A RANDOMIZED, DOUBLE-BLIND, PLACEBOCONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA

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This study will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab (TCZ) compared with a matching placebo in combination with standard of care (SOC) in hospitalized patients with severe COVID-19 pneumonia. Specific...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON50069

Source
ToetsingOnline

Brief title
WA42380

Condition

- Respiratory tract infections

Synonym
inflammation lungs, Pneumonia, respiratory disorder

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann-La Roche Ltd
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd

Intervention

Keyword: COVID-19, EFFICACY, SAFETY, TOCILIZUMAB

Outcome measures

Primary outcome

Primary Efficacy Objective

The primary efficacy objective for this study is 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 the following endpoint:

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

Secondary outcome

1. Time to clinical improvement

2. Time to improvement of at least 2 categories relative to baseline on a

7-category ordinal scale of clinical status

3. Incidence of mechanical ventilation

4. Ventilator-free days

5. Incidence of intensive care unit (ICU) stay

6. Duration of ICU stay

7. Time to clinical failure

8. Mortality rate

9. Time to hospital discharge or "ready for discharge"

10. Duration of supplemental oxygen.

Study description

Background summary

Coronaviruses (CoV) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the 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 (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

COVID-19, which is the acronym of "coronavirus disease 2019," is caused by a new coronavirus strain that has not been previously identified in humans and was newly named on 11 February 2020 by the World Health Organization (WHO). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the WHO
Country Office in China on December 31, 2019. A pandemic was subsequently declared by the WHO on 11 March 2020.

According to the WHO, as of 17 March 2020 over 179,000 cases of COVID-19 were reported in over 100 countries worldwide, with over 7400 deaths. Up to ~20% of infected patients experienced complications related to a severe form of interstitial pneumonia, which may progress towards acute respiratory distress syndrome (ARDS) and/or multi organ failure (MOF) and death.

To date, there is no vaccine and no specific antiviral medicine shown to be effective in preventing or treating COVID-19. Most patients with mild disease recover with symptomatic treatment and supportive care.

Study objective

This study will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab (TCZ) compared with a matching placebo in combination with standard of care (SOC) in hospitalized patients with severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

Study design

Overview of Study Design
This is a 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. The Sponsor intends to enroll approximately 330 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria in centers globally.
Patients must be at least 18 years of age with confirmed COVID-19 infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO2 * 93% or PaO2/FiO2 * 300 mmHg) despite being on SOC, which may include anti-viral treatment, low dose steroids, and supportive care.

Patients in whom, in the opinion of the treating physician, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments, will be excluded from the study. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19) will be excluded from the study.
Patients will be randomized as soon as possible after screening at a 2:1 ratio to receive blinded treatment of either TCZ or a matching placebo, respectively. Study treatment must be given in combination with SOC. The randomization will be stratified by geographic region (North America, Europe, and other) and mechanical ventilation (yes, no).
Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8*12 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify
for one re-screening opportunity (for a total of 2 screenings per participant) at the investigator*s
discretion. Patients are not required to re-sign the consent form if they are re-screened within 7
days after previously signing the consent form. .
The study assessments to be conducted include the following: physical examination, vital signs,
oxygen saturation, assessment of consciousness, presence and absence of respiratory support,
adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs.

After Day 28
Patients will be followed up for a total of 60 days after first dose of study medication.
For patients who are discharged between Day 28 and study completion, visits may be
conducted via telephone.
During the study, standard supportive care will be given according to clinical practice.

Intervention

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8*12 hours after the initial infusion.

Study burden and risks

- We will perform a physical examination - at 1 timepoint
- We will measure your vital signs - at 33 timepoints
- We will perform an electrocardiogram (ECG) - at 1 timepoint
- We will perform a pregnancy test - at the screening day
- We will collect blood - at 36 timepoints, 4,5-39mL XX tubes at a time.
This is to monitor your response to the study drug and also to measure the amount of study drug that is in your body and how your body breaks it down
- We will perform a chest X-ray at a maximum of 7 timepoints. CT scans can be performed as alternative for the chest X-ray

- We will give you one or two infusions with study drug or placebo

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age >< = 18 years
- Hospitalized with COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- SpO2 <<= 93% or PaO2/FiO2 < 300 mmHg.

Exclusion criteria

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Active TB infection
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Have received oral anti-rejection or immunomodulatory drugs (including tocilizumab) within past 3 months
- Pregnant or lactating women
- Participating in other drug clinical trials (with possible exception of anti-viral trials)
- ANC < 1000/mm3

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RoActemra

Generic name:	Tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-001154-22-NL

Register	ID
ClinicalTrials.gov	NCT04320615
CCMO	NL73503.056.20