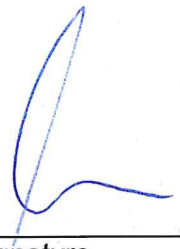
CLINICAL STUDY REPORT

A prospective, randomized, double blind placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia TOC-COVID

Name of test drug:	Tocilizumab solution for infusion
Indication studied:	Severe Covid-19 pneumonia
EudraCT No:	2020-001408-41
Protocol identification:	P003321
Drug development phase:	II
Study initiation date (first patient in):	03. May 2020
Date of early study termination	31. Aug 2021
Study completion date (last patient out):	23. Aug 2020
Principal or Co-ordinating investigator: (or Sponsor's responsible medical officer)	PD. Dr. Tobias Wengenmayer Medical Center – University of Freiburg Department of Medicine III Hugstetter Str. 55 79106 Freiburg, GERMANY
Sponsor:	Medical Center - University of Freiburg represented by the Chief Medical Officer (Leitender Ärztlicher Direktor) and the Chief Financial Officer (Kaufmännische Direktorin) Breisacher Str. 153 79110 Freiburg, GERMANY
Report ID:	TOC-COVID_CSR
Report version:	01
Report date:	13. Aug 2021
Number of pages:	16

Quality Assurance Statement:
This trial has been performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

1. APPROVAL

Coordinating Investigator (Leiter Klinische Prüfung) and Sponsor representative delegated to PD. Dr. Tobias Wengenmayer	10.8.2021 Date	 Signature
Project coordinator and Medical Writer Dr. Lydia Herbstritt	13.08.2021 Date	 Signature
Statistician Dr. Claudia Schmoor	13.08.2021 Date	 Signature

2. SYNOPSIS

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part < > of the Dossier	*(For National Authority Use only)*
Name of Finished Product: RoActemra® i.v.	Volume:	
Name of Active Ingredient: Tocilizumab	Page:	

Title of Study: A prospective, randomized, double blind placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia

Investigators:

Coordinating Investigator was PD Dr. med. Tobias Wengenmayer, Medical Center – University of Freiburg (Leiter der Klinischen Prüfung according to German Drug Law). Principal Investigator of the University Heart Center Bad Krozingen was Dr. med. Christian Marc Valina.

Study centers: The study was conducted at two different sites in Germany. Investigators from 1 site have enrolled patients to the study.

- Universitätsklinikum Freiburg, Klinik für Innere Medizin III, Hugstetter Str. 55, 79106 Freiburg.
- Universitäts-Herzzentrum Freiburg-Bad Krozingen, Klinik für Kardiologie und Angiologie II, Südring 15, 79189 Bad Krozingen.

Study period (years):	**Phase of development**:
First patient in: 30. May 2020 Last patient out: 23. Aug 2020	Phase II

Objectives:

To assess the efficacy and safety of tocilizumab in comparison to placebo in patients with severe COVID-19 pneumonia.

Trial Hypotheses:

The primary endpoint ventilator-free days (VFD) is defined as follows:

- VFD = 0 if the patient dies within 28 days after randomization
- VFD = x if ventilation (including Non-Invasive Ventilation (NIV), Invasive mechanical ventilation (IMV) and Extracorporeal membrane oxygenation (ECMO)) time = 28 – x.
- VFD = 0 if ventilation (including NIV, IMV and ECMO) time ≥ 28.

The Wilcoxon rank sum test stratified by center will be used for the primary analysis of the primary endpoint VFD up to day 28 after randomization. The hypothesis of equality of treatment arms with respect to VFD will be tested at a two-sided significance level of 0.05.

Methodology:

This is phase II multicenter, prospective, randomised, double blind, placebo-controlled trial.

Number of patients (planned and analyzed):

To be allocated to the trial / assessed for eligibility: 230 within 6 month- recruitment period.

To be analysed: 200 (2x100)

Three patients were enrolled to the trial within 3 months and randomized, namely 2 patients to placebo/control group, 1 to interventional group.

Date are summarized in this Clinical Study Report.

The trial was terminated prematurely by the Sponsor since preliminary results of the Covacta trial (DOI: 10.1056/NEJMoa2028700) were reported to the German Competent Authority (Paul Ehrlich Institute). In this trial no statistically significant differences between tocilizumab and placebo on clinical status and mortality could be detected.

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Diagnosis and main criteria for inclusion

Diagnosis

Female and male patients aged 18 years or above were enrolled into this trial with eligible proof of SARS-CoV2 and severe respiratory failure. Patients were only allowed to enter the trial, if they (or their legal authorized representative or investigator consilium) provided written informed consent and if the physician verified that the patient meets all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

1. Proof of SARS-CoV2
2. Severe respiratory failure:
   a. ambient air $SpO_2 \leq 92\%$ or
   b. Need of ≥ 6l O_2/min or
   a. NIV (non-invasive ventilation) or
   a. IMV (invasive mechanical ventilation)
3. ≥ 18 years
4. Written informed consent obtained from the patient or legal authorized representative or investigator consilium ("Gießener Modell") according to international guidelines and local laws.

Exclusion criteria

1. Non-invasive or invasive mechanical ventilation ≥ 48 hours
2. Pregnancy or breast feeding
3. Liver injury or failure (AST/ALT ≥ 5x ULN)
4. Leukocytes < 2×10^3/µl
5. Thrombocytes < 50×10^3/µl
6. Severe bacterial infection (Procalcitonin, PCT > 3ng/ml)
7. Acute or chronic diverticulitis
8. Immunosuppressive therapy (e.g. mycophenolate, azathioprine, methotrexate, biologicals, prednisolone >10mg/d; exceptions are: prednisolone ≤ 10mg/d, sulfasalazine or hydroxychloroquine)
9. Known active or chronic tuberculosis
10. Known active or chronic viral hepatitis
11. Known allergic reactions to tocilizumab or its ingredients
12. Life expectation of less than 1 year (independent of COVID-19)
13. Participation in any other interventional clinical trial within the last 30 days before the start of this trial
14. Simultaneous participation in other interventional trials (except for participation in COVID 19 trials) which could interfere with this trial; simultaneous participation in registry and diagnostic trials is allowed

15. Failure to use one of the following safe methods of contraception: female condoms, diaphragm or coil, each used in combination with spermicides; intra-uterine device; hormonal contraception in combination with a mechanical method of contraception.

Women could only take part in this study if the risk of becoming pregnant was absolutely minimized. Save contraceptive methods comprise: female condoms, diaphragm or coil, each used in combination with spermicides; intra-uterine device; hormonal contraception in combination with a mechanical method of contraception and have to be used while participating in the study.

Investigational Product, dose and mode of administration:

Table 1 Study intervention

Study medication	**Pharmaceutical form and route of administration**	**Dose**	**Duration/ or Regimen**
Tocilizumab	Concentrate for solution for infusion (sterile concentrate) i.v.	8 mg/kg for participants at or above 30kg BW 12 mg/kg for participants less than 30kg BW; doses exceeding 800 mg are not recommended	Only one administration
Placebo	solution for infusion; NaCl 0.9% i.v.	Not applicable	Only one administration

BW= body weight, i.v. = intravenous

Total dose of tocilizumab should not exceed 800 mg. It was recommended to apply IMP as a 60-minute intravenous infusion.

Moreover, all subjects in both arms (intervention or control) were treated for their COVID-19 pneumonia and the maybe resulting ARDS (acute respiratory distress syndrome) to best clinical practice.

Tocilizumab:

Proprietary name: RoActemra® i.v.

Name of substance: Tocilizumab

Dosage form: Solution for infusion

Strength: 80 mg; 200 mg, 400 mg

Manufacturer: Roche Pharma AG, Grenzach-Wyhlen, Germany

Approved indications:

- The treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX).

- The treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

- The treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Total daily dose: 8 mg/kg for participants at or above 30-kg weight; 12 mg/kg for participants less than 30-kg weight; doses exceeding 800 mg per infusion are not recommended.

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Placebo:

Proprietary name: NaCl 0,9% Solution for infusion

(100 ml infusion bag; 50 ml for patients < 30kg BW)

Name of substance: Placebo, NaCl

Dosage form: Solution for infusion

Strength: Not applicable

Manufacturer: Maco Pharma International GmbH, Langen, Germany

Approved indications: Not applicable

Total daily dose: Not applicable

Commercially available Tocilizumab (RoActemra® i.v., Roche Pharma AG) or sodium chloride (NaCl) 0.9% solution (Isotonische NaCL-Lösung 0,9%, Maco Pharma International GmbH) for infusion were used to prepare a patient individual infusion solution according to protocol and Specification of Product Characteristics (SmPC), as applicable. No specific labelling of stock solution was done. Final application form of both IMPs (solution for infusion) were labelled according to Good Clinical Practice (GCP) and German Drug Law (AMG) rules. To avoid unblinding the infusion bags were put into opaque plastic sleeves.

Duration of Treatment:

Patients randomized to the interventional group received one application of tocilizumab solution for infusion and patients randomized to the placebo group received one application of placebo solution for infusion. Both verum and placebo solution for infusion were prepared for the individual patient, respectively.

Criteria for evaluation

Efficacy

Primary efficacy endpoint:

To assess the efficacy of tocilizumab in comparison to placebo regarding:
Ventilator free days (d) (VFD) in the first 28 days after randomization

- NIV, IMV and ECMO are defined as ventilator days
- VFD=0, if the patient dies in the first 28 days after randomization

Secondary efficacy endpoints in the first 28 days after randomization (primary follow up):

- Mortality:
  - 28-day mortality (%) after randomization
  - Hospital mortality in the first 28 days (%)
- Admission to intensive care unit (ICU)
  - Admission to ICU (%)
  - Days on ICU in the first 28 days (d)
- Ventilation
  - IMV free days (d) in the first 28 days after randomization (IMV and ECMO are defined as ventilator days; IMV free days =0, if the patient dies in the first 28 days)
  - Time to successful extubation within 28 days after randomization (d)
- Renal function
  - Renal failure (%)
  - Renal replacement therapy (%)
- Change of ventilation mode and invasiveness
  - Horowitz Index (paO_2/fiO_2)
  - fiO_2 on NIV/IMV

- O_2-level on O_2-nasal cannula, O_2-mask and High-flow nasal cannula
- PEEP und compliance on NIV/IMV
- Extracorporeal membrane oxygenation (ECMO) support

- Scores
  - SOFA-Scores
  - APACHE-II Score
  - Seven-category scale
  - Richmond Agitation Sedation Scale (RASS)
  - Glasgow Coma Scale
- Laboratory
  - PCT
  - IL-6
  - Ferritin
  - D-Dimers

Assessment of efficacy until end of the study (extended follow up):

- Mortality: Overall survival after 12 months
- Quality of life (QOL) 6 and 12 months after randomization:
  - 36-Item Short Form survey Instrument (SF-36)
  - St George's Respiratory Questionnaire
  - Hospital Anxiety and Depression Scale (HADS-D)

Safety

Assessment of safety in the first 28 days after randomization (primary follow up):

- Secondary infections and complications
  - Bacterial infection
  - Septic shock
  - Hepatitis / acute liver injury
  - Acute liver failure
  - Myocarditis and concomitant cardiogenic shock
  - Renal failure
- Adverse events: (Serious) adverse events
- Laboratory parameters (including white blood cells, thrombocytes, Quick value, INR, PTT, ferritin, urea, creatinine, uric acid, lactat dehydrogenase, proBNT, aspartate amino transferase / Glutamat-Oxalat-Transaminase (AST/GOT), alanine amino transferase / glutamat-pyruvat-transaminase (ALT/GPT), triglyceride, cholesterol, hemoglobin, sodium, potassium, bilirubin, hematocrit)

Assessment of safety until end of the study (extended follow up):

- Related SAEs
  - SAEs related to IMP as per investigator's judgment

Definition of (serious) adverse events

As this trial involves patients suffering from severe COVID-19 associated with significant mortality/morbidity and respiratory failure and that these parameter are secondary endpoints (i.e. anticipated clinical outcomes) collected on the specific eCRF pages and taking into consideration recommendations of the CIOMS working group VI concerning management of safety information from clinical trials, the following events have not to be notified to the sponsor as SAEs:

- Death due to severe COVID-19
- Respiratory failure
- Expected COVID-19 complications, which are defined as secondary safety endpoints (see above) and were documented on the separate CRF-pages designated for this purpose.

In addition, symptoms, medically significant laboratory, or instrumental (e.g. electrocardiographic) abnormalities of a pre-existing disease are not to be considered an AE. Occurrences of new symptoms or laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, are considered AEs.

A Serious Adverse Event (SAE) is any untoward medical occurrence that results in any of the following outcomes:

• Death,
• Life-threatening situation (patient is at immediate risk of death),
• Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy and/or assessments, placement of an indwelling catheter, social/convenience admissions, respite care, elective or pre-planned treatment/surgery)
• Persistent or significant disability/incapacity,
• Congenital anomaly/birth defect,
• Other, medically important condition: conditions which, in the investigator's opinion, may not be immediately life-threatening or result in hospitalization, but may jeopardize the patient's safety or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious. Examples of such conditions include: allergic bronchospasm requiring treatment in an emergency room or at home, unexpected convulsions (i.e. convulsions which cannot be explained by the underlying illness) that do not result in hospitalization, development of IMP dependency or drug abuse, suspected transmission of infectious agents by medicinal product, etc.

• NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe.

Statistical methods were planned as follows:

Description of the primary efficacy analysis and population:

The primary endpoint ventilator-free days (VFD) is defined as follows:

- VFD = 0 if the patient dies within 28 days after randomization
- VFD = x if ventilation (including NIV, IMV and ECMO) time = 28 – x.
- VFD = 0 if ventilation (including NIV, IMV and ECMO) time ≥ 28.

The Wilcoxon rank sum test stratified by center will be used for the primary analysis of the primary endpoint VFD up to day 28 after randomization. The hypothesis of equality of treatment arms with respect to VFD will be tested at a two-sided significance level of 0.05.

Efficacy analyses will be performed primarily in the full analysis set (FAS) according to the intention-to-treat (ITT) principle. This means that the patients will be analysed in the treatment arms to which they were randomised, irrespective of whether they refused or discontinued the treatment or whether other protocol violations are revealed.

The per-protocol (PP) population is a subset of the FAS and is defined as the group of patients who had no major protocol violations. The protocol deviations leading to an exclusion of patients from the PP population will be defined in the SAP. The analysis of the PP population will be performed for the purpose of a sensitivity analysis.

Safety:

Safety analyses will be performed in the safety population. Patients in the safety population are analysed as belonging to the treatment arm defined by treatment received. Patients are included in the respective treatment arm, if treatment was started / if they received at least one dose of trial treatment.

Secondary endpoints:

Planned statistical analyisis of secondary endpoints is described in the clinical trial protocol.

Due to early trial termination of the trial only a description of the three patients randomized is provided in this clinical study report (CSR).

PATIENT POPULATION

Three patients were randomized in this trial within 3 months of recruitment period. The first patient (ID 121-1) was randomized on 03.May 2020, the second (ID 121-2) on 31. May 2020 and the third (ID 121-3) on 23. Jul 2020.
The patients were 77 (female; 121-1), 64 (male, 121-2), and 69 (male, 121-3) years old.
In this abbreviated clinical study report, main results are described by patient. Details are available in the tables received from the clinical database (electronic Case Report Form, eCRF).

TREATMENT

The patients received one administration of the randomized IMP according to protocol, respectively. Two patients received placebo and one patient tocilizumab infusion.

EFFICACY RESULTS

Three patients have been randomized, thereof one patient to the tocilizumab group (121-2) and two patients to the placebo group (121-1 and 121-3). The patients received one administration of the randomized IMP, respectively.

The primary efficacy endpoint is Ventilator free days (d) (VFD) in the first 28 days after randomization whereby NIV, IMV and ECMO are defined as ventilator days and VFD=0, if the patient died in the first 28 days after randomization.

No ventilator-free days were described in any of the patients.
Two patients died. One patient passed away in the first 28 days after randomization (121-2: at Day 12, due to intestinal ischemia) and the other patient after this time period (121-3 at Day 31, due to respiratory failure), see Table 2.

Table 2 Result of primary efficacy endpoint: Ventilator free days (VFD)

Patient ID	Randomized group	Ventilator-free days (NIV, IMV, ECMO)	Death within the first 28 days after randomization ([yes/no]
121-1	Placebo	0	No
121-2	Tocilizumab	0	Yes
121-3	Placebo	0	No[(1)]

(1) Patient 121-3: Death on Day 31

The results on secondary efficacy endpoints by patient are summarized in Table 3.

Table 3 Results of secondary efficacy endpoints

Secondary efficacy endpoints	**Patient (ID)**		
	121-1	**121-2**	**121-3**
Mortality			
28-day mortality (%) after randomization	No	Yes (Day 12)	Yes (Day 24)
Hospital mortality in the first 28 days (%)	No	Yes	Yes
Admission to intensive care unit (ICU)			
Admission to ICU (%):	Yes	Yes	Yes
Days on ICU in the first 28 days (d)	21	12	28
Ventilation			
IMV free days (d) in the first 28 days after randomization	28	0	5
Time to successful extubation within 28 days after randomisation (d)	n.a.	n.a.	n.a.
Renal function			
Renal failure (%)	No	Yes	No
Renal replacement therapy (%)	No	Yes (D11-12)	No
Change of ventilation mode and invasiveness			
Horowitz Index (paO_2/fiO_2) (mmHg) D 0	207,7	128,4	78,2
fiO_2 on NIV/IMV (%), D 0	26 (estimated)	55 (real)	90 (real)
O_2-level on O_2-nasal cannula, O_2-mask and High-flow nasal cannula D 0	1 l/min (oxygen flow, nasal cannula)	n.a. (IMV)	n.a. (NIV)
PEEP (mbar) and compliance (ml/mbar) on NIV/IMV D 0	n.a.	15 and 39.2	8 and 98.3
Extracorporeal membrane oxygenation (ECMO) support	No	Yes	Yes
Scores (within 28 days after randomization)			
SOFA-Scores (range x-x)			
Sum D 0	2	7	5
Sum min, max (D1-Dx)	3, 4	11, 12	4, 12
APACHE-II Score			
Sum D 0	17	21	10
Sum min, max (D1-Dx)	14, 17	18, 25	10, 25
Seven-category scale			

Sum D 0	4	6	5
Sum min, max (D1-Dx)	2, 5	6, 7	5, 6
Glasgow Coma Scale			
Sum D 0	15	7	15
Sum min, max (D1-Dx)	15, 15	3, 3	3, 15
Laboratory (min,max)			
Procalcitonin (PCT) (ng/ml)	0.09-0-0.47	0.23-2.90	0.14-0.78
Interleukin-6 (IL-6) (pg/ml)	6.7-347.0	503.0-6294.0	68.8-1877.0-
Ferritin (ng/ml)	100.0-644.0	896.0-6391.0	405.0-766.0
D-Dimers (mg/l)	1.79-6.65	4.06-27.25	1.17-35.2

Source: eCRF-Documentation

n.a.: not applicable.
Please note: Instead of %-vales only absolute numbers are given due to the small number of patients
Details regarding Richmond Agitation Sedation Scale (RASS) are given in eCRF-Documentation.

Assessment of efficacy until end of the study (extended follow up):

The trial was prematurely terminated without extended follow-up period. Thus, no data are available for extended follow-up.

SAFETY RESULTS:

Results on the "secondary safety endpoints "secondary infections and complications as well as "(serious) adverse events" are summarized in detail by patient in Table 4 and Table 5, respectively. Results on safety "laboratory parameters" are given in the eCRF documentation.

Secondary infections and complications

In 2 of 3 patients secondary infections and complications were observed.

One patient (121-2) suffered from abdominal bacterial infection and sepsis / septic shock with fatal outcome on Day 12 after randomization. In addition, hepatitis / acute liver failure, myocarditis, and renal failure were observed.

The second patient (121-3) suffered from pneumonia, sepsis (life-threatening) and septic shock (life-threatening) with fatal outcome on Day 31 after randomization.

Table 4 Results of secondary safety endpoints: Secondary infections and complications

Secondary efficacy endpoints:	**Patients (ID)**		
	121-1	**121-2**	**121-3**
Secondary infections and complications			
Bacterial infection	No	Yes Bacterial infection presumed focus: abdominal	Yes Bacterial infection presumed focus: pneumonia
Onset	Not applicable	D 10	D 8
Stop		D 12	D 31
Severtity (1-5 Scale)		5-Death	3-Severe
Outcome		Fatal	Not resolved / not recovered
Septic shock / Sepsis	No	Yes Sepsis, septic shock	Yes Sepsis
Onset		D 10	D 8
Stop		D 12	D 31
Severity (1-5 Scale)		5-Death	3-Severe
Outcome		Fatal	Not recovered / not resolved
			Septic shock
Onset			D 8
Stop			D 10
Severity (1-5 Scale)			4-Life threatening
Outcome			Recovered / resolved
Hepatitis / acute liver injury	No	Yes Hepatitis / acute liver injury	No
Onset		D12	
Stop		D 12	
Severity		3-Severe	
Outcome		Not recovered / not recovered	

Acute liver failure Onset Stop Severity Outcome	No	Yes Acute liver failure D12 D 12 4-Life threatening Not recovered / not resolved	No
Myocarditis and concomitant cardiogenic shock Onset Stop Severity Outcome	No	Yes Myocarditis D 12 D 12 3-Severe Not recovered / not resolved	No
Renal failure Onset Stop Severity Outcome	No	Yes Renal failure D 11 D 12 3-Severe Not recovered / not resolved	No

Source: eCRF-Documentation

(Serious) adverse events

A total of 14 adverse events were descried in the 3 patients included in the trial: Anemia, lymphopenia and thrombocytopenia in all 3 patients, leukopenia in 2 patients and seizure, intestinal ischemia, neutropenia, and pulmonary hemorrhage were reported in 1 patient, respectively.

No AE was considered related to the IMP. All AEs were considered related to the underlying disease. One AE was serious (intestinal ischemia, considered not related to IMP, fatal outcome). For further details see Table 5.

Results on safety laboratory parameters are documented in eCRF.

Table 5 Results of secondary safety endpoints: Adverse Events, Serious Adverse Events

Secondary efficacy endpoints:		**Patients (ID)**		
Adverse events (Type, Preferred Term[1])		**121-1**	**121-2**	**121-3**
Anemia	Frequency (n) Onset (day) Stop (day) Severity[2] Relatedness to IMP underlying disease Outcome Serious (yes/no)	1 D 8 Ongoing after study end 1-Mild No Yes Recovering / resolving No	1 D 1 D 13 2-Moderate No Yes Not recovered / not resolved No	1 D 1 D 31 3-Severe No Yes Not revered / not resolved No
Seizure	Frequency (n) Onset (day) Stop (day) Severity Relatedness to IMP underlying disease Outcome Serious (yes/no)	0	1 D 6 D 6 2-Moderate No Yes Recovered / resolved No	0
Intestinal ischemia	Frequency (n) Onset (day) Stop (day) Severity Relatedness to IMP underlying disease Outcome Serious (yes/no)	0	1 D 12 D 13 5-Death No Yes Fatal Yes	0
Leucopenia	Frequency (n) Onset (day) Stop (day) Severity Relatedness to IMP underlying disease Outcome Serious (yes/no)	0	1 D 11 D 12 2-Moderate No Yes Recovered / resolved No	0
Lymphopenia	Frequency Onset (day) Stop (day) Severity	1 D 0 D 25 1-Mild	1 D 2 D 8 2-Moderate	1 D 1 D 31 3-Severe

	Relatedness to IMP underlying disease Outcome Serious (yes/no)	No Yes Recovered / resolved No	No Yes Recovered / resolved No	No Not recovered / not resolved No
Neutropenia	Frequency Onset (day) Stop (day) Severity Relatedness to IMP underlying disease Outcome Serious (yes/no	0	1 D 12 D 13 2-Moderate No Yes Not recovered / not resolved No	0
Pulmonary hemorhage	Frequency (n) Onset (day) Stop (day) Severity Relatedness to IMP to underlying diesease Outcome Serious (yes/no)	0	0	1 D 23 D 31 4-Life-threatening No Yes Not recovered / nor resolved No
Thrombocyto penia	Frequency (n) Onset (day) Stop (day) Severity Relatedness to IMP underlying diesease Outcome Serious (yes/no)	1 D 1 D 12 1-Mild No Yes Recovered / resolved No	1 D 5 D 13 2-Moderate No Yes Not recovered / not resolved No	1 D -1 D 25 1-Mild No Yes Recovered / resolved No

Source: eCRF-Documentation
(1)Coding: MedDRA 24.0
(2)Severity according to the current version of Common Terminology Criteria for Adverse Events (CTCAE).

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PROTOCOL AMENDMENTS

No amendments were done during the study.

SUMMARY - CONCLUSIONS

The study has been terminated early by the Sponsor. The main reason for premature study termination was the publication of results obtained from the Covacta trial in 438 patients which demonstrated, that no effect of tocilizumab on clinical status and mortality exists as compared to placebo.

Three patients were randomized in this study, two males and one female, aged between 64 and 77 years. One patient was randomized to the toclimizumab group and two patients were randomized to the placebo group. No formal statistical analysis could be performed due to the small number of patients. The patients were described individually. In the sole patient randomized to the tocilizumab arm as well as in the two placebo-treated patients, no ventilator-free days were described. Two patients died, one in the tocilizumab group (due to intestinal ischemia) and one in the placebo group (due to respiratory failure).

One serious adverse event (SAE) was reported (intestinal ischemia in the patient receiving tocilizumab, considered not related to IMP, fatal outcome). No serious adverse reactions (SAR) or suspected unexpected serious adverse reaction (SUSAR) was reported in the study. A total of 14 adverse events were descried in the 3 patients included in the trial: Anemia, lymphopenia and thrombocytopenia in all 3 patients, leukopenia in 2 patients and seizure, intestinal ischemia, neutropenia, and pulmonary hemorrhage were reported in 1 patient, respectively. No AE was considered related to the IMP.

No new safety issues have been observed during the study period that would alter the assumed benefit/risk profile at study start and necessitating premature study termination. No safety concerns have arisen during the trial.

Date of the Report:

Date: 13. Aug 2021