient in the PBO arm received tocilizumab and was included in the TCZ. More than 80% of patients belonged to a minority race/ethnic group, more than 75% had at least one coexisting condition, and more than 25% of the patients were older than 65 years of age.

For the indication as sought in the SmPC with concomitant corticosteroid treatment: 312/377 patients 201 / 250 (80.4%) in the TCZ arm and 111/ 127 (87.4%) in the PBO arm

Exposure to study treatment was comparable between the TCZ and PBO arms. A total of 377 patients received at least 1 dose of study treatment. Of those patients, 274/377 (72.7%) received 1 dose of study treatment (TCZ or PBO) and 103/377 (27.3%) received 2 doses. The mean total cumulative dose of tocilizumab received in the TCZ arm was 852.84 mg (range: 218.6 to 1601.2 mg).

**REMDACTA (WA42511)**

Safety-evaluable population: 642 patients (431 in TCZ + RDV arm and 211 in PBO+ RDV arm).

Duration

Patients were followed for 60 days after first dose of study medication.

All 429 patients in the TCZ+RDV arm received TCZ (80.2% received one dose and 19.8% 2 doses). Two hundred and eleven (211) out of 213 in the PBO+RDV arm received PBO (77.3% received one dose and 22.7% 2 doses). The baseline corticosteroid treatment was 358 (83.3%) in the TCZ+RDV arm vs 181 (86.2%) in the PBO+RDV – as mentioned above, the concomitant corticosteroid treatments were 43.6% in the TCZ+RDV and 45.5% in the PBO+RDV arm by Day 28.

**MARIPOSA**

Safety-evaluable population: 97 patients (49 in the 4 mg/kg TCZ arm and 48 in the 8 mg/kg TCZ arm).

Duration

Patients were followed for 60 days after first dose of study medication.

The majority of patients in both treatment groups received one dose of TCZ; 37 (75.5%) patients in the 4 mg/kg + SOC group and 39 (81.3%) patients in the 8 mg/kg + SOC group. All remaining patients in the safety population received 2 doses of TCZ.

Concomitant corticosteroid treatment (excluding those reported as topical, inhalant, or dermatological) was reported for 12 (24.5%) patients in the 4 mg/kg +SOC group and 16 (33.3%) patients in the 8 mg/kg + SOC group

## *Adverse events*

### RECOVERY

In the publication submitted in lieu of a CSR for the RECOVERY study (Hornby et al. 2021) Table 33 and Table 34 in the online Appendix contain patient numbers and frequency data for cause-specific mortality (Table 33) and major cardiac arrhytmia (presented among other cardiac arrhythmia categories in Table 34) in both TCZ+SoC and SoC arms, this was later considered as the PBO arm.

**Table 33** Effect of allocation to tocilizumab on cause-specific 28-day mortality

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

All-cause day 28 mortality was mainly due to COVID-19 mortality, both were higher in the SoC group. Other mortalities were of low frequency and similar for the two treatment groups, except for the "other infection" mortality, which occurred with numerically higher frequency in the SoC group.

**Table 34** Effect of allocation to tocilizumab on cardiac arrhythmia

| | Treatment allocation | |
|---|---|---|
| | Tocilizumab (n=2022) | Usual care (n=2094) |
| Number with follow-up form* | 1931 | 2013 |
| Atrial flutter or fibrillation | 83 (4%) | 99 (5%) |
| Other supraventricular tachycardia | 14 (1%) | 24 (1%) |
| Subtotal: Supraventricular tachycardia | 95 (5%) | 118 (6%) |
| Ventricular tachycardia | 9 (0%) | 14 (1%) |
| Ventricular fibrillation | 1 (0%) | 3 (0%) |
| Subtotal: Ventricular tachycardia or fibrillation | 10 (1%) | 15 (1%) |
| Atrioventricular block requiring intervention | 5 (0%) | 1 (0%) |
| Total: Any major cardiac arrhythmia | 108 (6%) | 133 (7%) |

*Information on new cardiac arrhythmias was only collected on follow-up forms from 12 May 2020 onwards; percentages are of those with such a form completed.

Frequencies of major cardiac arrhythmia as well as other types of cardiac arrhythmias were similar in the TCZ and SoC treatment groups. Note that percentages of patients with follow-up forms were also similar in the two treatment groups (94.5% (1931/2022 patients with follow-up form) and 96.1% (2013/2094 patients with follow-up form) in TCZ and SoC groups, respectively).

**EMPACTA (ML42528)**

Overall, 127/250 (50.8%) patients in the TCZ arm reported a total of 357 AEs and 67/127 (52.8%) patients in the PBO arm reported a total of 187 AEs.

- The most common AEs (≥10% of patients) reported by System Organ Class in the TCZ arm were Gastrointestinal disorders (16.0%), Respiratory, thoracic, and mediastinal disorders (13.2%), and Infections and infestations (10.0%).
- The most common AEs (≥10% of patients) reported by system organ class in the PBO arm were Respiratory, thoracic, and mediastinal disorders (17.3%), Gastrointestinal disorders and Infections and infestations (12.6% each), Metabolism and nutrition disorders (11.0%), and Nervous system disorders (10.2%).

Only one AE in the TCZ arm (1/250 [0.4%] patient) led to a dose interruption. No SAEs led to a dose interruption in either treatment arm. Excluding those who died (see below), no patients in either treatment arm discontinued from treatment or study due to an AE or SAE.

Treatment-related AEs occurred in 32/250 (12.8%) patients in the TCZ arm and in 5/127 (3.9%) patients in the PBO arm.

- Thirty two (32) patients in the TCZ arm experienced a total of 42 treatment-related AEs. The most common treatment-related AEs (≥2% of patients) were reported in system organ class of Investigations (3.2%), Gastrointestinal disorders (2.8%), and Infections and infestations (2.0%). The most common treatment-related AEs by PT in the TCZ arm were transaminases increased, leukopenia, and hypertension (each reported in 3/250 [1.2%] patients).
- In the PBO arm, 5/127 (3.9%) patients experienced a total of 13 related AEs. The most common treatment-related AEs (≥2% of patients) were reported in system organ class of Gastrointestinal disorders (2.4%). In the PBO arm, no single AE by PT was reported in more than 1 patient.

Severe AEs (NCI CTCAE Grade ≥3) were reported in 46/250 (18.4%) patients in the TCZ arm and in 31/127 (24.4%) patients in the PBO arm.

- The most common Grade ≥3 AEs by PT (reported in >2% of patients in either treatment arm) were acute respiratory failure (TCZ arm: 1.6% vs. PBO arm: 2.4%), acute respiratory distress syndrome (TCZ arm: 2.0% vs. PBO arm: 0.8%), septic shock (TCZ arm: 2.0% vs. PBO arm: 2.4%), pneumonia (TCZ arm: 0.4% vs. PBO arm: 3.1%), COVID-19 pneumonia (TCZ arm: 0.8% vs. PBO arm: 2.4%), pneumonia bacterial (TCZ arm: 0.0% vs. PBO arm: 2.4%), and acute kidney injury (TCZ arm: 0.4% vs. PBO arm: 2.4%).

The incidence of Adverse Events of Special Interest (AESIs) (Hy's Law, (serious) infections, malignancies, hepatic events, stroke, myocardial infarction, hypersensitivity/anaphylaxis, GI perforations, bleeding events, demyelinating events) was generally balanced between the two arms (49/250 [19.6%] in the TCZ arm versus 26/127 [20.5%] in the PBO arm).

- Hypersensitivity was reported at a higher incidence in the TCZ arm compared to PBO (4.4% vs. 2.4%). One patient in the TCZ arm experienced anaphylaxis.

- Two patients had GI perforations in the TCZ arm.

Infections (system organ class of Infections and infestations) were reported in 25/250 (10.0%) patients in the TCZ arm and in 16/127 (12.6%) patients in the PBO arm. Serious infections were reported in 13/250 (5.2%) patients in the TCZ arm and in 9/127 (7.1%) patients in the PBO arm.

- In the TCZ arm, 16 serious infections were reported in 13 patients (5.2%) who also had Grade 3 or 4 neutrophil decrease.
- In the PBO arm, 11 serious infections were reported in 9 patients (7%) who also had Grade 3 or 4 neutrophil decrease.

**COVACTA (WA42380)**

Overall, 240/295 (81.4%) patients in the TCZ arm reported a total of 949 AEs and 118/143 (82.5%) patients in the PBO arm reported a total of 433 AEs.

- The incidence of AEs by SOC was generally comparable between the two arms (<5% difference) with the exception of Respiratory, thoracic and mediastinal disorders, which were less frequent in the TCZ+SOC arm (21.7% [64/295 patients]) than in the PBO+SOC arm (30.1% [43/143 patients]).
- Other commonly reported AEs ≥5% of patients in either arm) were (TCZ+SOC arm and PBO+SOC arm, respectively):
    - Urinary tract infection (8.1% [24/295] vs. 3.5% [5/143] patients)
    - Anaemia (5.8% [17/295] vs. 7.0% [10/143])
    - Diarrhoea (6.1% [18/295] vs. 2.1% [3/143] patients)
    - Acute kidney injury (7.1% [21/295] vs. 4.9% [7/143] patients)
    - Hypertension (7.1% [21/295] vs. 2.1% [3/143 patients)
    - Constipation (6.1% [18/295] vs. 5.6% [8/143] patients)
    - Hypotension (3.7% [11/295] vs. 5.6% [8/143] patients)
    - Septic shock (2.7% [8/295] vs. 5.6% [8/143] patients);

Excluding those who died (see below), no patients in either treatment arm discontinued from treatment or study due to an AE. There were 4 dose interruptions due to AEs in the TCZ arm.

Treatment-related AEs occurred in 54/295 (18.3%) patients in the TCZ arm and in 26/143 (18.2%) patients in the PBO arm.

- The most common treatment-related AEs by PT in the TCZ+SOC arm were neutropenia and thrombocytopenia (2.0% [6/295 patients] each), followed by ALT increased (1.7% [5/295 patients]).
- Whereas, in the PBO+SOC arm, the most common treatment-related AEs by PT were pneumonia (4.2% [6/143 patients]), septic shock (2.1% [3/143 patients]), bacteraemia, hepatic enzyme increased, and thrombocytosis (1.4% [2/143 patients] each).

AESI: A total of 237 (54.1%) patients experienced at least one AESI during the study. AESIs were generally balanced between the two arms (54.6%  in the TCZ arm vs 53.1% in the PBO arm).

- Hypersensitivity was reported at a higher incidence in the TCZ arm compared to PBO (6.4% vs. 2.8%).

- The most common hypersensitivity events by PT (≥2 patients in either arm) were Neutropenia (1.0% [3/295] patients + 1 patient with "neutrophil count decreased").
    - 14 patients in the TCZ + SOC arm, experienced Grade 3 or 4 neutropenia post-dose,
    - Lab: "neutrophils low – any grade " TCZ 21.9% vs PBO 3.1%.
- White blood cell count decreased (0.7% [2/295]patients); all in the TCZ arm.

*Bleeding events* were higher in the TCZ arm (15.9% vs PBO 12.6%). This also holds true for serious bleeding events (TCZ 4.4% vs PBO 3.5%) : 7 patients, 6 in the TCZ+SOC arm and 1 in the PBO+SOC arm experienced Grade 5 (fatal) serious bleeding events (Lab platelets low – any grade TCZ 24.5% vs PBO 17.5%)

The most common *hepatic events* by PT (> 2 patients in either arm) were Hepatitis acute (1.4% [4/295] patients) and Hepatitis (0.7% [2/295] patients); all of which were reported by patients in the TCZ+SOC arm. The remaining events, reported in both arms, were all individual occurrences. (Lab: GPT high –any grade TCZ 56.3% vs PBO 49.0) and GOT high –any grade TCZ 47.7% vs PBO 37%).

- Overall, the proportion of patients who experienced at least one stroke event was 1.0% (3/295 patients) in the TCZ+SOC arm and 2.8% (4/143 patients) in the PBO+SOC arm (all 7 stroke events were considered not to be related).
- A total of 3 events in 3 patients were identified as gastrointestinal perforations using the wide SMQ during the study. These were 1 serious event of Abdominal hernia perforation in the TCZ+SOC arm (0.3%) and 2 non-serious events of Pneumoperitoneum in the PBO+SOC arm (1.4%).

*Infections*: the proportion of patients who experienced infections was 43.1% (127/295 patients) in the TCZ+SOC arm and 44.1% (63/143 patients) in the PBO+SOC arm. Ninety-one serious infections were reported in 71 patients (24.1%) in the TCZ+SOC arm and 57 in 42 patients (29.4%) in the PBO+SOC arm through Day 60. As mentioned above Urinary tract Infection was higher (> 5% difference) in the TCZ arm.

- Of the 14 patients in the TCZ +SOC arm, who experienced Grade 3 or 4 neutropenia post-dose, 1 patient also experienced a serious infection and the other died due to COVID-19 pneumonia.
- One patient in the PBO+SOC arm, who experienced Grade 3 neutropenia post-dose, also experienced a serious infection. This patient with Urosepsis and Pseudomonal sepsis (onsets on Days 3 and 21, respectively), experienced Grade 3 low ANC abnormality on Day 46.

**REMDACTA (WA42511)**

The proportion of patients with at least one AE in the TCZ+RDV arm (332 patients [77.4%] was higher than in the PBO+RDV arm (153 patients [71.8%]). TCZ+RDV AEs were increased with a > 1% difference compared to PBO+RDV for the following PTs: pneumonia (but less COVID 19 pneumonia in the TCZ+RDV group), hypokalemia, insomnia, nausea ,anxiety, hypoglycaemia, thrombocytopenia, pain, AST increased, renal failure, hypertension, D-dimer increased, liver injury, pneumonia aspiration, shock.

<u>Related AEs (ADRs)</u>

- 108 patients [25.2%] in the TCZ+RDV arm and 47 patients [22.1%] in the PBO+RDV arm).
- Infection ADRs: 143 patients (33.3%) vs. 76 patients (35.7%)

- AEs were increased with a > 1% difference compared to PBO+RDV for the following ADRs (PTs): pneumonia and transaminases increased. Multiple other PTs occurred only in individual patients relatively balanced in either group.
- There were more Grade 5 ADRs in the TCZ+RDV arm (2.6%) than in the PBO+RDV arm (0.9%).

Withdrawal of study drug /withdrawal from study

Similar proportions of patients in each treatment arm were reported to have had either study drug withdrawn because of an AE: 46 patients (10.7%) in the TCZ+RDV arm vs. 28 patients (13.1%) in the PBO+RDV arm (mainly due to acute kidney injury (2.8% in TCZ+RDV vs 3.3% in PBO+RDV and transaminases increased 2.1% in TCZ+RDV vs 0.5% in PBO+RDV). The proportion of patients who experienced AEs that led to withdrawal of the patient from the study was comparable (22.6% vs 25.8%).

AESIs

The proportion of patients who experienced any AESI as of Day 60 was comparable between treatment arms: 40.1% in the TCZ+RDV arm vs 39.9% in the PBO+RDV arm. Most AESIs were comparable in both arms; bleeding events were higher in the TCZ+RDV arm (14.2% vs 11.3%; serious bleeding events were reported at the same frequency between the 2 arms) and (serious) infections, stroke were more prevalent in the PBO+RDV arm.

**MARIPOSA**

The incidence of all AEs was higher in the 4 mg/kg + SOC group compared to the 8 mg/kg group (57.1% vs.45.8%), the incidence of SAEs (30.6% vs. 25.0%), Grade 3-5 AEs (32.7% vs. 27.1%), and deaths (16.3% vs. 12.5%) were similar for both TCZ doses, and no patient discontinued the study due to a non-fatal AE. Infection and Infestation AEs were reported more frequently in the 4 mg/kg + SOC group, whereas Renal and Urinary Disorders (all acute kidney injury) were reported more frequently in the 8 mg/kg + SOC group.

By preferred term (the most frequently reported AEs (>5% of patients in either treatment group) were fatal COVID-19 pneumonia (3 patients [6.1%] vs. 1 patient [2.1%]), ALT increased (3 patients [6.1%] vs. 0 patients), and AST increased (3 patients [6.1%] vs. 0 patients) in the 4 mg/kg + SOC group, and acute kidney injury (1 patients [2.0%] vs. 6 patients [12.5%]) and hypokalaemia (2 patients [4.1%] vs. 3 patients [6.3%]) in the 8 mg/kg + SOC group

Related AEs were reported for a total of 3 patients, 2 (4.1%) in the 4 mg/kg + SOC group and 1 (2.1%) in the 8 mg/kg + SOC group. The related AEs in the 4 mg/kg + SOC group were neutropenia and liver function test increased, while the related AE in the 8 mg/kg + SOC group was drug-induced liver injury

Severity

The proportion of patients with at least one NCI-CTCAE Grade 3-5 AE was similar in both treatment groups; 16 patients (32.7%) in the 4 mg/kg + SOC group and 13 patients (27.1%) in the 8 mg/kg + SOC group. With the exception of one Grade 4 event in the 8 mg/kg + SOC group (drug-induced liver injury), all Grade 3-5 AEs were considered to be unrelated to study drug.

AESIs

The most frequently reported TCZ AESIs were infections and bleeding events. Hepatic events, stroke, hypersensitivity reaction events, and anaphylactic reaction events occurred in a maximum of 2 patients

per treatment group. No opportunistic infections, malignancies, myocardial infarctions, gastrointestinal perforations, or demyelinating events were reported during the study.

- Hepatic lab abnormalities ( up to >5x ULN) were consistent with COVID-19 and the TCZ safety profile. One Grade 4 event of drug-induced liver injury in the 8 mg/kg + SOC group was reported as an SAE and was considered by the Investigator to be related to study treatment. It started on Day 9 and resolved within 17 days. Median ALT concentrations, and to a lesser extent median AST concentrations, showed a temporary increase from baseline after dosing in both TCZ treatment groups. Median concentrations peaked around Day 7 and declined thereafter, returning to baseline levels or lower by approximately Day 21 for ALT and by Day 10 for AST. No confirmed Hy's law cases were reported.
- One Grade event of cerebral infarction in the 8 mg/kg + SOC group was reported as an SAE and was considered by the Investigator to be unrelated to study treatment. It started on Day 8 and resolved with sequelae within 27 days.
- Three patients (2x in the 8 mg/kg + SOC group, 1x in the 4mg/kg + SOC group – unrelated and related respectively), experienced a hypersensitivity reaction.
- A total of 6 patients experienced at least one bleeding AESI during the study; 4 (8.2%) patients experienced 4 events in the 4 mg/kg + SOC group and 2 (4.2%) patients experienced 3 events in the 8 mg/kg + SOC group. None of the bleeding events resulted in death, and all were considered by the Investigator to be unrelated to study treatment.
- A total of 3 patients, all in the 8 mg/kg + SOC group, had at least one post-baseline ANC depression to <1 x109/L. No clear association between low ANC abnormalities and serious infections was observed; only one of 6 patients with a serious infection in the 4 mg/kg + SOC group and no patients with a serious infection in the 8 mg/kg + SOC group experienced a post-dose low ANC abnormality.
- A total of 2/49 (4.1%) patients in the 4 mg/kg + SOC group and 7/48 (14.6%) patients in the 8 mg/kg + SOC group had at least one post-baseline platelet count depression to <100 x109/L. Two of 3 patients with a serious bleeding event experienced a post-dose low platelet count abnormality.

## *Serious adverse event/deaths/other significant events*

**RECOVERY**

Twenty eight days (28 days) mortality in the ITT population was the primary endpoint in the RECOVERY study - thus it is discussed in details in the Clinical Efficacy section – See Section 2.4.2.1. Please also refer to the specific discussion on RECOVERY in the safety section.

**EMAPCTA**

At least one *SAE* was reported in 38/250 (15.2%) patients in the TCZ arm and in 25/127 (19.7%) patients in the PBO arm.

Four *treatment-related SAEs* were reported in 3/250 (1.2%) patients in the TCZ arm and in no patient in the PBO arm (bacteremia, cholecystitis infective, device-related infection, and pneumonia staphylococcal).

*Deaths*: A total of 44 patients died during the study: 29/250 (11.6%) patients in the TCZ arm and 15/127 (11.8%) patients in the PBO arm. Among patients who died in the TCZ arm, 26/29 (89.7%) patients died within 28 days of first study treatment and 3/29 (10.3%) died after 28 days of first study

treatment. Among patients who died in the PBO arm, 11/15 (73.3%) died within 28 days of first study treatment and 4/15 (26.7%) died after 28 days of first study treatment.

- Forty-one (10.9%) patients had fatal AEs, (28/250 (11.2%) in the TCZ arm and in 13/127 (10.2%) in the PBO arm). The majority of AEs leading to death (Safety- Evaluable population) were reported within the system organ classes of Respiratory, thoracic and mediastinal disorders (19 patients: 5.2% in TCZ arm and 4.7% in PBO arm), Infections and infestations (11 patients: 2.4% in TCZ arm and 3.9% in PBO arm)), and Cardiac disorders (7 patients: 5 in TCZ arm (2.0%) and 2 (1.6%) in PBO arm). By PT, the most common AEs leading to death (reported in ≥1% of patients in either treatment arm) were acute respiratory distress syndrome (TCZ arm: 2.0% vs. PBO arm: 0.8%), acute respiratory failure (TCZ arm: 1.6% vs. PBO arm: 1.6%), respiratory failure (TCZ arm: 1.6% vs. PBO arm: 1.6%), and COVID-19 pneumonia (TCZ arm: 0.8% vs. PBO arm: 2.4%).
- Other individually occurring causes of death by PT: brain stem stroke, CVA, intestinal perforation, MOF only occurred in the TCZ arm.

**COVACTA**

The proportion of patients with at least one *SAE* in the TCZ+SOC arm (39.3% [116/295 patients]) was lower than in the PBO+SOC arm (44.8% [64/143 patients]).

- COVID-19 pneumonia (12.2% [36/295 patients] and 14.0% [20/143 patients]).
- COVID-19 (4.7% [14/295 patients] and 1.4% [2/143 patients]).
- Septic shock (2.4% [7/295 patients] and 4.9% [7/143 patients]).
- Respiratory failure (1.7% [5/295 patients] and 4.2% [6/143 patients]).
- Cardiac arrest (1.4% [4/295 patients] and 3.5% [5/143 patients]).
- Acute kidney injury (3.4% [10/295 patients] and 2.8% [4/143 patients]).

**Table 35 Summary of serious adverse events related to Study Drug to Day 60 in Study WA42380 (COVACTA)**

| MedDRA System Organ Class<br>MedDRA Preferred Term | PBO (N=143) | TCZ 8 mg/kg (N=295) | All Patients (N=438) |
|---|---|---|---|
| Total number of patients with at least one adverse event | 13 (9.1%) | 18 (6.1%) | 31 (7.1%) |
| Overall total number of events | 17 | 26 | 43 |
| Infections and infestations | | | |
| Total number of patients with at least one adverse event | 11 (7.7%) | 12 (4.1%) | 23 (5.3%) |
| Total number of events | 13 | 17 | 30 |
| Septic shock | 3 (2.1%) | 3 (1.0%) | 6 (1.4%) |
| Pneumonia | 3 (2.1%) | 2 (0.7%) | 5 (1.1%) |
| Pneumonia bacterial | 1 (0.7%) | 3 (1.0%) | 4 (0.9%) |
| Bacteraemia | 1 (0.7%) | 2 (0.7%) | 3 (0.7%) |
| Sepsis | 1 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| Bacterial sepsis | 0 | 1 (0.3%) | 1 (0.2%) |
| Candida infection | 1 (0.7%) | 0 | 1 (0.2%) |
| Cytomegalovirus hepatitis | 0 | 1 (0.3%) | 1 (0.2%) |
| Enterobacter pneumonia | 0 | 1 (0.3%) | 1 (0.2%) |
| Pneumonia escherichia | 0 | 1 (0.3%) | 1 (0.2%) |
| Pseudomonal sepsis | 1 (0.7%) | 0 | 1 (0.2%) |
| Stenotrophomonas infection | 1 (0.7%) | 0 | 1 (0.2%) |
| Urinary tract infection | 0 | 1 (0.3%) | 1 (0.2%) |
| Urosepsis | 1 (0.7%) | 0 | 1 (0.2%) |
| Blood and lymphatic system disorders | | | |
| Total number of patients with at least one adverse event | 1 (0.7%) | 4 (1.4%) | 5 (1.1%) |
| Total number of events | 2 | 4 | 6 |
| Neutropenia | 0 | 4 (1.4%) | 4 (0.9%) |
| Pancytopenia | 1 (0.7%) | 0 | 1 (0.2%) |
| Thrombocytopenia | 1 (0.7%) | 0 | 1 (0.2%) |
| Gastrointestinal disorders | | | |
| Total number of patients with at least one adverse event | 0 | 3 (1.0%) | 3 (0.7%) |
| Total number of events | 0 | 3 | 3 |
| Lower gastrointestinal haemorrhage | 0 | 1 (0.3%) | 1 (0.2%) |
| Pancreatitis | 0 | 1 (0.3%) | 1 (0.2%) |
| Retroperitoneal haemorrhage | 0 | 1 (0.3%) | 1 (0.2%) |
| General disorders and administration site conditions | | | |
| Total number of patients with at least one adverse event | 0 | 1 (0.3%) | 1 (0.2%) |
| Total number of events | 0 | 1 | 1 |
| Multiple organ dysfunction syndrome | 0 | 1 (0.3%) | 1 (0.2%) |
| Hepatobiliary disorders | | | |
| Total number of patients with at least one adverse event | 1 (0.7%) | 0 | 1 (0.2%) |
| Total number of events | 1 | 0 | 1 |
| Cholecystitis | 1 (0.7%) | 0 | 1 (0.2%) |
| Investigations | | | |
| Total number of patients with at least one adverse event | 0 | 1 (0.3%) | 1 (0.2%) |
| Total number of events | 0 | 1 | 1 |
| Citrobacter test positive | 0 | 1 (0.3%) | 1 (0.2%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Total number of patients with at least one adverse event | 1 (0.7%) | 0 | 1 (0.2%) |
| Total number of events | 1 | 0 | 1 |
| Respiratory failure | 1 (0.7%) | 0 | 1 (0.2%) |

Serious AEs related to study treatment include serious AEs deemed related to treatment by the investigator.
Investigator text for AEs encoded using MedDRA version 23.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Thirty one (31) *treatment-related SAEs* were reported in 18/295 (6.1%) patients in the TCZ arm and in 13/143 (9.1%) patients in the PBO arm (these were not further specified in one overview).

- Severe AEs (NCI CTCAE Grade ≥3) were reported in 173/295 (58.6%) patients in the TCZ arm and in 87/143 (60.8%) patients in the PBO arm.
- The most common Grade ≥3 AEs by PT (reported in ≥5% of patients) in TCZ vs PBO arms was pneumonia 5.4% vs 7.7%.
- The Grade 3-4 AEs by SOC with differences ≥ 5% between the arms occurred in (TCZ+SOC arm and PBO+SOC arm, respectively): Blood and lymphatic system disorders SOC (8.5% [25/295 patients] and 3.5% [5/143 patients]).

- Grade 5 AEs were the second most commonly reported AEs. The proportion of patients with at least one NCI-CTCAE Grade 5 AE in the TCZ+SOC arm (24.4% [72/295 patients]) was comparable to the PBO+SOC arm (25.2% [36/143 patients]).
    - Grade 5 related AEs occurred in 3 (1.0%) in the TCZ arm (none in the PBO arm).

*Deaths*: A total of 108 deaths were reported up to the end of the study. In the Safety-evaluable population, the proportion of patients who died in the TCZ+SOC arm (24.4% [72/295 patients]) was comparable to the PBO+SOC arm (25.2% [36/143 patients]). The most commonly reported cause of death was COVID-19 pneumonia. Mortality at Day 28 was 19.7% vs 19.4 % (p= 0.94).

- Almost all patients who died had pre-existing medical conditions. There were no clear differences in the types of AEs leading to death between the 2 arms, except "COVID-19" (4.4% vs 1.4%).
- Other occurring causes of death by PT only in the TCZ arm:
    - haemorrhage,
    - 2x retroperitoneal haemorrhage,
    - coagulopathy,
    - haemorrhagic transformation stroke,
    - acute kidney injury,
    - 5 x multiple organ dysfunction syndrome

At the CHMP's request, the MAH clarified the numbers of Multiple Organ Dysfunction (MOF) deaths (n=6) in the COVACTA trial and provided details on relatedness (only 1/6 death was deemed to be related to TCZ).

**Table 36 Summary of Patients with Multiple Organ Dysfunction Syndrome Adverse Events up to Day 60 in Study WA42380 (COVACTA), Safety Evaluable Population**

| Patient | Treatment arm | Serious | Caused by Study Drug | Outcome |
|---|---|---|---|---|
| A | PBO+SoC | Yes | No | Not recovered |
| B | TCZ+SoC | Yes | No | Fatal |
| C | TCZ+SoC | Yes | No | Fatal |
| D | TCZ+SoC | Yes | Yes | Fatal |
| E | TCZ+SoC | Yes | No | Fatal |
| F | TCZ+SoC | Yes | No | Fatal |

PBO=placebo; SoC=standard of care; TCZ=tocilizumab.

**REMDACTA**

As of Day 60, 217 patients (33.8%) in the study experienced 442 *SAEs*. The proportion of patients who experienced SAEs in the TCZ+RDV arm (141 patients [32.9%]) was slightly lower than that in the PBO+RDV arm (76 patients [35.7%]).

- Serious infections were reported in 22.6% in the TCZ+RDV arm vs 27.7% in the PBO+RDV arm

*Death* up to Day 28 was 18.1% vs 19.5% (TCZ + RDV vs PBO+ RDV) (p = 0.78) The mortality rate at Day 60 was 97 patients (22.6%) in the TCZ+RDV arm and 54 patients (25.7%) in the PBO+RDV arm (p= 0.39).

As of study completion, 152 patients (23.7%) had died as a result of fatal AEs. The most commonly reported fatal AEs at study end (reported in ≥2% patients in either arm) were COVID-19 pneumonia, COVID-19, and septic shock. A total of 120 fatal AEs were reported up to Day 28; (18.2% vs 19.7%).

**MARIPOSA**

By preferred term, the most frequently reported *SAEs* in the overall safety population were acute kidney injury (1 patient [2.0%] in the 4 mg/kg + SOC group vs. 4 patients [8.3%] in the 8 mg/kg + SOC group) and fatal COVID-19 pneumonia (3 patients [6.1%] vs. 1 patient [2.1%], respectively). All acute kidney injury events were Grade 4 and, with the exception of one patient in the 8 mg/kg group, occurred in patients who died from respiratory failure or pneumonia (including COVID-19 pneumonia).

SAEs occurring in 2 patients in either treatment group were septic shock (1 patient in the 4 mg/kg + SOC group vs. 2 patients in the 8 mg/kg + SOC group), failure to thrive (2 patients in the 4 mg/kg + SOC group), diarrhea (2 patients in the 4 mg/kg + SOC group), and respiratory failure (2 patients in the 8 mg/kg + SOC group.

*Deaths*

A total of 14 patients died during the study, 8 (16.3%) in the 4 mg/kg + SOC group and 6 (12.5%) in the 8 mg/kg + SOC group. The majority of deaths occurred within 28 days of the last study drug administration (12 of 14 deaths) and, in all cases, the primary cause of death was an AE.

The causes of death were consistent with observed patterns of COVID-19 progression. By preferred term, the most frequent cause of death overall was COVID-19 pneumonia, which affected 3 patients in the 4 mg/kg group and 1 patient in the 8 mg/kg group. Other AEs leading to death in more than one patient overall were failure to thrive (2 patients in the 4 mg/kg + SOC group) and respiratory failure (2 patients in the 8 mg/kg + SOC group).

**Bleeding events**

Assessment of bleeding risk in COVID-19 patients receiving TCZ is confounded due to bleeding risks imparted by the disease under study, concomitant medications, and comorbidities. Although there were minor numerical differences between the TCZ and PBO arms in COVACTA, the incidence of serious or fatal bleeding events was low and may be attributed to multiple causes, including the aggressive use of anticoagulant medications which was standard of care.

For all bleeding adverse events (AEs) reported in Study WA42380 (COVACTA), the incidences within each System Organ Class (SOC) were low, with generally very small numerical differences between the treatment groups. The only SOC where there was both a >1% difference in treatment arms and a higher incidence in TCZ vs PBO, was Vascular disorders: 2.7% (8/295) vs 0.7% (1/143). For serious bleeding events, the difference in overall incidence was smaller (4.4% vs 3.5% compared with 15.9%

vs 12.6% for all bleeding AEs, TCZ vs PBO arms respectively). Within SOCs, incidence differences were low; the largest difference in the SOCs where there was a higher incidence in the TCZ arm compared to PBO was in the Vascular disorders SOC (1.7% vs 0.7%).

Given that the vascular disorders SOC was the only SOC with a >1% numerical imbalance towards TCZ (2.7% vs. 0.7%, i.e. a 2% difference), the pattern of bleeding AEs in this SOC was analyzed in further detail by preferred term (PT). On closer examination, it became evident that the 2% imbalance was driven largely by 4 reports of haematoma (1.4% in TCZ vs. 0% with PBO). Three of these case reports of haematoma were non-serious events with one case report of serious haematoma. Evaluation of this single serious case of haematoma showed that the event was reported as a tracheostomy cuff haematoma. Causality as per the reporter was 'not related' to TCZ and related to other causes. Eight days after receiving TCZ, the patient was found to have a tracheostomy cuff leak and migration secondary to a haematoma. This was corrected by surgical washout and tracheostomy tube change. The haematoma resolved on the same day.

Current understanding of COVID-19 pathophysiology suggests that SARS-CoV-2 infection triggers inflammation and microvascular dysfunction which can result in thrombotic complications and contribute to multiorgan dysfunction (reviewed in Coccheri 2020 and Haimei 2020). This resulted in the aggressive use of anticoagulants for prophylaxis or treatment and less commonly thrombolytic therapies for treatment of COVID-19, particularly in patients with more severe disease who presented during the initial months of the pandemic like those included in the COVACTA trial. More recently, others have noted that thrombotic risk decreases while bleeding risk increases over the course of severe COVID-19, possibly reflecting dynamics of the inflammatory response (Godier et al. 2021; Boira et al. 2021).

It should also be noted that 23.1% of patients in the TCZ arm and 27.1% in the PBO arm in the COVACTA study were in ordinal scale category 6 at baseline i.e. in the ICU, requiring ECMO or mechanical ventilation and additional organ support. Of the 6 patients with fatal bleeding events in the COVACTA TCZ arm, 3 began ECMO support prior to randomization. Bleeding is a major risk of ECMO occurring in as many as 50% of patients (Mazzeffi et al. 2016) and is a key confounder regarding causality of several serious bleeding events in this trial.

All COVACTA patients who experienced bleeding events were treated with concomitant anticoagulants, which was a likely contributing factor to the observed bleeding events. In contrast, among patients in the COVACTA trial who did not have concomitant anticoagulant exposure in either treatment arm (PBO or TCZ), there were no serious or non-serious bleeding events reported.

While decreases of platelet counts have been recognized as an effect of TCZ treatment as stated in section 4.8 of the SmPC, the MAH is of the opinion that no clear association was observed in COVACTA between serious bleeding events and Grade ≥3 thrombocytopenia AEs after TCZ treatment.

The findings in the COVACTA study are further supported by results in the pooled Safety-Evaluable population (from COVACTA, EMPACTA and REMDACTA), wherein bleeding events (TCZ arm: 12.3% and PBO arm: 10.4%) and serious bleeding events (TCZ arm: 2.9% and PBO arm: 3.1%) were generally well balanced between the treatment arms. The vast majority of patients in both arms in the pooled Safety-Evaluable population received previous or concomitant anti-thrombotic medications (TCZ: 925 [95.0%] and PBO: 460 [95.2%]). Among these patients who received anti-thrombotic medications, the incidence of serious bleeding events (TCZ: 28 [3.0%] and PBO: 15 [3.3%]) and fatal bleeding events (TCZ: 10 [1.1%] and PBO: 4 [0.9%]) was low and balanced between the treatment arms. No serious/fatal events were reported in patients within the pooled Safety-Evaluable population who did not receive previous or concomitant anti-thrombotic medications.

These results from the pooled Safety-Evaluable population are also supported by the findings regarding major bleeding events reported in the RECOVERY study. The incidence of major bleeding events reported in both arms (TCZ and usual care) of the RECOVERY study was same (2.0%).

At the CHMP's request, the MAH has submitted data from the RECOVERY trial on major bleeding events (collected from 1 November 2020 onwards) Table 35 below.

**Table 37 Effect of allocation to tocilizumab on bleeding events (RECOVERY)**

| | **Treatment allocation** | |
|---|---|---|
| | **Tocilizumab (n=2022)** | **Usual care (n=2094)** |
| Number with follow-up form* | 1220 | 1278 |
| | | |
| Major bleeding | | |
| Intra-cranial | 2 (0.2%) | 3 (0.2%) |
| Gastrointestinal | 12 (1.0%) | 11 (0.9%) |
| Other/unrecorded site | 10 (0.8%) | 11 (0.9%) |
| Requiring blood transfusion | 16 (1.3%) | 18 (1.4%) |
| Requiring surgery | 0 (0.0%) | 3 (0.2%) |
| Requiring endoscopy | 7 (0.6%) | 3 (0.2%) |
| Requiring vasoactive drugs | 7 (0.6%) | 6 (0.5%) |
| Subtotal: Any major bleeding | 24 (2.0%) | 25 (2.0%) |

*Information on new bleeding events was only collected on follow-up forms from 1 November 2020 onwards; percentages are of those with such a form completed.
Source: Documentation provided by RECOVERY Investigators.

At the CHMP's request, the MAH clarified that anti-thrombotic therapy was applied in all patients who reported serious/fatal bleeding events in the COVACTA, EMPACTA and REMDACTA studies. A summary of the patients in the pooled Safety-Evaluable population who received previous or concomitant antithrombotic medications and reported bleeding events is provided (Table 38). Of note, antithrombotic medications included those belonging to the heparin group, platelet aggregation inhibitors (excluding heparin), direct Factor XA inhibitors, enzymes, direct thrombin inhibitors, Vitamin K antagonists and other antithrombotic agents.

The vast majority of patients in both arms in the pooled Safety-Evaluable population received previous or concomitant anti-thrombotic medications (TCZ: 925 [95.0%] and PBO: 460 [95.2%]). Among these patients who received anti-thrombotic medications, the incidence of serious bleeding events (TCZ: 28 [3.0%] and PBO: 15 [3.3%]) and fatal bleeding events (TCZ: 10 [1.1%] and PBO: 4 [0.9%]) was low and balanced between the treatment arms.

No serious/fatal patients were reported patients within the pooled Safety-Evaluable population who did not receive previous or concomitant anti-thrombotic medications.

**Table 38 Summary of bleeding, serious bleeding and fatal bleeding adverse events with antithrombotic medications, pooled safety evaluable population**

Protocol: WA42511, WA42380, ML42528

| | PBO (N=483) | TCZ 8 mg/kg (N=974) | All Patients (N=1457) |
|---|---|---|---|
| Total number of patients treated with antithrombotic agent* | 460 (95.2%) | 925 (95.0%) | 1385 (95.1%) |
| Bleeding events** | 50 (10.9%) | 119 (12.9%) | 169 (12.2%) |
| Serious Bleeding** | 15 ( 3.3%) | 28 ( 3.0%) | 43 ( 3.1%) |
| Fatal Bleeding events** | 4 ( 0.9%) | 10 ( 1.1%) | 14 ( 1.0%) |

Investigator text for AEs encoded using MedDRA version 23.1. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

* Previous or concomitant antithrombotic agents and percentages are based on N in the column headings.

** Percentages are based on the number of patients with at least one antithrombotic agent.

## *Laboratory findings*

Laboratory data from studies were not pooled for meta-analysis and are presented by study. A summary of laboratory abnormalities by worst CTCAE grade as reported at any time up to Day 60 in COVACTA, EMPACTA and REMDACTA is presented in Table 39.

The majority of laboratory abnormalities were Grade 1 or Grade 2; however, slightly higher incidences of Grade 3–4 low platelets and/or neutrophils, were seen in the TCZ arm compared with PBO in each study. There were no notable trends in terms of Grade 3–4 elevated ALT or AST.

**Table 39 Summary of Laboratory Abnormalities by Worst CTCAE, at Any Time up to Day 60, Grade by Study (Safety-Evaluable Populations**

| | 1. Highest | 2. COVACTA | | 3. EMPACTA | | 4. REMDACTA | |
|---|---|---|---|---|---|---|---|
| Direction of abnormality | 5. NCI CTC AE Grade | 6. PBO n=143 | 7. TCZ n=295 | 8. PBO n=127 | 9. TCZ n=250 | 10. PBO n=213 | 11. TCZ n=429 |
| Platelets, low | 12. 1 | 13. 19/122 (15.6%) | 14. 50/262 (19.1%) | 15. 7/113 (6.2%) | 16. 13/222 (5.9%) | 17. 29/197 (14.7%) | 18. 100/392 (25.5%) |
| | 19. 2 | 20. 3/142 (2.1%) | 21. 9/292 (3.1%) | 22. 0/126 (0.0%) | 23. 1/246 (0.4%) | 24. 2/212 (0.9%) | 25. 15/423 (3.5%) |
| | 26. 3 | 27. 3/143 (2.1%) | 28. 9/294 (3.1%) | 29. 1/126 (0.8%) | 30. 3/250 (1.2%) | 31. 3/212 (1.4%) | 32. 12/424 (2.8%) |
| | 33. 4 | 34. 0/143 (0.0%) | 35. 4 (294 (1.4%) | 36. 0/126 (0.0%) | 37. 1/250 (0.4%) | 38. 0/212 (0.0%) | 39. 1/424 (0.2%) |
| | 40. Any | 41. 25/143 (17.5%) | 42. 72/294 (24.5%) | 43. 8/126 (6.3%) | 44. 18/250 (7.2%) | 45. 34/212 (16.0%) | 46. 128/424 (30.2%) |
| Neutrophils, | 47. 1 | 48. 2/122 (1.6%) | 49. 18/264 (6.8%) | 50. 8/89 (9.0%) | 51. 55/192 (28.6%) | 52. 3/181 (1.7%) | 53. 18/346 (5.2%) |
| Total Absolute, | 54. 2 | 55. 1/124 (0.8%) | 56. 27/269 (10.0%) | 57. 2/101 (2.0%) | 58. 8/207 (3.9%) | 59. 4/184 (2.2%) | 60. 19/349 (5.4%) |
| low | 61. 3 | 62. 1/125 (0.8%) | 63. 11/270 (4.1%) | 64. 0/103 (0.0%) | 65. 2/208 (1.0%) | 66. 1/184 (0.5%) | 67. 6/352 (1.7%) |
| | 68. 4 | 69. 0/127 (0.0%) | 70. 3/270 (1.1%) | 71. —[a] | 72. —[a] | 73. 0/184 (0.0%) | 74. 5/352 (1.4%) |
| | 75. Any | 76. 4/127 (3.1%) | 77. 59/270 (21.9%) | 78. 10/103 (9.7%) | 79. 65/209 (9.7%) | 80. 8/184 (4.3%) | 81. 48/352 (13.6%) |
| ALT, high | 82. 1 | 83. 49/143 (34.3%) | 84. 123/295 (41.7%) | 85. 37/127 (29.1%) | 86. 85/250 (34.0%) | 87. 75/212 (35.4%) | 88. 220/423 (52.0%) |
| | 89. 2 | 90. 14/143 (10.5%) | 91. 25/295 (8.5%) | 92. 2/127 (1.6%) | 93. 18/250 (7.2%) | 94. 15/212 (7.1%) | 95. 45/423 (10.6%) |
| | 96. 3 | 97. 5/143 (3.5%) | 98. 14/295 (4.7%) | 99. 3/127 (2.4%) | 100. 3/250 (1.2%) | 101. 10/212 (4.7%) | 102. 21/423 (5.0%) |
| | 103. 4 | 104. 1/143 (0.7%) | 105. 4/295 (1.4%) | 106. 0/127 (0.0%) | 107. 3/250 (1.2%) | 108. 4/212 (1.9%) | 109. 3/423 (0.7%) |

| Direction of abnormality | 1. Highest 5. NCI CTC AE Grade | 2. COVACTA 6. PBO n=143 | 7. TCZ n=295 | 3. EMPACTA 8. PBO n=127 | 9. TCZ n=250 | 4. REMDACTA 10. PBO n=213 | 11. TCZ n=429 |
|---|---|---|---|---|---|---|---|
| | 110. Any | 111. 70/143 (49.0%) | 112. 166/295 (56.3%) | 113. 42/127 (43.6%) | 114. 109/250 (43.6%) | 115. 104/212 (49.1%) | 116. 289/423 (68.3%) |

**Table 39 Summary of Laboratory Abnormalities by Worst CTCAE, at Any Time up to Day 60, Grade by Study (Safety-Evaluable Populations (cont.)**

| | 117. Highest | 118. COVACTA | | 119. EMPACTA | | 120. REMDACTA | |
|---|---|---|---|---|---|---|---|
| **Direction of abnormality** | **121. NCI CTCAE Grade** | **122. PBO n=143** | **123. TCZ n=295** | **124. PBO n=127** | **125. TCZ n=250** | **126. PBO n=213** | **127. TCZ n=429** |
| AST, high | 128. 1 | 129. 35/138 (25.4%) | 130. 99/281 (35.2%) | 131. 27/127 (21.3%) | 132. 61/250 (24.4%) | 133. 67/212 (31.6%) | 134. 185/423 (43.7%) |
| | 135. 2 | 136. 10/138 (7.2%) | 137. 22/281 (7.8%) | 138. 0/127 (0.0%) | 139. 4/250 (1.6%) | 140. 9/212 (4.2%) | 141. 23/423 (5.4%) |
| | 142. 3 | 143. 3/138 (2.2%) | 144. 8/281 (2.8%) | 145. 2/127 (1.6%) | 146. 2/250 (0.8%) | 147. 10/212 (4.7%) | 148. 12/423 (2.8%) |
| | 149. 4 | 150. 3/138 (2.2%) | 151. 5/281 (1.8%) | 152. 0/127 (0.0%) | 153. 2/250 (0.8%) | 154. 5/212 (2.4%) | 155. 3/423 (0.7%) |
| | 156. Any | 157. 51/138 (37.0%) | 158. 134/281 (47.7%) | 159. 29/127 (27.6%) | 160. 69/250 (67.6%) | 161. 91/212 (42.9%) | 162. 223/423 (52.7%) |
| Bilirubin, high | 163. 1 | 164. 11/143 (7.7%) | 165. 23/294 (7.8%) | 166. 2/126 (1.6%) | 167. 9/247 (3.6%) | 168. 20/212 (9.4%) | 169. 46/423 (10.9%) |
| | 170. 2 | 171. 7/143 (4.9%) | 172. 2/294 (0.7%) | 173. 0/126 (0.0%) | 174. 4/247 (1.6%) | 175. 10/212 (4.7%) | 176. 19/423 (4.5%) |
| | 177. 3 | 178. 3/143 (2.1%) | 179. 6/294 (2.0%) | 180. 0/126 (0.0%) | 181. 3/247 (1.2%) | 182. 0/212 (0.0%) | 183. 5/423 (1.2%) |
| 184. | 185. 4 | 186. 1/143 (0.7%) | 187. 0/294 (0.0%) | 188. — [a] | 189. — [a] | 190. 2/212 (0.9%) | 191. 1/423 (0.2%) |
| 192. | 193. Any | 194. 22/143 (15.4%) | 195. 31/294 (10.5%) | 196. 2/126 (1.6%) | 197. 16/247 (6.5%) | 198. 32/212 (15.1%) | 199. 71/423 (16.8%) |

| | 117. Highest | 118. COVACTA | | 119. EMPACTA | | 120. REMDACTA | |
|---|---|---|---|---|---|---|---|
| **Direction of abnormality** | **121. NCI CTCAE Grade** | **122. PBO n=143** | **123. TCZ n=295** | **124. PBO n=127** | **125. TCZ n=250** | **126. PBO n=213** | **127. TCZ n=429** |
| AST, high | 128. 1 | 129. 35/138 (25.4%) | 130. 99/281 (35.2%) | 131. 27/127 (21.3%) | 132. 61/250 (24.4%) | 133. 67/212 (31.6%) | 134. 185/423 (43.7%) |
| | 135. 2 | 136. 10/138 (7.2%) | 137. 22/281 (7.8%) | 138. 0/127 (0.0%) | 139. 4/250 (1.6%) | 140. 9/212 (4.2%) | 141. 23/423 (5.4%) |
| | 142. 3 | 143. 3/138 (2.2%) | 144. 8/281 (2.8%) | 145. 2/127 (1.6%) | 146. 2/250 (0.8%) | 147. 10/212 (4.7%) | 148. 12/423 (2.8%) |
| | 149. 4 | 150. 3/138 (2.2%) | 151. 5/281 (1.8%) | 152. 0/127 (0.0%) | 153. 2/250 (0.8%) | 154. 5/212 (2.4%) | 155. 3/423 (0.7%) |
| | 156. Any | 157. 51/138 (37.0%) | 158. 134/281 (47.7%) | 159. 29/127 (27.6%) | 160. 69/250 (67.6%) | 161. 91/212 (42.9%) | 162. 223/423 (52.7%) |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CSR=clinical study report; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PBO=placebo; TCZ=tocilizumab.

Note: Baseline is the patient's last pre-treatment assessment. A laboratory event occurred if the NCI CTCAE grade for a post-baseline laboratory measurement increased from baseline. For a patient with multiple post-baseline lab abnormalities in the specified direction, the highest (worst) grade of these abnormalities for the given lab test is reported. Patients with at least one post-baseline assessment are included in the analysis. For the "Any" grade, denominators include patients with a baseline NCI Grade less than 4. For a specific NCI grade (e.g. Grade 2) the denominator includes patients with a baseline grade lower than the post-baseline grade being tabulated (i.e. lower than Grade 2). Patients with missing values or abnormalities in the opposite direction at baseline are included in the denominator. "Any" represents the number of patients with any increase in grade in the specified direction of abnormality.

[a] Not reported in source CSR

## *Safety in special populations*

**Corticosteroid use**

A the CHMP's request, a tabular summary of deaths up to Day 28 by systemic corticosteroid use in Study ML42528 (EMPACTA), Study WA42380 (COVACTA) and Study WA42511 (REMDACTA) are provided in the tables below.

**Table 40 Summary of deaths up to Day 28 by Systemic Corticosteroid Use in Study ML42528 (EMPACTA)**

| | | | PBO | TCZ 8 mg/kg |
|---|---|---|---|---|
| **EMPACTA (ML42528)** | | | | |
| **mITT Population (TCZ = 249, PBO = 128)** | **All Patients** | **n** | 128 (100%) | 249 (100%) |
| | | **Death** | 11/128 (8.6%) | 26/249 (10.4%) |
| | **Baseline Steroid Use (a)** | **n** | 91 (71.1%) | 183 (73.5%) |
| | | **Death** | 10/91 (11.0%) | 23/183 (12.6%) |
| **Safety Population (TCZ = 250, PBO = 127)** | **Previous Steroid Use (b)** | **n** | 4 (3.1%) | 7 (2.8%) |
| | | **Death** | 1/4 (25.0%) | 1/7 (14.3%) |
| | **Concomitant Steroid Use (c)** | **n** | 107 (84.3%) | 194 (77.6%) |
| | | **Death** | 10/107 (9.3%) | 23/194 (11.9%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 111 (87.4%) | 201 (80.4%) |
| | | **Death** | 11/111 (9.9%) | 24/201 (11.9%) |

mITT=modified intent-to-treat; PBO=placebo; TCZ=tocilizumab.
EMPACTA: Steroid use includes steroid treatments up to Day 28 limited to corticosteroids excluding those reported as being topical, inhalants or dermatological.
Percentages in the 'n' rows are based on the N for that row. Percentages for the 'Death' rows are based on the 'n' for that subgroup.
'Previous Steroid Use' and 'Concomitant Steroid Use' subgroups are mutually exclusive.
a. Patients who have steroid use between Day -7 and Day 1.
b. Patients who only have steroid use prior to Day 1, with no other steroid use past this point.
c. Patients who have steroid use on or after Day 1. (Includes patients with use prior to Day 1 as long as they also have use on or after Day 1.)
d. Patients who have steroid use at any time.

**Table 41 Summary of deaths up to Day 28 by Systemic Corticosteroid Use in Study WA42380 (COVACTA)**

| | | | PBO | TCZ 8 mg/kg |
|---|---|---|---|---|
| **COVACTA (WA42380)** | | | | |
| **mITT Population (TCZ = 294, PBO = 144)** | **All Patients** | **n** | 144 (100%) | 294 (100%) |
| | | **Death** | 28/144 (19.4%) | 58/294 (19.7%) |
| | **Baseline Steroid Use (a)** | **n** | 41 (28.5%) | 57 (19.4%) |
| | | **Death** | 12/41 (29.3%) | 14/57 (24.6%) |
| **Safety Population (TCZ = 295, PBO = 143)** | **Previous Steroid Use (b)** | **n** | 4 (2.8%) | 7 (2.4%) |
| | | **Death** | 2/4 (50.0%) | 2/7 (28.6%) |
| | **Concomitant Steroid Use (c)** | **n** | 75 (52.4%) | 99 (33.6%) |
| | | **Death** | 16/75 (21.3%) | 27/99 (27.3%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 79 (55.2%) | 106 (35.9%) |
| | | **Death** | 18/79 (22.8%) | 29/106 (27.4%) |

mITT=modified intent-to-treat; PBO=placebo; TCZ=tocilizumab.
COVACTA: Steroid use includes steroid treatments up to Day 28 limited to Corticosteroids excluding those reported as being topical, inhalants or dermatological.
Percentages in the 'n' rows are based on the N for that row. Percentages for the 'Death' rows are based on the 'n' for that subgroup.
'Previous Steroid Use' and 'Concomitant Steroid Use' subgroups are mutually exclusive.
a. Patients who have steroid use between Day -7 and Day 1.
b. Patients who only have steroid use prior to Day 1, with no other steroid use past this point.
c. Patients who have steroid use on or after Day 1. (Includes patients with use prior to Day 1 as long as they also have use on or after Day 1.)
d. Patients who have steroid use at any time.

**Table 42 Summary of deaths up to Day 28 by Systemic Corticosteroid Use in Study WA42511**

| | | | PBO | TCZ 8 mg/kg |
|---|---|---|---|---|
| **REMDACTA (WA42511)** | | | | |
| **mITT Population (TCZ = 430, PBO = 210)** | **All Patients** | **n** | 210 (100%) | 430 (100%) |
| | | **Death** | 41/210 (19.5%) | 78/430 (18.1%) |
| | **Baseline Steroid Use (a)** | **n** | 181 (86.2%) | 358 (83.3%) |
| | | **Death** | 39/181 (21.5%) | 69/358 (19.3%) |
| **Safety Population (TCZ = 429, PBO = 213)** | **Previous Steroid Use (b)** | **n** | 6 (2.8%) | 3 (0.7%) |
| | | **Death** | 1/6 (16.7%) | 0/3 (0.0%) |
| | **Concomitant Steroid Use (c)** | **n** | 188 (88.3%) | 378 (88.1%) |
| | | **Death** | 40/188 (21.3%) | 74/378 (19.6%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 194 (91.1%) | 381 (88.8%) |
| | | **Death** | 41/194 (21.1%) | 74/381 (19.4%) |

mITT=modified intent-to-treat; PBO=placebo; TCZ=tocilizumab.
REMDACTA: Steroid use includes systemic steroid treatments up to Day 28 limited to corticosteroids excluding fludrocortisone or those reported as being topical, inhalants or dermatological, or with reported dose units of OTHER, %, AMPULE, or UNKNOWN.

Percentages in the 'n' rows are based on the N for that row. Percentages for the 'Death' rows are based on the 'n' for that subgroup.
'Previous Steroid Use' and 'Concomitant Steroid Use' subgroups are mutually exclusive.
a. Patients who have steroid use between Day -7 and Day 1.
b. Patients who only have steroid use prior to Day 1, with no other steroid use past this point.
c. Patients who have steroid use on or after Day 1. (Includes patients with use prior to Day 1 as long as they also have use on or after Day 1.)
d. Patients who have steroid use at any time.

A tabular summary of deaths up to Day 28 by systemic corticosteroid use for each study is provided below in Table 43.

**Table 43 Deaths (%) up to Day 28 by Systemic Corticosteroid Use (TCZ vs PBO/Usual Care)**

| | | | PBO/Usual Care | TCZ 8 mg/kg |
|---|---|---|---|---|
| **COVACTA (WA42380)** | | | | |
| **mITT Population (TCZ = 294, PBO = 144)** | **All Patients** | **n** | 144 (100%) | 294 (100%) |
| | | **Death** | 28/144 (19.4%) | 58/294 (19.7%) |
| | **Baseline Steroid Use (a)** | **n** | 41 (28.5%) | 57 (19.4%) |
| | | **Death** | 12/41 (29.3%) | 14/57 (24.6%) |
| **Safety-Evaluable Population (TCZ = 295, PBO = 143)** | **Previous Steroid Use (b)** | **n** | 4 (2.8%) | 7 (2.4%) |
| | | **Death** | 2/4 (50.0%) | 2/7 (28.6%) |
| | **Concomitant Steroid Use (c)** | **n** | 75 (52.4%) | 99 (33.6%) |
| | | **Death** | 16/75 (21.3%) | 27/99 (27.3%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 79 (55.2%) | 106 (35.9%) |
| | | **Death** | 18/79 (22.8%) | 29/106 (27.4%) |
| **EMPACTA (ML42528)** | | | | |
| **mITT Population (TCZ = 249, PBO = 128)** | **All Patients** | **n** | 128 (100%) | 249 (100%) |
| | | **Death** | 11/128 (8.6%) | 26/249 (10.4%) |
| | **Baseline Steroid Use (a)** | **n** | 91 (71.1%) | 183 (73.5%) |
| | | **Death** | 10/91 (11.0%) | 23/183 (12.6%) |
| **Safety-Evaluable Population (TCZ = 250, PBO = 127)** | **Previous Steroid Use (b)** | **n** | 4 (3.1%) | 7 (2.8%) |
| | | **Death** | 1/4 (25.0%) | 1/7 (14.3%) |
| | **Concomitant Steroid Use (c)** | **n** | 107 (84.3%) | 194 (77.6%) |
| | | **Death** | 10/107 (9.3%) | 23/194 (11.9%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 111 (87.4%) | 201 (80.4%) |
| | | **Death** | 11/111 (9.9%) | 24/201 (11.9%) |
| | | | **PBO/Usual Care** | **TCZ 8 mg/kg** |
| **REMDACTA (WA42511)** | | | | |
| **mITT Population (TCZ = 430, PBO = 210)** | **All Patients** | **n** | 210 (100%) | 430 (100%) |
| | | **Death** | 41/210 (19.5%) | 78/430 (18.1%) |
| | **Baseline Steroid Use (a)** | **n** | 181 (86.2%) | 358 (83.3%) |
| | | **Death** | 39/181 (21.5%) | 69/358 (19.3%) |
| **Safety-Evaluable Population (TCZ = 429, PBO = 213)** | **Previous Steroid Use (b)** | **n** | 6 (2.8%) | 3 (0.7%) |
| | | **Death** | 1/6 (16.7%) | 0/3 (0.0%) |
| | **Concomitant Steroid Use (c)** | **n** | 188 (88.3%) | 378 (88.1%) |
| | | **Death** | 40/188 (21.3%) | 74/378 (19.6%) |
| | **Previous or Concomitant Steroid Use (d)** | **n** | 194 (91.1%) | 381 (88.8%) |
| | | **Death** | 41/194 (21.1%) | 74/381 (19.4%) |
| **RECOVERY** | | | | |
| **ITT Population** | **All Patients** | **n** | 2094 (100%) | 2022 (100%) |
| | | **Death** | 729/2094 (35%) | 621/2022 (31%) |

| | | | | |
|---|---|---|---|---|
| **(TCZ = 2022, Usual Care = 2094)** | **Baseline Use of systemic corticosteroids (e)** | **n** | 1721 (82%) | 1664 (82%) |
| | | **Death** | 600/1721 (35%) | 482/1664 (29%) |
| | **Previous Steroid Use** | Not available | | |
| | **Concomitant Steroid Use (e)** | **n** | 1568 (77%) | 1462 (74%) |
| | | **Death** | 540/1568 (34%) | 417/1462 (29%) |
| | **Previous or Concomitant Steroid Use** | Not available | | |

ITT=intent-to-treat; mITT=modified intent-to-treat; PBO=placebo; TCZ=tocilizumab.
COVACTA: Steroid use includes steroid treatments up to Day 28 limited to Corticosteroids excluding those reported as being topical, inhalants or dermatological.
REMDACTA: Steroid use includes systemic steroid treatments up to Day 28 limited to corticosteroids excluding fludrocortisone or those reported as being topical, inhalants or dermatological, or with reported dose units of OTHER, %, AMPULE, or UNKNOWN.
EMPACTA: Steroid use includes steroid treatments up to Day 28 limited to corticosteroids excluding those reported as being topical, inhalants or dermatological.
Percentages in the 'n' rows are based on the N for that row. Percentages for the 'Death' rows are based on the 'n' for that subgroup.
'Previous Steroid Use' and 'Concomitant Steroid Use' subgroups are mutually exclusive.
a. Patients who have steroid use between Day -7 and Day 1.
b. Patients who only have steroid use prior to Day 1, with no other steroid use past this point.
c. Patients who have steroid use on or after Day 1. (Includes patients with use prior to Day 1 as long as they also have use on or after Day 1.)
d. Patients who have steroid use at any time.
e. Based on RECOVERY publication (Figure 3 and Webtable 1) which presents corticosteroid use frequency during open-label (after TCZ cohort randomization) by randomized treatment group out of those patients who completed follow-up form.

Of note, the 'Previous Steroid Use' and 'Concomitant Steroid Use' subgroups presented in Table 40 are mutually exclusive as they consider systemic corticosteroid use of any type, whereas in the previous and concomitant medication summaries in the CSR, a patient could be included in both summaries if, for example, they had previous use of one type of systemic corticosteroid treatment and concomitant use of a different type of systemic corticosteroid treatment.

The mortality rates for the concomitant systemic corticosteroid subgroup should be interpreted with caution given the high risk for bias in this post-randomization subgroup, including selection, performance and immortal time bias. Any apparent effect may not be a true effect of treatment but rather the result of inherent patient characteristics that led to treatment with systemic corticosteroids after randomization.

## *Post marketing experience*

The estimated cumulative clinical trial exposure to TCZ from the Developmental International Birth Date (28 April 1997) and until 10 April 2021 (data-lock point for the most recent PBRER) is 24,790 patients. Since the International Birth Date (11 April 2005), the estimated cumulative market exposure to TCZ until 10 April 2021 is 2,567,502 patients (2,213,381 patient years ).

The safety profile of 4 mg/kg and 8 mg/kg TCZ IV in RA has remained largely unchanged since its original marketing authorization. Based on the comprehensive assessment of the safety information received from all available sources on TCZ (including off-label use in COVID-19), no new safety signals were observed during the reporting interval for the most recent PBRER.

## 2.5.1. Discussion on clinical safety

The safety evaluation of RoActemra in COVID-19 was mainly based on 3 MAH-sponsored trials (studies ML42528, WA42380, and WA42511). The main study that shows a favourable outcome, namely the RECOVERY trial has presented limited safety data thus it is not presented in the SmPC.

1. EMAPCTA (ML42528)

In general, in the EMPACTA study the risk profile of RoActemra that has hitherto been described in the Sections 4.4 and 4.8 of the SmPC has been confirmed in this trial. No new type of safety signal arose. The majority of patients received previous and concomitant corticosteroid treatment: 80.4% in the TCZ arm and 87.4% in the PBO arm.

In the EMPACTA trial the "concomitant use of steroids" did not provide a survival benefit for TCZ (deaths TCZ 11.9% vs PBO 9.3% - table 40). This pattern also holds true for the group "previous and concomitant steroid use". However, the CHMP recognised that there was an imbalance in the concomitant steroid use in both arms: TCZ 77.6% vs PBO 87.4%, which may have contributed to the difference in death rates, making it difficult to draw any clear conclusions (see also discussion below).

2. COVACTA (WA42380)

The CHMP was of the view that the type of ADRs seen in COVACTA correspond to those that have been described in the SmPC and in the EMPACTA study. However, the frequencies are increased compared to those seen in EMPACTA which is consistent with the more severely ill COVID population in COVACTA with ~ 56% of patients in the ICU and ~ 37% on mechanical ventilation at baseline and many patients had pre-existing medical conditions.

Concomitant corticosteroids were used in 99 (33.6%) in the TCZ+SOC vs 75 (52.4%) in the PBO+SOC. In the COVACTA trial, the "concomitant use of steroids" did not provide a survival benefit for TCZ (deaths TCZ 27.3% vs PBO 21.3% - table 41). This pattern also holds true for the group "previous and concomitant steroid use". However, the CHMP recognised that there was an imbalance in the concomitant steroid use in both arms: TCZ 33.6% vs PBO 52.4%, which may have contributed to the difference in death rates, making it difficult to draw any clear conclusions (see also discussion below).

The main increases in ADRs for TCZ were seen for hepatotoxicity including transaminase increases, hypersensitivity (6.4% vs 2.8%) which included cytopenias: neutropenia and thrombocytopenia, bleeding events (15.9% vs 12.6%) and serious bleeding events (4.4 % vs 3.5%). At the CHMP's request, the MAH has delineated possible other causes of bleeding events (in particular the aggressive use of anticoagulants for prophylaxis/treatment in severe COVID-19 patients and the confounding factor of ECMO) and showed the generally well balanced occurrence of bleeding events in both arms of the controlled TCZ trials. These data are, in turn, supported by the outcomes seen for major bleeding events in the RECOVERY trial. Hence, the CHMP concluded that there was no need to add a cautionary statement in the SmPC (see also discussion below).

Urinary tract infection (8.1% vs 3.5%) and hypertension (7.1% vs 2.1%) were higher in the TCZ arm; both have added to the Section 4.8 SmPC.

At the CHMP's request, the MAH provided overview by SOC and PT of those SAEs that were related to TCZ and to PBO. It was concluded that, except for "neutropenia" (1.4% vs 0), no noticeable differences were seen for SAEs between the TCZ and PBO arms in the COVACTA study. This risk is adequately described in the SmPC (see also discussion below).

3. REMDACTA (WA42511)

The CHMP was of the view that the type of ADRs seen in REMDACTA correspond to those that have been described in the SmPC and the previous studies.

Concomitant corticosteroids were used in 187 (43.6%) in the TCZ+SOC vs 97 (45.5%) in the PBO+SOC. In the REMDACTA trial, the rate of death for "concomitant corticosteroid" and "previous + concomitant corticosteroid use" are slightly better in the TCS+RDV arm compared to the PBO+RDV arm (~ 19% vs 21%). The actual use of concomitant steroids was high (~88%) and balanced between both arms.

4. MARIPOSA

The CHMP was of the view that the type of ADRs seen in MARIPOSA correspond to those that have been described in the SmPC and the previous studies. Of note, the safety data from the MARIPOSA study are not reflected in the SmPC.

The evaluation of any differences arising between the 2 dose groups (4 mg/kg vs 8 mg/kg TCZ) is difficult, as the numbers are small and do not provide a robust database.

*Hepatotoxicity*

Although hepatotoxicity with transaminase increases were previously described in the SmPC for RoActemra, specific monitoring and warnings have now been introduced in Sections 4.2 and 4.4 of the SmPC with regard to COVID-19 patients. Indeed, monitoring of ALT /AST according to current standard clinical practices is recommended in COVID-19 patients and specific warnings have been added to inform physicians about the risks of elevated ALT or AST levels and multi-organ failure with involvement of the liver. As supported by the data and literature concerning TCZ and hepatotoxicity especially in the COVID setting, the CHMP agrees with the recommendations that the decision to administer tocilizumab should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with tocilizumab and that, in COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of RoActemra treatment is not recommended.

*Cardiovascular risk*

In the SmPC it is mentioned that "*RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care*". Three patients had TCZ treatment-related hypertension, one had a fatal brain stem stroke and one a fatal CVA. At the CHMP's request, the MAH submitted data and literature to allay concerns about possibly increased risk of cardiovascular disorders. The CHMP concluded that a separate wording on the risk cardiovascular disorders under TCZ in COVID patients is not deemed necessary.

*Gastrointestinal Perforation*

Two patients had GI perforations in the TCZ arm. At the CHMP's request, the MAH has clarified that the rate of gastrointestinal perforations in the current RoActemra SmPC (0.26 events per 100 patient years with TCZ therapy) is based on an observation of 29 events among 4009 patients with immunologic conditions receiving chronic TCZ treatment during 6-month controlled clinical trials; this represents in aggregate 10993.6 patient-years of exposure in these patients. Given the acute TCZ dosing (1–2 doses) in the COVID-19 setting as well as the low incidence of GI perforation events reported in the TCZ arm in COVID-19 studies (both in Study ML42528 and the pooled safety population) together with the literature reports of gastrointestinal perforation secondary to COVID-19, the CHMP concluded that the rate of GI perforations in the SmPC does not require amending.

*Deaths*

One of the most common AEs leading to death was acute respiratory distress syndrome, which was increased in the TCZ arm: (2.0% vs. PBO arm: 0.8%). However, other respiratory disorders leading to death were either balanced between the two arms or, in the case of COVID-19 pneumonia placebo patients fared worse (TCZ arm: 0.8% vs. PBO arm: 2.4%). No clear differences between TCZ and PBO arose for pulmonary fatalities.

At the CHMP's request, the MAH clarified the cause of death was in the 7 patients (3 TCZ and 4 PBO) who died after 28 days of the study. The cause of death is not available for three patients (1 patient in TCZ arm and 2 patients in PBO arm), for the remaining 4 patients the cause of death was acute respiratory failure, COVID pneumonia, septic shock and respiratory failure. These four causes of death are deemed COVID-related and not due to TCZ adverse events.

Concomitant corticosteroids were used in 200 (80.3%) in the TCZ+SOC vs 112 (87.5%) in the PBO+SOC. The MAH has provided at CHMP's request the table 43 on death rates for concomitant corticosteroid use in the double-blind placebo-controlled trials and for open-label RECOVERY trial. The results of COVACTA and EMPACTA conflict with those of REMDACTA and RECOVERY i.e. in the former TCZ does not offer a survival advantage when given with corticosteroids. However, as mentioned previously, the use of concomitant corticosteroid was not balanced between the treatment arms (TCZ lower than PBO) in the COVACTA and EMPACTA trials; this may have thus influenced the results. The survival benefit for TCZ is meagre in the REMDACTA study (1.7%) and increases in the RECOVERY (5%) when using concomitant corticosteroids. The recommendations on the use of concomitant corticosteroids are adequately reflected in the SmPC.

*Bleeding*

At the CHMP's request, the MAH discussed whether or not anticoagulant therapy was applied in patients with serious/fatal bleeding events in Phase 3 studies COVACTA, EMPACTA and REMDACTA as RoActemra is known to cause decrease in platelet number. The frequencies of concomitant anticoagulant medications were also provided for the TCZ and SoC treatment groups of COVACTA, EMPACTA and REMDACTA. The majority (~95%) of patients were treated with antithrombotic medications, all patients with serious or fatal bleeding events had received antithrombotic medications. In COVACTA the incidence of serious or fatal bleeding is slightly higher in the TCZ arm compared to PBO, (4.5% vs 3.6% and 2.1% vs 0.7%, respectively); however, in the pooled safety population no major imbalances with regard to serious or fatal bleeding are seen between the TCZ and PBO arms.

Data from the RECOVERY trial on major bleeding events (collected from 1 November 2020 onwards) do not reveal any relevant differences between TCZ and usual care.

The MAH delineates possible other causes of bleeding events (in particular the aggressive use of anticoagulants for prophylaxis/treatment in severe COVID-19 patients and the confounding factor of ECMO) and shows the generally well balanced occurrence of bleeding events in both arms of the controlled TCZ trials. These data are, in turn, supported by the outcomes seen for major bleeding events in the RECOVERY trial.

The CHMP concluded that the addition of a cautionary statement in the SmPC was not required.

*Infections*

In the pooled safety-evaluable population from studies ML42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COVID-19 patients receiving tocilizumab (30.3%/18.6%, n=974) versus placebo (32.1%/22.8%, n=483). The safety profile observed in the baseline systemic corticosteroids treatment group was consistent with the safety profile of tocilizumab from the overall population. In this subgroup, infections and serious infections occurred in 27.8% and

18.1% of patients treated with IV tocilizumab and in 30.5% and 22.9% of patients treated with placebo, respectively.

Section 4.4 of the SmPC was updated to state that, in COVID-19 patients, RoActemra should not be administered if they have any other concurrent severe active infection. Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections.

In addition, Section 4.3 of the SmPC was modified to reflect that tocilizumab should not be used in active, severe infections with the exception of COVID-19. This was considered acceptable to the CHMP.

*Laboratory Abnormalities*

The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of TCZ-IV compared with those who received placebo in the randomized, double-blind, placebo controlled trials with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving TCZ-IV versus placebo. Hence, in COVID-19 patients who develop an ANC < 1 x 109 /L or a platelet count < 50 x 103 /µL, administration of treatment is not recommended. In addition, Neutrophil and platelet counts should be monitored according to current standard clinical practices. This is adequately reflected in the Sections 4.2, 4.4 and 4.8 of the SmPC.

*Corticosteroid use*

Tocilizumab may be associated with increased risk of death in those patients who are not treated with corticosteroids. RoActemra should not be administered to COVID-19 patients who are not receiving systemic corticosteroids. This is adequately reflected in Sections 4.1, 4.4 and 5.1 of the SmPC.

In line with the above evaluation, Serious infection, Complications of diverticulitis, Neutropenia and Hepatotoxicity are listed as Important identified risks in the RMP. At the PRAC's request, hypersensitivity, as important risk has been deleted for all indications, as it is well known and no additional risk minimisation measures are in place. The RMP and Annex II have been updated accordingly.

## 2.5.2. Conclusions on clinical safety

The safety evaluation of RoActemra in COVID-19 was mainly based on 3 randomized, double-blind, placebo controlled trials (studies ML42528, WA42380, and WA42511). A total of 974 patients were exposed to RoActemra in these studies. The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab for COVID-19) were hepatic transaminases increased, constipation, and urinary tract infection.

The main study that shows a favourable outcome, namely the RECOVERY trial has presented limited safety data thus it is not presented in the SmPC.

No new or unknown unfavourable effects could be discerned from this mainly severely ill population who often had pre-existing co-morbidities. The safety signals arising from the trials mainly encompass hepatotoxicity with transaminase increases, hypersensitivity reactions, cytopenias (neutropenia and thrombocytopenia), (serious) bleeding events.

The SmPC adequately reflects the safety profile of Roactemra in this indication. The CHMP considered that the data submitted was acceptable from a safety perspective.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 27.1 is acceptable.

The CHMP endorsed this advice without changes.

### *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| **Important identified risks** | • Serious infection *<br>• Complications of diverticulitis *<br>• Neutropenia<br>• Hepatotoxicity |
| **Important potential risks** | • Thrombocytopenia and the potential risk of bleeding<br>• Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events<br>• Malignancies<br>• Demyelinating disorders<br>• Immunogenicity |
| **Missing information** | None |

COVID = coronavirus disease 19; TCZ = tocilizumab

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing but are assessed as important potential risks for the indication of COVID-19.

### *Pharmacovigilance plan*

| **Study** | **Summary of Objectives** | **Safety Concerns Addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| NA | NA | NA | NA | NA |

| Study | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| NA | NA | NA | NA | NA |
| **Category 3-** Required additional pharmacovigilance studies conducted to evaluate the effectiveness of risk minimisation activities | | | | |
| ML28664 (formerly tracked as GA28719) (RABBIT) registry study<br><br>Ongoing | To provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA | Serious infections, Complications of diverticulitis (including GI perforation), Neutropenia, Thrombocytopenia and the potential risk of bleeding, Hepatotoxicity, Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events, Malignancies, Demyelinating disorders | Routine updates to be provided in the scheduled PSURs<br><br>Final CSR | <br><br>Q4 2022 |
| WA29358 (Paediatrics registry study)<br><br>Ongoing | Collecting long-term efficacy and safety data for TCZ in the treatment of pJIA | Impact of TCZ therapy on the increased risk of atherosclerosis (cardiovascular events) growth and development, influence on the occurrence/treatment of uveitis and to evaluate the risk of malignancies, serious infections, and gastrointestinal perforation, and the efficacy of the 10 mg/kg IV Q4W regimen, and the impact of RF status on efficacy | Routine updates to be provided in the scheduled PSURs<br>Recruitment End<br><br>Study Completion<br><br>Final Report Submission | <br>June 2020<br><br>June 2025<br><br>Q1 2026 |

CSR=Clinical Study Report; GI = gastrointestinal; IV = intravenous; NA = not applicable; pJIA=polyarticular juvenile idiopathic arthritis; PSUR = Periodic Safety Update Report; Q = quarter; Q4W = once every 4 weeks; RA=rheumatoid arthritis; RF=rheumatoid factor; TCZ=tocilizumab.

## *Risk minimisation measures*

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Serious infections * | **Routine risk communication:**<br>**SmPC**<br>**IV and SC formulation**:<br>Section 4.3 Contraindications Active, severe infections (see Section 4.4)<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>**Patient Information Leaflet:**<br>**IV and SC Formulation**<br>Section 2. What you need to know before you are given TCZ<br>Section 4 Possible serious side effects: tell a doctor straightaway.<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the**<br>**Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine.<br>**Additional risk minimization measures:**<br>Patient Alert Card<br>Patient Brochure<br>Healthcare Provider Brochure<br>Dosing Guide | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br>Collect and analyze information on hematogenous bacterial arthritis in the sJIA population < 18 years of age<br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT, WA29358) |
| Complications of Diverticulitis * | **Routine risk communication:**<br>**SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>**Patient Information Leaflet:**<br>Section 2 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br>**Additional pharmacovigilance activities:** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | Warnings and precautions<br>Section 4 Possible side effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br><br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine.<br><br>**Additional risk minimization measures:**<br>Patient Alert Card<br>Patient Brochure<br>Healthcare Provider Brochure<br>Dosing Guide | Epidemiology data<br>EU registries<br>(Ongoing: RABBIT, WA29358) |
| Neutropenia | **Routine risk communication:**<br><br>**<u>SmPC</u>**<br>Section 4.2 Posology and method of administration<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects/Laboratory evaluations<br><br>**<u>Patient Information Leaflet</u>**<br>Section 2 What you need to know before you used RoActemra<br>Section 4 Possible Side Effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br><br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status: | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions, i.e. for events of special interest will collect neutrophil data in cases of serious infection<br><br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT, WA29358) |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | RoActemra is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>Patient Brochure<br>Healthcare Provider Brochure<br>Dosing Guide | |
| Hepatotoxicity | **Routine risk communication:**<br>**<u>SmPC</u>**<br>Section 4.2 Posology and method of administration (IV formulation)<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br><br>**<u>Patient Information Leaflet</u>**<br>(IV/SC formulation)<br>Section 2 Warning and precautions<br>Section 4 Possible side effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In patients with RA, GCA, pJIA, sJIA, ALT and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.<br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>Patient Brochure<br>Healthcare Provider Brochure<br>Patient Alert Card<br>DHPC | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br><br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT) |
| Thrombocytopenia and the potential risk of bleeding | **Routine risk communication:**<br>Section 4.4 Special warnings and precautions for use | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | Section 4.8 Undesirable effects<br>Section 4.2 Posology and method of administration (IV formulation)<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br>**Additional risk minimization measures:**<br>Patient Brochure<br>Healthcare Provider Brochure | Guided questionnaire for specific adverse reactions<br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT) |
| Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events | **Routine risk communication:**<br>**SmPC**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>**Patient Information Leaflet**<br>Section 2 Warnings and precautions<br>Section 4 Possible side effects<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br>**Additional risk minimization measures:**<br>Patient Brochure<br>Healthcare Provider Brochure | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT, WA29358) |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | Dosing Guide | |
| Malignancies | **Routine risk communication:**<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br><br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>Patient Brochure<br>Healthcare Provider Brochure<br>Dosing Guide | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br><br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT, WA29358) |
| Demyelinating Disorders | **Routine risk communication:**<br>Section 4.4 Special warnings and precautions for use<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br><br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>Healthcare Provider Brochure | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Guided questionnaire for specific adverse reactions<br><br>**Additional pharmacovigilance activities:**<br>Epidemiology data<br>EU registries<br>(Ongoing: RABBIT) |
| Immunogenicity | **Routine risk communication:**<br>**SmPC**<br>Section 4.8 Undesirable effects | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | **Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>Pack size: None<br>Medicine's legal status:<br>RoActemra is a prescription only medicine<br>No Additional Risk Minimization Measure. | Collect and analyze anti-TCZ antibodies in patients who experience hypersensitivity reactions that led to study withdrawal in ongoing clinical trials and investigate the risk of developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted. This is specific to the ongoing clinical trials and does not apply to spontaneous post-marketing cases<br>**Additional pharmacovigilance activities:**<br>None |

IV=intravenous; SC=subcutaneous; sJIA = systemic juvenile idiopathic arthritis; SmPC=Summary of Product Characteristics; TCZ=tocilizumab.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing but are assessed as important potential risks for the indication of COVID-19.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC for RoActemra 20 mg/mL concentrate for solution for infusion are updated. The Package Leaflet has been updated accordingly.

Annex II has been updated to reflect the deletion of "Hypersensitivity", as important risk from the RMP for all indications, as it is well known and no additional risk minimisation measures are in place.

Editorial changes were made to Section 4.8 of the SmPC for all presentations (including the tabular listing of ADRs).

Changes were also made to the PI to bring it in line with the current QRD template which were reviewed accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Hungary.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- There are limited updates to the Package Leaflet because of this extension of indication and no significant changes to the key safety messages already approved. The additional text follow the same structure and use similar descriptions and terminology as used in the approved package

leaflet for other indications, particularly the treatment of severe or life-threatening cytokine release syndrome (CRS).

- The target group of users will be similar between the approved indications (adults hospitalized with severe or life-threatening cytokine release syndrome) and the proposed indication of (adults hospitalized with COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation).
- The posology proposed in this application is the same as for the approved indications for RoActemra in the treatment of severe or life-threatening cytokine release syndrome (CRS).

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The COVID-19 outbreak was declared a pandemic health emergency by the WHO on 11 March 2020 and presents a global healthcare challenge. COVID-19 is associated with high morbidity and mortality.

According to the WHO, as of 22 June 2021, there have been over 177 million confirmed cases of COVID-19, with approximately 3.9 million deaths reported to the WHO (WHO 2021a). As of 24 June 2021, a total of 33.0 million cases have been reported in EU/EEA, with over 736,000 deaths (ECDC).

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an ICU, to systemic manifestations of sepsis, septic shock, and multiple organ dysfunction (Cascella et al. 2020).

Most people with COVID-19 develop only mild or uncomplicated illness, presenting with symptoms of an upper respiratory tract infection, including fever, cough, sore throat, nasal congestion, headache, muscle pain or malaise without evidence of viral pneumonia or hypoxia. Loss of taste (ageusia) and/or smell (anosmia) have also emerged as characteristic symptoms of COVID-19. Respiratory symptoms such as fever, cough, dyspnea and tachypnea without significant hypoxia are indicative of moderate pneumonia. Long-term symptoms have been reported even in non-hospitalized patients who have had mild COVID-19.

Approximately 15% of COVID-19 patients develop severe pneumonia characterized by the same clinical signs as moderate pneumonia with the addition of one of the following: respiratory rate (>30 breaths/minute); severe respiratory distress; or hypoxia requiring hospitalization and oxygen support (WHO 2020; Cascella et al. 2020). In approximately 5% of infected patients, the severe form of interstitial pneumonia with alveolar damage may rapidly progress to critical manifestations of the disease characterized by respiratory failure associated with ARDS that necessitates mechanical ventilation and support in an ICU, sepsis, septic shock, and/or multi organ failure including acute kidney and cardiac injury, and even death (WHO 2020).

Mortality rate varies among regions and hospitals and with associated risk factors. In a cohort study of 64,781 patients with COVID-19 treated in 592 US hospitals during April and May 2020, the in-hospital mortality rate was 20.3% (Rosenthal et al. 2020). In a multicenter cohort study that included 3924 critically ill patients, 40.6% of patients not treated with TCZ within 2 days of ICU admission died (Gupta et al. 2021). Among patients admitted to ICU in a randomized platform trial (REMAP-CAP), the mortality in patients not receiving TCZ was 35.3% (REMAP-CAP Investigators et al 2021).

## 3.1.2. Available therapies and unmet medical need

**Prevention**

To date, four vaccines have been granted conditional marketing authorization (MA) in the EU. Several other are currently under evaluation in Europe.

**Treatments**

Treatment options for COVID-19 have been evolving since the pandemic was declared in March 2020. Initially, treatment was largely supportive in the outpatient or hospitalized setting and included the use of antipyretics, fluids, antibiotics if bacterial secondary infection or co-infection was suspected, and supplemental oxygen.

Systemic corticosteroids were not routinely recommended until emerging data from clinical trials, including the RECOVERY trial dexamethasone cohort (Horby et al. 2021), indicated a mortality benefit among patients requiring supplemental oxygen or mechanical ventilation. The EMA issued recommendations on the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation on 18 September 2020 (Article 5(3) procedure).

Velkury (remdesivir, RDV), a broad spectrum anti-viral, was granted conditional marketing authorisation on 3 July 2020 and is indicated for use in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at the start of treatment).

Regkirona (regdanvimab) is an antiviral, a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection. It has been granted a marketing authorisation on 12 November 2021 for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Ronapreve (casirivimab / imdevimab) is a human IgG1 mAbs that bind simultaneously to the S protein receptor binding domain (RBD) and block its interaction with the host receptor, angiotensin-converting enzyme 2 (ACE2). It has been granted a marketing authorisation on 12 November 2021 for the treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 and the prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

EMA's human medicines committee (CHMP) has issued recommendations on the use of Lagevrio (also known as molnupiravir or MK 4482) for the treatment of COVID-19 on 19 November 2021 (Article 5(3) procedure). The medicine, which is currently not authorised in the EU, can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19. Lagevrio should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. The medicine, which is available as capsules, should be taken twice a day for 5 days.

Several other therapeutics are currently under evaluation in Europe. Despite ongoing advances in the development of vaccines and treatments for COVID-19, significant unmet medical need remains in the treatment of COVID-19, especially in hospitalized patients with severe COVID-19 who may progress to multiple organ failure and death and often require extensive healthcare resources, including ICU admission and mechanical ventilation.

### 3.1.3. Main clinical studies

The submission is based on the totality of clinical evidence from the investigator-initiated Randomised Evaluation of COVID-19 Therapy (RECOVERY) study (RECOVERY Collaborative Group 2021) and three MAH-sponsored Phase III studies (WA42380 (COVACTA), ML42528 (EMPACTA), and WA42511 (REMDACTA)), as well as a pooled meta-analysis of these three studies:

- RECOVERY TCZ cohort: MAH-supported, investigator-initiated, randomized, controlled, open-label, platform trial of TCZ vs no TCZ, both on top of usual care plus randomized combinations of additional experimental therapies or no additional treatment in patients hospitalized with COVID-19
- COVACTA: Phase III, randomized, double blind, placebo-controlled, multicenter study of TCZ plus SoC therapy in hospitalized patients with severe COVID 19 pneumonia
- EMPACTA: Phase III, randomized, double blind, placebo-controlled, multicenter study of TCZ plus SoC therapy in hospitalized patients with COVID 19 pneumonia
- REMDACTA: Phase III, randomized, double-blind, placebo-controlled, multicentre study of TCZ in combination with remdesivir (RDV) in hospitalized adult patients with severe COVID-19 pneumonia

Further supportive data are provided from the completed Phase II Study CA42481 (MARIPOSA). This was an open-label, randomized, multicenter study assessing the pharmacodynamics, pharmacokinetics, safety, and efficacy of two different doses of TCZ (4 mg/kg and 8 mg/kg) plus SoC therapy in hospitalized adult patients with moderate and severe COVID-19 pneumonia.

## *3.2. Favourable effects*

The tocilizumab arm of RECOVERY met its primary endpoint and shows that administration of tocilizumab was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone. Furthermore, allocation to tocilizumab was associated with a greater probability of discharge from hospital within 28 days (57% vs 50%). These results are regarded as clinically relevant.

Study EMPACTA met the primary endpoint. The proportion of patients who required mechanical ventilation or died by Day 28 was 12.0% for TCZ+SoC and 19.3% for PBO+SoC. This difference of 7.3% points was statistically significant with a p-Value of 0.0360.

The dosing recommendation of 8 mg/kg (not exceeding 800 mg flat) IV for treatment was considered acceptable to the CHMP.

## *3.3. Uncertainties and limitations about favourable effects*

Although EMPACTA met the primary endpoint as described, the secondary endpoints are not supportive for these findings. The secondary endpoint with the highest clinical relevance, mortality rate at Day 28 and Day 60 was not significantly different between the treatment arms, with a slightly higher proportion of deaths in the tocilizumab group as compared to placebo (10.4% vs 8.6%). Also for the day 60 evaluation, no difference in mortality between tocilizumab and placebo arms was seen.

The studies COVACTA and REMDACTA did not meet the primary endpoints and could not show statistical significant benefit of addition of tocilizumab to SOC or a superiority to Remdesivir. The secondary endpoints of these studies do not provide further supportive evidence. However, the CHMP

recognised that the situation of rapidly evolving standard of care treatment, ongoing and fluently changing pandemic situation with different virus variants emerging in different parts of the world hinder a clear and straight forward study conduct and efficacy evaluation.

A thorough discussion was provided by the MAH with the focus on the observed inconsistency regarding D28 mortality across the different trials. Only the RECOVERY study was appropriately powered to detect differences in mortality. Meta-analysis e.g. by the WHO also point in the same direction as the results of RECOVERY and showed that that tocilizumab reduces all-cause mortality at Day 28 compared to usual care/placebo. This was considered acceptable to the CHMP. Considering that the demonstration of the efficacy is based on the data from the RECOVERY study, only this information is included in Section 5.1 of the SmPC.

The CHMP concluded that tocilizumab has benefit on top of corticosteroids but not without corticosteroids. Consequently, the CHMP recommended that tocilizumab should not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup. This is adequately reflected in Sections 4.1, 4.4 and 5.1 of the SmPC.

Since patients with CRP levels <75 mg/L were not included in RECOVERY, it is uncertain whether the treatment effect can be extrapolated to patients with CRP levels <75 mg/L. Therefore, a corresponding warning statement was included into section 4.4 of the SmPC.

## *3.4. Unfavourable effects*

The safety signals arising from the trials mainly encompass hepatotoxicity with transaminase increases, hypersensitivity reactions, cytopenias (neutropenia and thrombocytopenia), (serious) bleeding events.

The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab for COVID-19) were hepatic transaminases increased, constipation, and urinary tract infection.

Patients 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 tocilizumab should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with tocilizumab. In COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of TCZ treatment is not recommended. In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices. This is adequately reflected in the SmPC.

In the pooled safety-evaluable population from studies ML42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COVID-19 patients receiving tocilizumab (30.3%/18.6%, n=974) versus placebo (32.1%/22.8%, n=483). The safety profile observed in the baseline systemic corticosteroids treatment group was consistent with the safety profile of tocilizumab from the overall population. In this subgroup, infections and serious infections occurred in 27.8% and 18.1% of patients treated with IV tocilizumab and in 30.5% and 22.9% of patients treated with placebo, respectively. Section 4.4 of the SmPC was updated to state that, in COVID-19 patients, RoActemra should not be administered if they have any other concurrent severe active infection. Healthcare professionals are warned to exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections. In addition, Section 4.3 of the SmPC was modified to reflect that tocilizumab should not be used in active, severe infections with the exception of COVID-19.

The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of TCZ-IV compared with those who received placebo in the randomized,

double-blind, placebo controlled trials with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving TCZ-IV versus placebo. Hence, in COVID-19 patients who develop an ANC < 1 x $10^9$ /L or a platelet count < 50 x $10^3$ /µL, administration of treatment is not recommended. Neutrophil and platelet counts should be monitored according to current standard clinical practices. This is adequately reflected in the Sections 4.2, 4.4 and 4.8 of the SmPC.

## *3.5. Uncertainties and limitations about unfavourable effects*

No new or unknown unfavourable effects could be discerned from this mainly severely ill population who often had pre-existing co-morbidities. However, the main study that shows a favourable outcome, namely the RECOVERY trial has presented limited safety data thus it is not presented in the SmPC.

Tocilizumab may be associated with increased risk of death in those patients who are not treated with corticosteroids. RoActemra should not be administered to COVID-19 patients who are not receiving systemic corticosteroids. This is adequately reflected in Sections 4.1, 4.4 and 5.1 of the SmPC.

## *3.6. Effects Table*

**Table 44** Effects Table for RoActemra treatment of coronavirus disease 2019 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **Mortality by Day 28** | RECOVERY (overall)<br><br>Pts on steroids | % | 31%<br><br>29% | 35%<br><br>34% | Large (n= 4116) open label study, underlying efficacy of steroid therapy unclear. | RECOVERY Publication Lancet |
| | EMPACTA (overall)<br><br>Pts on baseline steroids | % | 10,4%<br>N.s<br><br>12.6& | 8,6%<br><br>11.0% | Small sample size (n=377), high-risk minority populations, all secondary endpoints not met | EMPACTA study report |
| | COVACTA (overall)<br><br>Pts on baseline steroids | % | 19.7%<br>N.s<br><br>25% | 19.4%<br><br>29.3% | Small sample size (n=438) | COVACTA study report |
| | REMDACTA (overall)<br><br>Pts on baseline steroids | % | 18.1%<br>N.s.<br><br>19.3% | 19.5%<br><br>21.5% | | REMDACTA study report |
| **Incidence of MV/ Time to MV or Death/** | RECOVERY | % pts by Day 28 | 35% | 42% | | RECOVERY publication |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Use of invasive MV (including ECMO) or Death[b]** | | | | | | |
| | EMPACTA | | 11.6% | 18.8% | | EMPACTA study report |
| **Unfavourable Effects** | | | | | | |
| | RECOVERY | | | | Limited safety data – 2/4 pre-specified parameters<br><br>B/R thus difficult to assess. | RECOVERY publication |
| | COVACTA | % | | | No major differences in rates of AEs, SAEs, or ADRs and SAEs. The type of ADRs are those described in the updated SPC | COVACTA study report |
| AEs | | | 81.4% | 82.5% | | |
| ADRs | | | 18.3% | 18.2% | | |
| SAEs | | | 24.4% | 25.2% | | |
| Related SAEs | | | 6.1% | 9.1% | | |
| | EMPACTA | % | | | ADRs and related SAEs for TCZ are more frequent in this less ill population (compared to COVACTA) | EMPACTA study report |
| AEs | | | 50.8% | 52.8% | | |
| ADRs | | | 12.8% | 3.9% | | |
| SAEs | | | 15.2% | 19.7% | | |
| Related SAEs | | | 1.2% | 0 | | |
| | REMDACTA | % | | | No major differences in rates of AEs, SAEs, or ADRs and SAEs. The type of ADRs are those described in the updated SPC | REMDACTA study report |
| AEs | | | 77.4% | 71.8% | | |
| ADRs | | | 25.2% | 22.1% | | |
| SAEs | | | 32.9% | 35.7% | | |
| Related SAEs | | | 9.8% | 9.4% | | |
| 28-day mortality | RECOVERY<br><br>Pts not on baseline steroids | % | 39% | 35% | Subgroup finding, Small subgroup sample size (n=724), 95% CI for risk ratio includes 1 | RECOVERY publication |
| 28-day mortality | Pooled analysis of COVACTA, EMPACTA and REMDACTA<br><br>Pts not on baseline steroids | % | 15% | 11% | Subgroup finding, Small subgroup sample size (n=545), 95% CI for hazard ratio includes 1 | Summary of clinical efficacy |

Notes:

*For an easy overview of a direct comparison of the study endpoints see table below (important endpoints marked in yellow:*

**Table 45 Side-by-Side Comparison of Key Efficacy Outcomes from RECOVERY (ITT), COVACTA (mITT), EMPACTA (mITT) and REMDACTA (mITT)**

| | COVACTA (mITT) | | EMPACTA (mITT) | | REMDACTA (mITT) | | RECOVERY (ITT) | |
|---|---|---|---|---|---|---|---|---|
| | TCZ N=294 | PBO N=144 | TCZ N=249 | PBO N=128 | TCZ N=430 | PBO N=210 | TCZ N=2022 | Usual Care N=2094 |
| **Mortality by Day 28** | | | | | | | | |
| Mortality (%) by Day 28 | TCZ: 19.7%, PBO: 19.4% | | TCZ: 10.4%, PBO: 8.6% | | TCZ: 18.1%, PBO: 19.5% | | TCZ: 31%,Usual Care: 35% | |
| (Weighted) difference (TCZ-PBO) in % (95% CI) | 0.3% (–7.6%, 8.2%)* | | 2.0% (-5.2%, 7.8%)* | | –1.3% (–7.8%, 5.2%)* | | -4.1% (-7.0%, -1.3)[$] | |
| Hazard Ratio (TCZ/PBO)(95% CI) | 1.07 (0.68, 1.67) ^ | | 1.20 (0.61, 2.38) ^ | | 0.94 (0.64, 1.37) ^ | | 0.85 (0.76 to 0.94)^ | |
| p-value | 0.9410[§§§] | | 0.5146[r§] | | 0.6944[§§§] | | 0.0028^ | |
| **Time to Hospital discharge or ready for discharge[a]** | | | | | | | | |
| Proportion of patients at Day 28 | TCZ: 56.8%, PBO: 50.0% | | TCZ: 87.1%, PBO: 82.8% | | TCZ: 66.0%, PBO: 67.1% | | TCZ: 57%, Usual Care: 50% | |
| Median time (days) | TCZ: 20, PBO: 28[‡] | | TCZ: 6, PBO: 7.5[‡] | | TCZ: 14.0, PBO: 14.0[‡] | | TCZ: 19, Usual Care: >28 | |
| Hazard ratio (TCZ/PBO) (95% CI) | 1.35 (1.02, 1.79)[†††] | | 1.16 (0.91, 1.48)[†] | | 0.965 (0.78, 1.19)[†††] | | 1.22 (1.12 to 1.33)^ | |
| p-value | 0.037[†††] | | 0.2417[†§] | | 0.7414[†††] | | <0·0001^ | |

| | COVACTA (mITT) | | EMPACTA (mITT) | | REMDACTA (mITT) | | RECOVERY (ITT) | |
|---|---|---|---|---|---|---|---|---|
| | TCZ N=294 | PBO N=144 | TCZ N=249 | PBO N=128 | TCZ N=430 | PBO N=210 | TCZ N=2022 | Usual Care N=2094 |
| **Incidence of MV/ Time to MV or Death/ Use of invasive MV (including ECMO) or Death[b]** | | | | | | | | |
| | n=183 | n=90 | | | n=371 | n=188 | n=1754 | n=1800 |
| Cumulative proportion** of patients at Day 28 | - | | TCZ: 12.0%, PBO: 19.3% | | - | | - | |
| Proportion of patients by Day 28 | TCZ: 27.9%, PBO: 36.7%^^ | | TCZ: 11.6%, PBO: 18.8% | | TCZ: 27.5%, PBO: 29.8% | | TCZ: 35%, Usual Care: 42%*** | |
| Weighted difference (TCZ-PBO) in % (95% CI) | -8.9% (-20.7%, 3.0%)[‡‡] | | - | | –2.2% (–10.2%, 5.9%)[‡‡] | | - | |
| Hazard ratio (TCZ/PBO) (95% CI) | - | | 0.56 (0.33, 0.97)[†] | | - | | - | |
| Risk Ratio (TCZ/PBO) (95% CI) | - | | - | | - | | 0.84 (0.77 to 0.92) | |
| p value | 0.1355^^^ | | 0.0360[†§] | | 0.5915^^^ | | <0.0001 | |

ICU=intensive care unit; ITT=intention-to-treat population; mITT=modified intention-to-treat population, MV=mechanical ventilation.

[a] Defined as days from randomization to hospital discharge or "Ready for Discharge" not followed by ordinal scale category >1, hospital readmission or death for REMDACTA.

[b] COVACTA and REMDACTA results include incidence of mechanical ventilation by Day 28 in patients not on mechanical ventilation at baseline in the mITT Population. Time to mechanical ventilation or death by Day 28 was reported in EMPACTA mITT. RECOVERY reported use of invasive mechanical ventilation (including ECMO) or death among patients not on invasive mechanical ventilation at baseline in ITT population.

* Mortality included all cause up to Day 28. The Cochran- Mantel-Haenszel weighting approach was used to calculate the weighted difference with stratification factors (two stratification factors (region [North America, Europe] and mechanical ventilation [yes, no]) for COVACTA, one stratification factor (age group [≤60, >60 years]) for EMPACTA, two stratification factors (region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]) for REMDACTA). The Newcombe method was used to estimate the 95% CI for the weighted difference.

[β] Mortality included all cause up to Day 28. In RECOVERY, mortality difference (TCZ-PBO) at Day 28 estimated by the Kaplan−Meier approach (using Zee and Xie 2018 method) on time to death endpoint.
^ The log-rank 'observed minus expected' statistic (and its variance) was used (Peto et al 1977). The log-rank test driven rate ratios and its 95% CI are identical to unstratified Cox hazard ratio and its 95% CIs.
§§§ P value based on extended Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].
[‖] P value for this EMPACTA endpoint was calculated with the stratified Cochran-Mantel-Haenszel test with age group (≤ 60, >60 years) as a stratification factor.
[†††]Cox Proportional Hazards model includes stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6]
[†]Hazard ratios and associated 95% CIs were estimated for EMPACTA with stratified Cox proportional hazard model with age group (≤60, >60 years) as a stratification factor.
†††P value based on log-rank test stratified by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe] and mechanical ventilation [yes, no]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].
†P values for EMPACTA were calculated with the stratified Log-rank test with age group (≤60, >60 years) as a stratification factor.
§Significance testing for EMPACTA was performed hierarchically to control for study-wide Type I error rate at a two-sided 5% significance level. Nominal P values are presented for secondary endpoints because first secondary endpoint failed to reach significance.
^^ For this analysis, COVACTA and REMDACTA patients who withdrew prior to discharge or died prior to Day 28 were assumed to have required mechanical ventilation by Day 28.
** Mortality included all cause up to Day 28. For EMPACTA, cumulative proportion of patients and associated 95% CI were estimated using the Kaplan-Meier method.
‡‡ Weighted difference in proportions as calculated using the Cochran-Mantel- Haenszel test stratified by stratification factor at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].
***Analyses include only those patients on no ventilator support or non-invasive ventilation at baseline (1754 patients in TCZ+Usual Care arm and 1800 in Usual Care arm).
^^^ P value based on extended Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization. For COVACTA mITT, the stratification factors included: region [North America, Europe]. For REMDACTA mITT, the stratification factors included: region [North America, Europe, Other] and baseline ordinal scale [4-5, 6].
‡ Median time-to-event were estimated using the Kaplan-Meier method.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Tocilizumab therapy in RECOVERY was able to reduce 28-day mortality compared with usual care alone (31% vs 35%) and was associated with a greater probability of discharge from hospital within 28 days (57% vs 50%).

Tocilizumab should not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup. This is adequately reflected in Sections 4.1, 4.4 and 5.1 of the SmPC.

No new or unknown unfavourable effects could be discerned from this mainly severely ill population who often had pre-existing co-morbidities. The risks and monitoring thereof are adequately described in the SmPC.

### 3.7.2. Balance of benefits and risks

Tocilizumab therapy in RECOVERY was able to reduce 28-day mortality compared with usual care alone (31% vs 35%) and was associated with a greater probability of discharge from hospital within 28 days (57% vs 50%). These results are regarded as clinically relevant. In the current pandemic situation, the treatment could play a role in reducing numbers of death and numbers of patients progressing to a more severe disease stage.

No new safety signal arose from the data submitted.

The CHMP concluded that the data supported the indication in the "*treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation*."

## *3.8. Conclusions*

The overall B/R of RoActemra in the "*treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation*" is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA and IIIB |

C.I.6 - Extension of indication to include the treatment of coronavirus disease 2019 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation for RoActemra; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC for RoActemra 20 mg/mL concentrate for solution for infusion are updated. The Package Leaflet has been updated in accordance. The RMP is updated to Version 27.1 and the Annex II has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev. 1. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Hungary.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan (including means of distribution), with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- Reference to the Summary of Product Characteristics (e.g., link to EMA website)
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
- The product must not be given to patients with active or suspected infection
- The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
- Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.

- In RA, GCA, pJIA and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC section 4.2.

- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Details on how to report serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Guidance on how to diagnose Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion related reactions
- Preparation of injection/infusion
- Infusion rate
- Monitoring of the patient for injection/infusion related reactions
- Details on how to report serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC) (e.g., link to EMA website)
- Patient alert card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.

- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.

- to address the risk that patients using RoActemra may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion Roactermra-H-C-000955-II- 0101.

# Attachments

1. SmPC, Annex II, Labelling, and Package Leaflet (changes highlighted) as adopted by the CHMP on 6 December 2021.