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Supplementary appendix

This online publication has been corrected. The corrected version first appeared at thelancet.com on July 30, 2021

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bauer A, Schreinlechner M, Sappler N, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. *Lancet Respir Med* 2021; published online June 11. http://dx.doi.org/10.1016/S2213-2600(21)00214-9.

Discontinuation *versus* Continuation of Renin-Angiotensin-System Inhibitors in COVID-19 (ACEI-COVID): A prospective randomized open label trial

Supplementary Material

1. Inclusion and exclusion criteria

Table S1: Inclusion and exclusion criteria

Inclusion criteria
Female and male patients competent to make a decision
Proven and symptomatic SARS-CoV-2 infection ≤ 5 days
Patient age ≥ 18 years
Provided written informed consent
Chronic (≥ 1 month) ACEI/ARB therapy for treatment of arterial hypertension, diabetes mellitus, heart failure or coronary artery disease
Stable hemodynamic conditions allowing to stop or continue treatment with ACEI/ARB (systolic blood pressure ≤180mmHg)
Exclusion criteria
Women capable of bearing children as well as pregnant and breastfeeding women
Participant in another interventional trial
At screening visit, no oral medication intake possible
Advanced heart failure NYHA Stage III-IV
Left ventricular ejection fraction <30% or NTproBNP ≥600pg/mL in case of clinical signs of heart failure
Acute coronary syndrome ≤ 3 months
Hospitalization due to decompensated heart failure ≤3 months
Severe arterial hypertension (concomitant use of more than 4 different antihypertensive drug classes)
Acute respiratory distress syndrome with need for mechanical ventilation
Patients who at not capable of home blood pressure monitoring
Patients who cannot be switched to an alternative medication

ACEI angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; NYHA New York Heart Association

2. Linear and generalized linear mixed-effects regression models

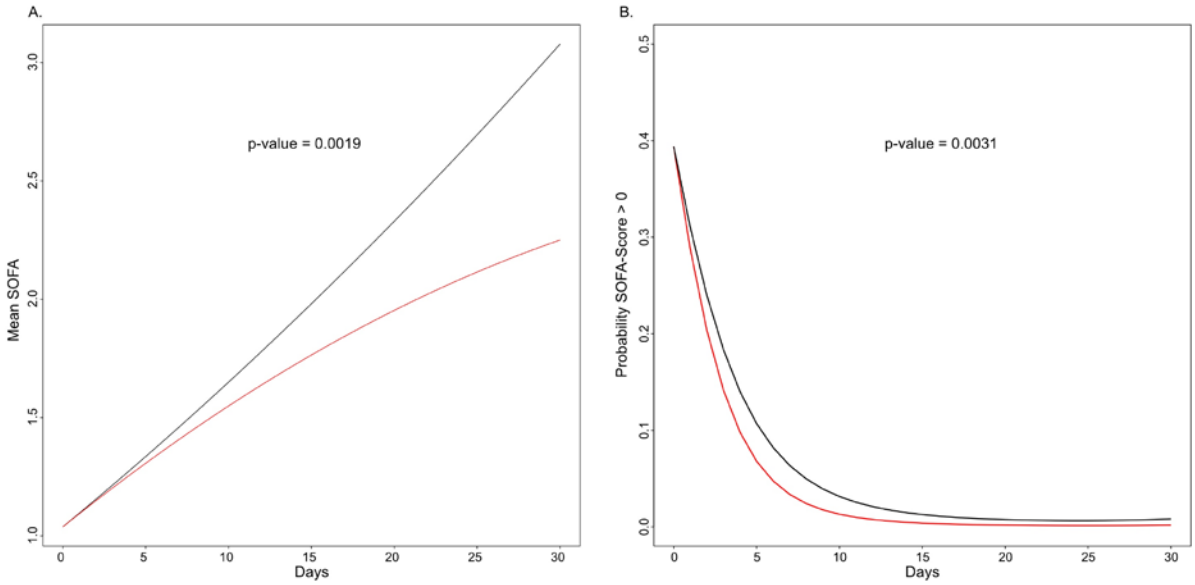

Figure S1 Effect of treatment on the mean SOFA score (A) and over SOFA category (0 vs. 1-24; B) over time using linear and generalized linear mixed-effects regression models (black curves = continuation group; red curve = discontinuation group). Left panel shows the effect on mean death-adjusted SOFA score in both groups, left panel shows the probability of a patient having a death-adjusted SOFA score of 1 or more for both groups.

3. Subgroup analyses

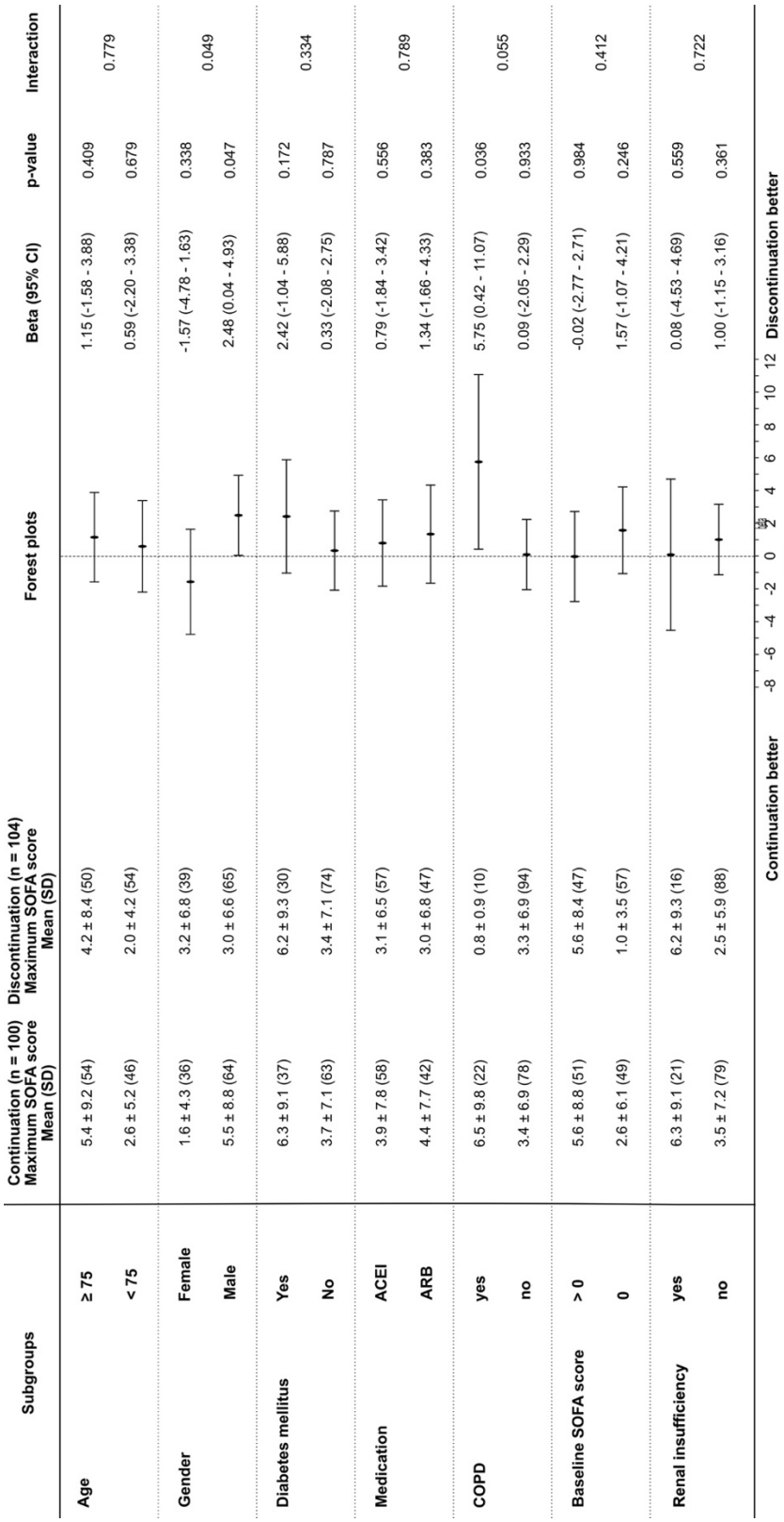

Figure S2

Subgroup analysis for the primary outcome. Plots indicate the linear regression's coefficient and corresponding 95% confidence intervals for predicting the maximum SOFA score.

4. Replacement drugs in the discontinuation group

Table S2: Use of replacement drugs in the discontinuation group (n=104)

Number of patients with replacements*	58 / 104 (55.8%)
Ca-antagonists	52 (89.7%)
Diuretics	4 (6.9%)
Betablockers	2 (3.4%)
Alpha blockers	2 (3.4%)

* in some patients, more than one drug has been used

5. Arterial blood pressures in treatment groups

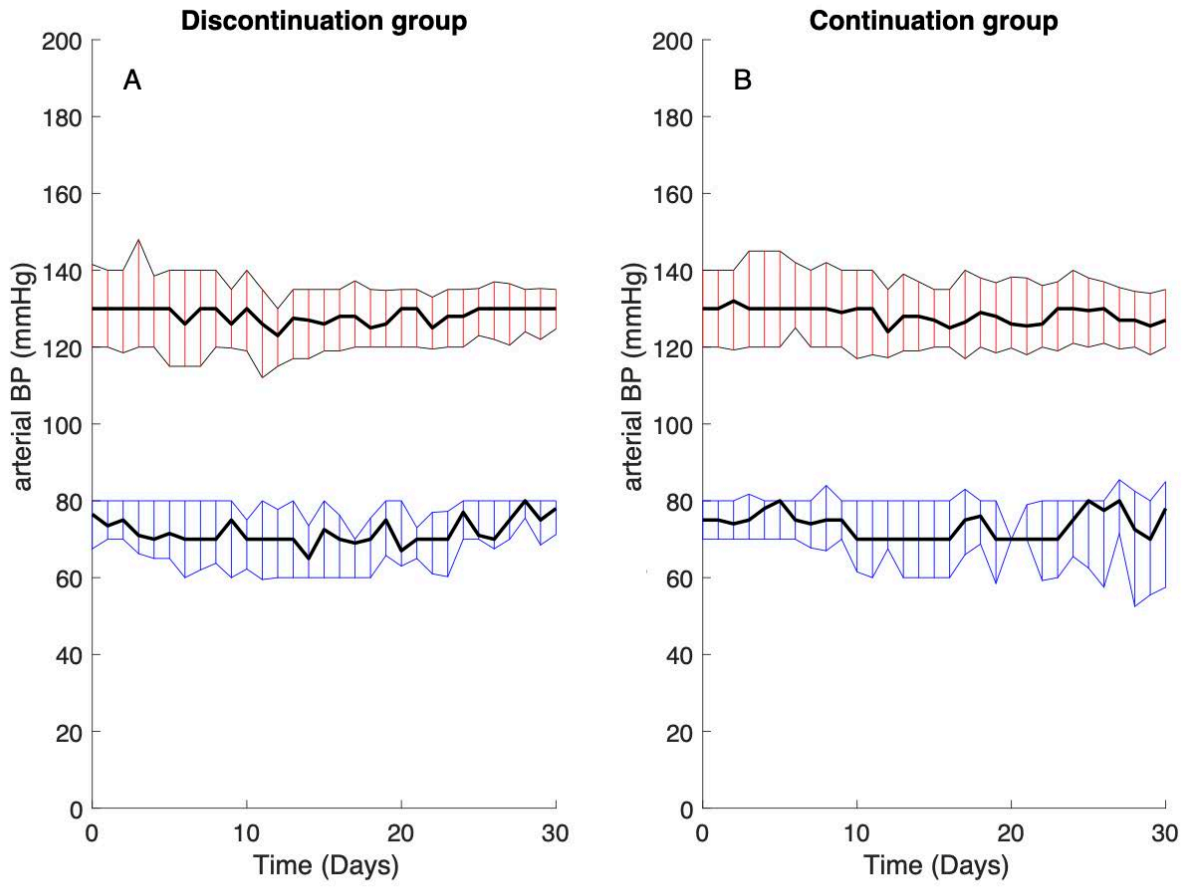

Figure S3 Median (IQR) Systolic (red) and diastolic (blue) arterial blood pressures (BP) in the discontinuation and continuation group, respectively. Time 0 denotes baseline.

6. Adverse events in both treatment groups

Table S3: Adverse events in both treatment groups

	Discontinuation (n=104)	**Continuation (n=100)**
Worsening of respiratory function	26	26
Ischemic events	0	2
Urinary tract infection	3	0
Elevation of creatinine level	0	1
Other	6	4
Ventricular tachycardia	1	0
Hypertension	2	2
hospitalizations due to decompensated heart failure	0	0

7. Primary and secondary analyses using modified SOFA score according to the REPLACE COVID trial

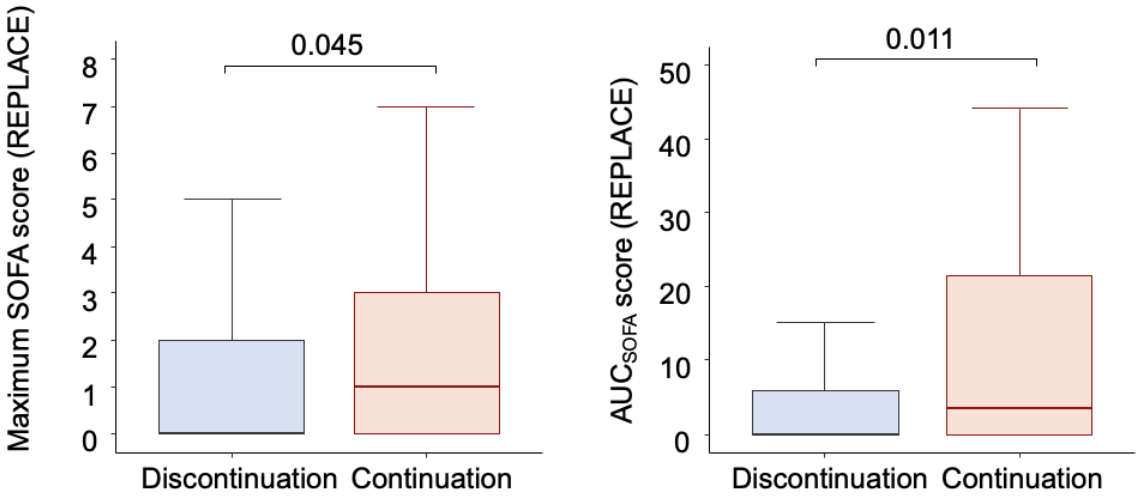

Figure S4 Boxplots of maximum modified SOFA score and area under the modified SOFA score. For calculation of the modified SOFA score Bilirubin and Glasgow coma scale are not considered.

Table S4 Primary, secondary and exploratory endpoints using modified SOFA score

	Discontinuation group (n=104)	**Continuation group (n=100)**	**p-value**
Primary endpoint			
Maximum SOFA score	0.00 (0.00-2.00)	1.00 (0.00-3.00)	0.045
Secondary endpoints			
Area under the SOFA score, days	0.00 (0.00-6.00)	3.50 (0.00-21.39)	0.011
Mean SOFA score	0.00 (0.00-0.20)	0.12 (0.00-0.71)	0.011
Exploratory endpoints			
SOFA score at 30 days*	0.00 (0.00-2.60)*	0 (0.00-16.00)*	0.035
SOFA score ≥1 at 30 days**	11 / 97 (11%)	22 / 94 (23%)	0.027

SOFA score included death and outpatient status as described in methods; ICU intensive care unit, SOFA sequential organ failure assessment score

* median (10^{th} - 90^{th} percentile)

** patients who withdrew consent or were lost to follow-up

*** global rank score as defined in the REPLACE-COVID trial

8. Comparison of study characteristics and outcomes of randomized trials

Table S5: Study characteristics and outcomes of randomized trials testing discontinuation vs. continuation of RAS inhibition in COVID

	BRACE-CORONA n= 659	**REPLACE COVID n=152**	**ACEI COVID n= 204**
Design	Pragmatic, registry-based, randomized	Controlled, randomized	Controlled, randomized
Country	Brazil	USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina	Austria, Germany
Sample size	659	152	204
Time from onset of symptoms to randomization	8 days (median)	7 days (mean)	4 days (median)
Duration of intervention	30 days	Restricted to hospitalization (median 5 days)	30 days
Age (years)	55 (median)	62 (mean)	75 (median)
Race	Not collected	Non-hispanic Black 15% Non-hispanic white 15% Hispanic 54% Other 16%	white
Diabetes	32%	52%	33%
BMI kg/m²	30.2	33.0	27.6
hospitalized/outpatients	100% / 0%	100% / 0%	93% / 7 %
Oxygen supply at baseline	27%*	80%	44%
Admission to ICU	unknown	20%	19%
30-day mortality rate	3%	14%	10%

BMI body mass index; ICU intensive care unit;
*refers to patients with Sp_{O2} <94% of room air at baseline

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Stopping ACE-inhibitors in COVID-19

ACEI-COVID-19

EudraCT 2020-001206-35

Version: 2.6

Date: 06.04.2020

Confidentiality

The information provided in this clinical investigation plan are strictly confidential and will only be available for potential investigators, involved investigators and their study team as well as for the medical director of the conducting hospital, health authorities and ethics committees to review, verify or implement the clinical trial. Any publication or disclosure to a third party without prior written consent of the sponsor is expressly prohibited. By signing the clinical investigation plan, the provisions of this clinical investigation plan are for all parties binding.

General Information

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Title:	Stopping ACE-inhibitors in COVID-19
Short Title:	ACEI-COVID-19
EudraCT-No.:	2020-001206-35
Investigational Medicinal Product:	Medicinal product of the ATC Group C09A, C09B, C09C, C09D.

Declaration of the Sponsor

The present clinical investigation plan (CIP) was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the investigational medicinal product (IMP) as well as with moral, ethical and scientific principles of good clinical practice (GCP), the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements.

With the signature below the person confirms to have read this Clinical Investigation Plan and to agree that it contains all information required for study performance. Furthermore, the person agrees to conduct the study as set in this CIP and to adhere to the sponsor's standard operation procedure (SOPs), if provided and as far as agreed. It has been understood that all documentation previously not published will be kept confidential. Furthermore the person agrees to take all necessary measures to ensure safety and confidentiality of the patient´s identities.

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Short Title:	ACEI-COVID-19
EudraCT-No.:	2020-001206-35
Investigational Medicinal Product:	Medicinal product of the ATC Group C09A, C09B, C09C, C09D.

Declaration of the Author, the Coordinating Principal Investigator and the Statistician

The present CIP was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the IMP as well as with moral, ethical and scientific principles of GCP, the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements. With their signature below the persons confirm to have read this Clinical Investigation Plan and to agree that it contains all information required for study performance. Furthermore, the persons agree to conduct the study as set in this CIP and to adhere to the sponsor's SOPs (as far as agreed and provided). It has been understood that all documentation previously not published will be kept confidential. Furthermore the persons agree to keep patient´s identities in strictest confidence and to take all required measures to ensure this confidentiality.

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Prof. Dr. rer. nat. Ulrich Mansmann Head of Institute for Medical Information Processing, Biometry, and Epidemiology, LMU Munich Statistican	Munich, 06.04.2020 _____ Place, Date, Signature

List of Study Sites

Names and addresses of all trial centres and their investigators are listed in the document "Participating Trial Centres" as amended

Site-specific Signatures

Study Title:	Stopping ACE-inhibitors in COVID-19
Short Title:	ACEI-COVID-19
EudraCT-No.:	2020-001206-35
Investigational Medicinal Product:	Medicinal product of the ATC Group C09A, C09B, C09C, C09D.

The statement(s) of the Principal Investigator and his/her deputy for each participating centre are documented in the centre-specific document.

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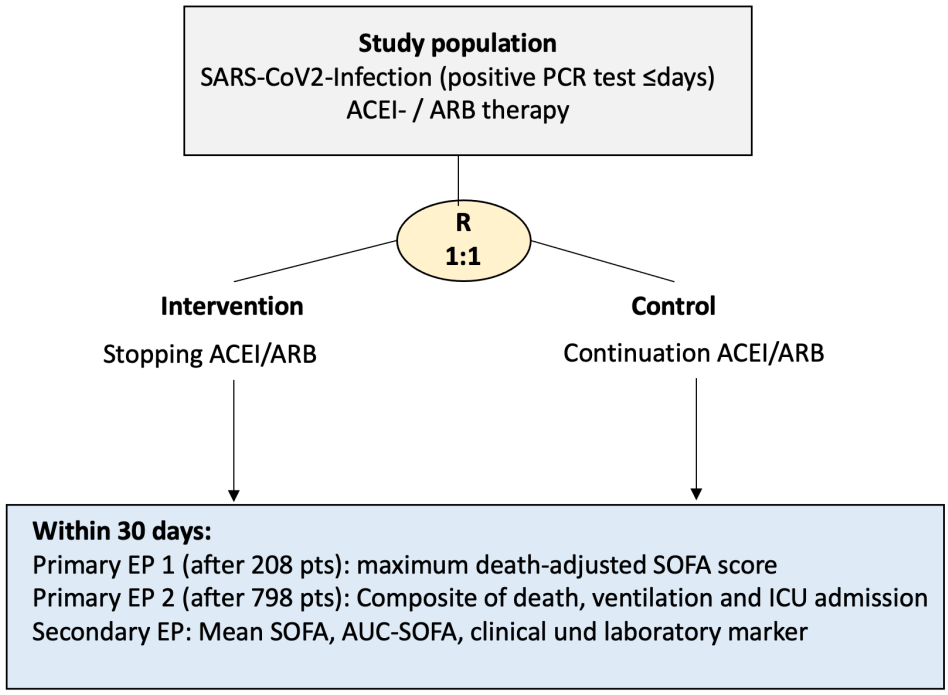
Table of Content

Abbreviations and Definitions

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	Austrian Pharmaceutical Act
CDM	Clinical Data Management
CDMS	Clinical Data Management System
CI	Coordinating Investigator
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
DIBD	Development International Birth Date
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
DVP	Data Validation Plan
eCRF	electronic Case Report Form
EEA	European Economic Area
EC	Ethics Committee
ECG	Electrocardiogram
EU	European Union
EudraCT	European Clinical Trials Database
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator‘s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Medicinal Product Dossier
IMP	Investigational Medicinal Product
IMPD	Independent data monitoring committee
IRB	Institutional Review Board
ISF	Investigator Site File
LPLV	Last Patient Last Visit
LTFU	Lost To Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Principal Coordinating Investigator

pCRF	paperbased Case Report Form
PFS	Progression-Free Survival
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEC	Self-Evident Corrections
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SPC	Supplementary Protection Certificate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

Synopsis

Title of Clinical Trial	Stopping ACE-inhibitors in COVID-19 (ACEI-COVID-19)
Graphical Overview	
Applicant	Univ.-Prof. Dr. Axel Bauer
Clinical Trial Type	multicenter, randomized, unmasked, controlled clinical trial
Objectives	To test the hypothesis that stopping chronic ACEI / ARB therapy in SARS-CoV2-infected patients improves outcome
Intervention	A strategy of stopping/replacing chronic ACEI / ARB therapy
Key inclusion and exclusion criteria	<u>Inclusion criteria:</u> • Female and male patients competent to make a decision • Proven and symptomatic SARS-CoV2 infection ≤ 5 days • Patient age ≥ 18 years • Provided written informed consent

	• Chronic (≥ 1 month) ACEI/ARB therapy for treatment of arterial hypertension, diabetes mellitus, heart failure or coronary artery disease • Stable hemodynamic conditions allowing to stop or continue treatment with ACEI/ARB (systolic blood pressure ≤180mmHg) <u>Exclusion criteria:</u> • Women capable of bearing children as well as pregnant and breastfeeding women • Participant in another interventional trail • At screening visit, no oral medication intake possible • Advanced heart failure NYHA Stage III-IV • Left ventricular ejection fraction <30% or NTproBNP ≥600pg/mL in case of clinical signs of heart failure • Acute coronary syndrome ≤ 3 months • Severe arterial hypertension (concomitant use of more than 4 different antihypertensive drug classes) • Acute respiratory distress syndrome with need for mechanical ventilation • Patients who at not capable of home blood pressure monitoring • Patients who cannot be switched to an alternative medication
Primary and Secondary Endpoints	<u>Co-primary endpoints (will be tested hierarchically after 208 and 798 pts.)</u> - Combination of maximum Sequential Organ Failure Assessment (SOFA) Score and death within 30 days. The minimal value of the SOFA Score will be 0 and the maximal value 24 points. All-cause death is classified as the maximum score (24 points). In case of a subclinical disease progress without need for hospitalization, the SOFA score will be 0. The SOFA score is referred to as “death-adjusted SOFA-Score”. - Composite of admission to an intensive care unit (ICU), the use of mechanical ventilation, or all-cause death. <u>Secondary endpoints:</u> - Maximum SOFA score (not adjusted for death)

	- Mean SOFA Score - Area under the SOFA curve (AUC) - Death - Hospitalization - Admission to ICU - Intubation - Non-invasive ventilation (high-flow, continuous positive airway pressure therapy) - Renal replacement therapy - Change of viral burden (if clinically obtained) - C-reactive protein (CRP), D-Dimer, interleukin 6 (IL-6), high-sensitive cardiac troponin (hsTnT), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), lymphocytes, eosinophil- and thrombocyte count, ferritin, transferrin, lactate dehydrogenase (LDH), procalcitonin, neopterin - Identification of biomarkers (cellular immune state, soluble biomarkers, CHiP, single cell level transcription patterns) - Seroconversion <u>Safety endpoints:</u> - Hypertensive crisis (systolic/diastolic blood pressure > 180/120 mmHg) - Hospitalisation due to cardiac decompensation and causal relationship to stopping of ACEI/ARB therapy.
Sample Size, Statistical Analyses, Power Calculation	Both primary endpoints will be hierarchically tested: To test a significant difference in the primary endpoint (maximum death- adjusted SOFA Score), 208 patients need to be included. If the primary endpoint is met, a total of 798 patients will be enrolled to test the co-primary endpoint (clinical event rate). with $\alpha = 0.05$, power = 0.80 and taking a 20% drop-out rate into account.
Trial duration	Estimated study start: first Patient first Visit (FPFV): Q2/2020 Estimated study end: last Patient last Visit (LPLV): Q2/2021 Study duration for individual patient: ≤ 30 days

Visit Plan

Visit plan for patients in a hospital (A) and domestic (B) setting

A) Patients in hospital setting

	Screening day -3-0	**Baseline visit day 0**	**Control visiten daily (Tag 1 – 29)**	**final visit day 30 ± 2 Tage**
Informed consent	X			
Inclusion- and exclusion criteria	X			
Demographic data		X		
Patient history		X		
Physical examination / vital parameters		X	X	X
Laboratory[1]		X	X	X
Concomitant medication		X		
AEs und SAEs		X	X	X
SOFA & qSOFA Score		X	X	X

[1] Beyond clinical routine, the following biosamples are optionally collected: Baseline: 2x10ml EDTA-Plasma (10ml each), 1x10ml Serum (10ml), 1x Heparin-Plasma (10ml)

Controls day 7, 10, 14 and 30 (+/- 1 day): 1x10ml EDTA-Plasma (10ml each), 1x10ml Serum (10ml), 1x Heparin-Plasma (10ml)

B) Patients in domestic setting

	Screening day -3-0	**Baseline visit day 0**	**Control visits daily (Tag 1 – 29)**	**final visit day 30 ± 2 Tage**
Informed consent	X			
Inclusion- and exclusion criteria	X			
Demographic data	X	X		
Patient history	X	X		
Physical examination / vital parameters		X		
Laboratory[1]		X		
Concomitant medication		X		
AEs und SAEs		X	X	X
Telephone visit			X	X

[1] Beyond clinical routine, the following biosamples are optionally collected: Baseline: 2x10ml EDTA-Plasma (10ml each), 1x10ml Serum (10ml), 1x Heparin-Plasma (10ml)

Note: For patients who are discharged home within the 30 days or who move from the outpatient area to the inpatient area, the respective visit plan can be changed from outpatient to inpatient and vice versa.

1. Introduction

1.1 Study Background

In December 2019 the first pneumonia case of unknown origin in Wuhan, capital city of Hubei province, was reported to the World Health Organization (WHO)[1]. Later on, the pathogen was identified as novel enveloped RNA betacoronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). This virus has phylogenetic similarities to SARS-CoV, which caused an epidemic in 2002- 2003.[2]

In the meantime, the lung disease caused by SARS-CoV2 has spread from Wuhan throughout China and the world.[3] The WHO declared coronavirus disease in 2019 (COVID-19) a public health emergency of international concern. On 11 March 2020, the COVID-19 outbreak was classified as a pandemic. Due to its rapid spread, COVID-19 became one of the greatest challenges for the health, social and economic systems of the century. WHO predicts that the number of cases and deaths will continue to rise rapidly in the coming weeks and months.

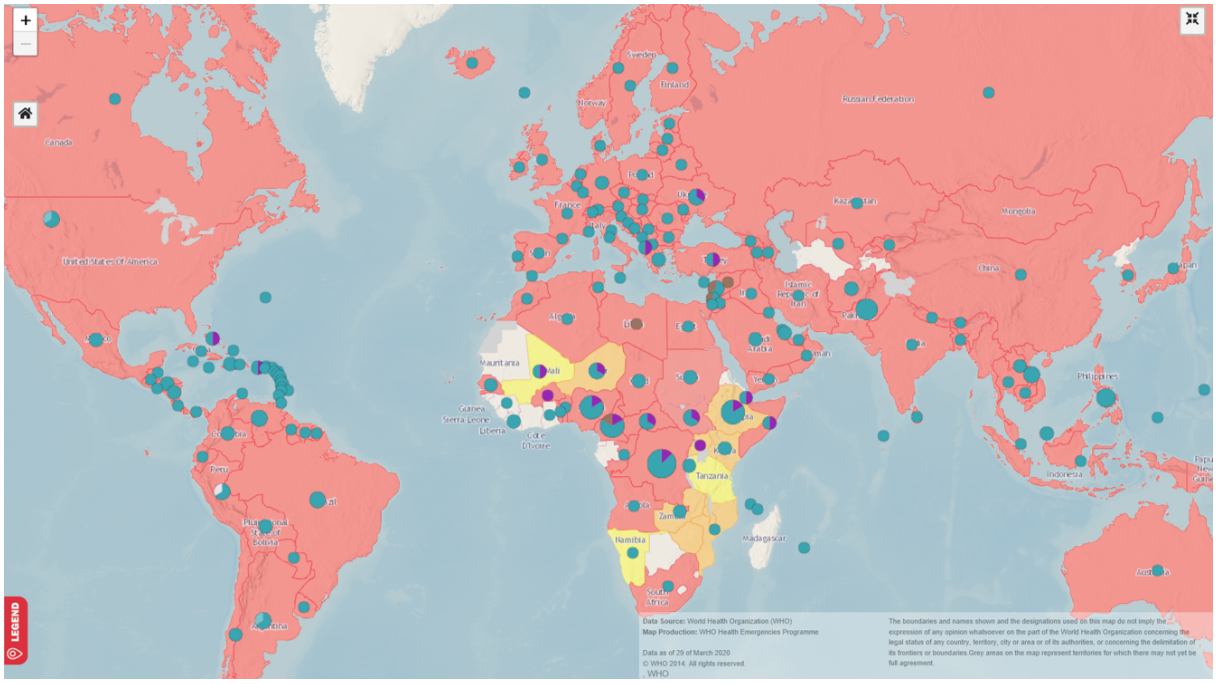


Figure 1: Global spread of COVID-19 and affected countries (source: who.int, 29 March 2020)

As of March 29, 2020, there were 616,742 patients in 203 different countries infected with SARS-CoV2 and the disease caused nearly 30,000 deaths. COVID-19 is also spreading rapidly in Europe. Italy is currently the country most affected by the disease, with 92,472 confirmed cases and 10,023 deaths. (Source: European Centre for Disease Prevention and Control). In Austria and Germany, too, infection rates are rising rapidly from day to day. On 29 March, there were 52,547 COVID-19 positive patients in

Germany, which is 3,965 more cases than the day before. In Austria there are even 8,291 cases and 68 patients died.

Currently, the estimated case fatality rates of COVID-19 are 0.3%- 1.0% as announce by the WHO. However, there are several factors, which can affect case fatality rates. In China, patients in their seventh decade of life with proven SARS-CoV-2 had a mortality rate of 8%, whereas in patients over 80 years the case fatality was 14.8%.[1] For accurate estimation of case fatality rates, also the COVID-19 outbreak on the Diamond Princess cruise ship provides robust data, given the defined population and territory. Case fatality rate was 0.99% with a clear trend for age. But not only age, also other comorbidities such as coronary artery disease, arterial hypertension and diabetes mellitus can markedly increase mortality rates.[4]

Recent studies showed that SARS-CoV2 enters human cells via the angiotensin converting enzyme II receptor 2 (ACE2) following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2) (Figure 2).[5,6]

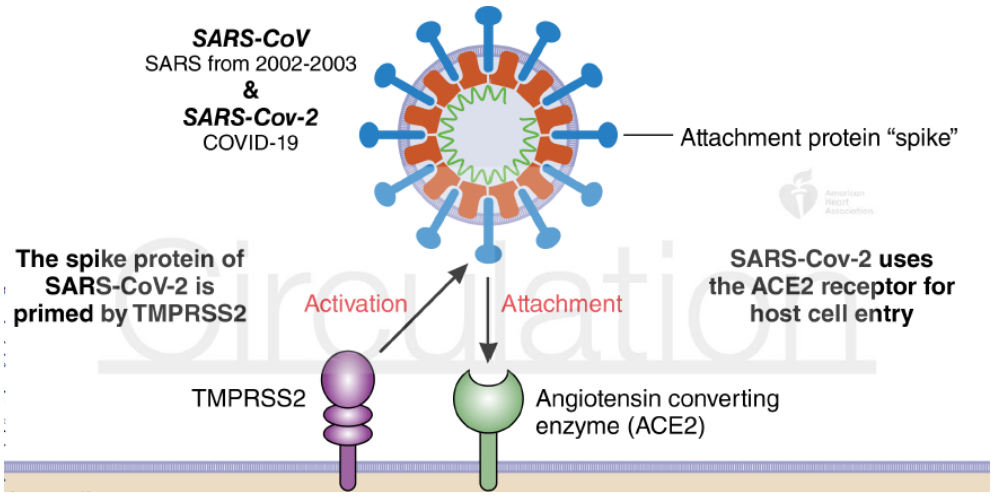


Figure 2*: Entry of SARS-CoV-2 into cell via angiotensin converting enzyme II receptor 2 (ACE2) and activation of the spike protein by transmembrane protease serine 2 (TMPRSS2) (adapted from* [4]*)*

As ACE2 is expressed in pulmonary Type II alveolar cells, it appears to be the predominant entry mechanism.[7] In addition to lung, ACE2 is highly expressed in the myocardial tissue as well, and acts as counterpart to angiotensin II in states with over-activation of the renin-angiotensin system (RAS) such as arterial hypertension, congestive heart failure and coronary artery disease. ACE2 is also expressed in other tissues like the intestinal and vascular epithelium as well as the kidneys, explaining a potential mechanism for multi-organ dysfunction in patients with SARS-CoV-2 infection. Experimental studies showed that pharmacological antagonist of the RAS such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) could increase the expression of ACE2 up to five times.[8] Accordingly, in patients treated with ACEI or ARB, virus uptake could be facilitated, thereby accelerating its spread in the body.

There are currently no clinical studies that have investigated the effects of RAAS blockade by ACEI or ARB. In the COVID-19 cohort studies published to date, however, a high prevalence of co-morbidities such as arterial hypertension, heart failure and diabetic nephropathy, which are commonly treated with RAAS blockade, was found in patients with severe disease (Table 1). Accordingly, there is great uncertainty among patients and physicians regarding RAAS blockade in the context with SARS-CoV2 infection. Due to the lack of data, national and international professional societies currently recommend continuing ACEI or ARB therapy until clinical data are available.[9] Nevertheless, there is an urgent clinical need for evaluating the potential effects of chronic ACEI/ARB therapy in COVID-19.

Table 1: Prevalences of comorbidities in severe cases of COVID-19

	Prevalences of comorbidities in severe COVID-19 cases	**Number of severe COVID-19 cases / total population**
Guan et al., NEJM 2020[10]	Arterial hypertension 23.7% Diabetes mellitus 16.2% Coronary artery disease 5.8%	173 / 1099 patients
Zhou et al., Lancet 2020[11]	Arterial hypertension 48% Diabetes mellitus 31%	57 diseased patients / 191 patients
Yang et al., Lancet Respir 2020[12]	Diabetes mellitus 22%	32 / 52 ICU-patients
Zhang et al., Allergy 2020[13]	Arterial hypertension 30% Diabetes mellitus 12%	140 patients
Bhatraju et al., NEJM 2020[14]	Diabetes mellitus 58%	24 ICU-patients in Seattle

1.2 Need of the Study

The COVID-19 pandemic is currently posing challenges of unprecedented proportions for the health systems of all countries. The disease is based on an infection with the new coronavirus SARS-CoV2. According to the WHO, the case lethality rate is currently 0.3-1.0%, with older patients with comorbidities such as high blood pressure, diabetes mellitus and cardiovascular diseases showing significantly higher mortality. Current studies show that the SARS-CoV2 virus enters human cells via the angiotensin converting enzyme II (ACE2) receptor 2 2-5 Experimental studies show that ACE inhibitors (ACEI) and

angiotensin receptor blockers (ARB) can increase the expression of ACE2 up to fivefold[15]. Accordingly, in patients treated with ACEI or ARB, virus uptake could be facilitated, thereby accelerating its spread in the body[16].

There are currently no clinical studies that have investigated the effects of RAAS blockade by ACEI or ARB. In COVID-19 cohort studies published to date, however, a high prevalence of co-morbidities such as arterial hypertension, heart failure and diabetic nephropathy treated with RAAS blockade was found in patients with severe disease (see table). Accordingly, there is great uncertainty among the population and the medical profession regarding RAAS blockade in connection with SARS-CoV2 infection (see also 1.3). Due to the lack of data, national and international professional societies currently recommend continuing ACEI or ARB therapy until clinical data are available[17].

In this study, we are therefore testing the hypothesis that discontinuation of chronic ACEI or ARB therapy in patients with proven SARS-CoV2 infection can have a beneficial effect on the course of COVID-19. Patients with proven SARS-CoV2 infection are randomized 1:1 to discontinuation of ACEI or ARB or to continuation of the existing ACEI or ARB. The primary endpoint is the maximum death- adjusted SOFA score that includes death (corresponding to a SOFA score of 24). In addition, the combination of admission to ICU, intubation and death is hierarchically tested as another primary endpoint.

1.3 Risk-Benefit Analysis

ACE2 has been identified as the central receptor for the uptake and spread of the new Sars-CoV-2 coronavirus in humans. Experimental and clinical data show that therapy with ACE inhibitors and angiotensin receptor blockers leads to an increased expression of ACE2 [15]. Cardiovascular diseases typically treated with ACEI or ARB are associated with a worse prognosis of COVID-19[18]. Based on these observations a controversial discussion has arisen: For example, it is speculated that treatment with the RAAS inhibitors ACEI or ARB has an unfavorable effect on the virulence of sars-cov-2 and thus on the course of COVID-19[19]. In fact, a study from China reports a mortality rate of 36.8% in patients treated with ACEI/ARBs compared to 25.6% in patients without RAAS inhibition. These observations, together with theoretical mechanistic considerations, led to the hypothesis that COVID-19 patients benefit from discontinuation of existing RAAS inhibitor therapy. However, this hypothesis is not uncontroversial. For example, a British group saw no difference in the rate of severe COVID-19 progression in patients undergoing ACEI therapy (https://www.researchgate.net/publication/340261837). Based on animal data, it has also been speculated that RAAS inhibition may have protective effects in COVID-19 patients, but this theory has not been supported by clinical data. In addition, discontinuation of RAAS inhibitors may lead to an increase in blood pressure or worsening of pre-existing heart failure. However, the latter two risks can be minimized by adjusting the therapy by (a) increasing the dose of other antihypertensive drugs already taken by the patients that do not belong to the ATC groups C09A, C09B, C09C, C09D and/or (b) by extending the existing therapy with drugs that do not belong to the mentioned ATC groups.

In any case, the controversial role of ACEI and ARBs in COVID-19 patients has led to great uncertainty even among experts: while some recognised groups strongly advocate discontinuing RAAS in COVID-19 patients 7[20], others recommend continuing a pre-existing RAAS inhibition also in COVID-19 24. In a review recently published in the New England Journal of Medicine, the authors conclude that there is insufficient data to make a clear recommendation in one direction or another[9]. Against the background of the widespread use of ACEI and ARBs worldwide and the increased mortality of COVID-19 patients with cardiovascular diseases, a scientific clarification of this question is urgently needed. Due to the enormous extent and dynamics of the COVID-19 pandemic, it is of paramount importance to answer the question as quickly as possible.

The risk of discontinuation or conversion of an ACEI or ARB depends on the underlying indication:

In patients with arterial hypertension, a change of therapy in a controlled study with close clinical follow-up is negligible, especially since patients with unstable circulatory conditions (RR >180mmHg) and patients with severe arterial hypertension (>4 antihypertensive drugs) are excluded. For the treatment of arterial hypertension we have numerous alternative preparations available today. In the large randomized SPRINT study on blood pressure control, it was accordingly shown that the actually achieved target values are decisive for the prognosis of blood pressure and not the substance class used.

In patients with heart failure and myocardial infarction, RAAS inhibitors also have prognostic significance as a substance class. For this reason, patients with severe heart failure (NYHA III, IV) or recent myocardial infarction (≤ 3 months) are excluded. In addition, the interruption of RAAS blockade is only temporary. Large randomized studies have clearly demonstrated a homogeneous long-term effect. A short-term interruption therefore seems justifiable. Short-term interruptions of the RAAS blockade, e.g. during in-patient stays, are already regularly carried out today without an increase in cardiac decompensation being observed under close clinical control.

In summary, the temporary discontinuation of an ACEI / ARB or the changeover to an alternative substance group represents a comparatively low risk. The potential benefit of discontinuation of the RAAS blockade in terms of morbidity and mortality of SARS-CoV2 infection, which can be expected on the basis of mechanistic considerations and the epidemiological observations described above, therefore clearly outweighs the risk of a temporary withdrawal. If the result of the study is positive, this would have an immediate and significant impact on the treatment of patients who have the highest mortality risk after SARS-CoV2 infection.

The theoretical benefit of discontinuing RAAS inhibition in COVID-19 is realized if the pause within a few days leads to a normalization of ACE2 expression. Studies in rats have shown that the RAAS-induced upregulation of ACE2 expression returns to the level of untreated animals when RAAS inhibitors are discontinued. Although the kinetics of this process have not yet been studied in detail, various findings suggest that ACE2 adaptation occurs very rapidly after discontinuation of ACEI or ARBs. RAAS inhibitors lead to a reduced activation of the AT1 receptor and thus to a de-inhibition with consecutive upregulation of ACE2 expression. After discontinuation of ACEI and ARBs, the activation of the AT1 receptor increases very rapidly. Accordingly, the antihypertensive effect of RAAS inhibitors stops within

a few hours when they are paused. It can therefore be assumed that the angiotensin-II-induced suppression of ACE2 synthesis is restored a few hours after stopping RAAS inhibitors. The half-life of ACE2 in the cell membrane has not been investigated. However, a high turnover has been described for most of the receptors and enzymes involved in blood pressure regulation. In the case of COVID-19, the turnover of ACE-2 is additionally increased, since ACE-2 is internalized together with the SARS-CoV-2 virus during virus uptake. Overall, it can therefore be assumed that the adaptation of ACE2 expression occurring after discontinuation of RAAS inhibitors is reflected in COVID-19.

2. Study Objectives

Patients with coronary heart disease, arterial hypertension, chronic kidney disease or diabetes are often treated with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Treatment with ACEI and ARB may be of great relevance to the course of COVID-19: Similar to SARS-CoV (epidemic 2002-2003), the novel SARS-CoV 2 is absorbed into human cells via angiotensin converting enzymes 2 (ACE2). Treatment with ACEI and ARB leads to a significant upregulation of the SARS-CoV 2 receptor ACE2. Increased expression of ACE2, in turn, correlates with increased uptake of SARS-CoV 2 and possibly promotes a more rapid spread of the virus in the organism of infected patients. In the context of the current pandemic, discontinuation of ACEI or ARB therapy (or switch to alternative antihypertensives) may therefore be appropriate in patients treated with ACEI or ARB.

The aim of this study is to test the hypothesis that discontinuation of chronic ACEI or ARB therapy in patients with proven SARS-CoV2 infection may have a beneficial effect on the course of COVID-19.

2.1 Primary Study Objective

The primary objective of the study is to test whether discontinuation of chronic ACEI or ARB therapy in patients with proven SARS-CoV2 infection leads to a more favourable course of COVID-19 than passing on the therapy.

2.2 Secondary Study Objectives

Secondary, the effect of discontinuation on clinical, virological and laboratory parameters of SARS-CoV2 therapy is investigated.

3. Study Design

3.1 Study Description

It is a multicenter, randomized, open clinical trial.

3.2 Endpoints

3.2.1 Primary Endpoint

Co-primary endpoints (will be tested hierarchically)

- Combination of maximum Sequential Organ Failure Assessment (SOFA) Score and death within 30 days. The minimal value of the SOFA Score will be 0 and the maximal value 24 points (see Figure 3). In case of death, the maximum score (24 points) will be applied. In case of a subclinical disease progress without need for hospitalization, the SOFA score is defined as zero. This definition is referred to as "maximum death- adjusted SOFA-Score".
- Composite of admission to an intensive care unit (ICU), the use of mechanical ventilation, or all-cause death

3.2.2 Secondary Endpoints

Secondary endpoints:

- Maximum SOFA score (not adjusted for death)
- mean SOFA Score
- Area under the SOFA curve (AUC)
- Death
- Hospitalization
- Admission to ICU
- Intubation
- Non-invasive ventilation (high-flow, continuous positive airway pressure therapy)
- Renal replacement therapy
- Quality of life (EQ-5D-3L)
- Change of viral burden (if clinically obtained)
- C-reactive protein (CRP), D-Dimer, interleukin 6 (IL-6), high-sensitive cardiac troponin (hsTnT), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), lymphocytes, eosinophil- and thrombocyte count, ferritin, transferrin, lactate dehydrogenase (LDH), procalcitonin, neopterin
- Identification of biomarkers (cellular immune state, soluble biomarkers, CHiP, single cell level transcription patterns)
- Seroconversion

3.2.3 Safety Endpoints

- Severe hypertension (systolic/diastolic blood pressure > 180/120 mmHg)

- Hospitalisation due to cardiac decompensation

Table 1. The Sequential Organ Failure Assessment (SOFA) Score*

Variables	SOFA Score 0	1	2	3	4
Respiratory Pao_2/Fio_2, mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets $\times 10^3/\mu L$‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d‖	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
‖To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

Table The Sequential Organ Failure Assessment (SOFA) Score

3.3 Timetable

Planned start first Patient first Visit (FPFV): Q2/2020

Planned end of clinical trial last Patient last Visit (LPLV): Q2/2021

Duration of participation for one patient: ≤ 30 days

Due to the unknown dynamics of the COVID-19 pandemic, it is currently not possible to define a precise timetable.

4. Study Population

Patients with proven SARS-CoV2 infection who are already taking an ATC C09A, C09B, C09C, C09D preparation to treat an underlying disease will be randomized into one of the two groups after agreement to participate in the clinical trial.

4.1 Number of Patients

Number of patients included:

Minimum: n=208 (testing of primary endpoint 1)

Maximum: n=798 (testing of primary endpoint 2)

4.2 Inclusion Criteria

- Female and male patients competent to make a decision
- Proven and symptomatic SARS-CoV2 infection ≤ 5 days
- Patient age ≥ 18 years

- Provided written informed consent
- Chronic (≥ 1 month) ACEI/ARB therapy for treatment of arterial hypertension, diabetes mellitus, heart failure or coronary artery disease
- Stable hemodynamic conditions allowing to stop or continue treatment with ACEI/ARB (systolic blood pressure ≤180mmHg)

4.3 Exclusion Criteria

- Women capable of bearing children as well as pregnant and breastfeeding women
- Participant in another interventional trail
- At screening visit, no oral medication intake possible
- Advanced heart failure NYHA Stage III-IV
- Left ventricular ejection fraction <30% or NTproBNP ≥600pg/mL in case of clinical signs of heart failure
- Acute coronary syndrome ≤ 3 months
- Severe arterial hypertension (concomitant use of more than 4 different antihypertensive drug classes)
- Acute respiratory distress syndrome with need for mechanical ventilation
- Patients who at not capable of home blood pressure monitoring
- Patients who cannot be switched to an alternative medication

4.4 Withdrawal of study subjects after study start

Reasons for removal investigational treatment or observation include:

- Withdrawal of consent
- Administrative decision by the investigator
- Pregnancy
- Significant protocol deviation
- Subject noncompliance
- Adverse event
- Other safety concern of the investigator or sponsor
- Death
- Lost to follow-up

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.
Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject

data up to withdrawal of consent will be included in the subject's study data, but no further information will be collected unless a separate consent has been given.
Withdrawal of partial consent means that the subject does not wish to take protocol-specific product(s) any longer but is still willing to collaborate in providing further data by continuing on study.
Should a subject request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the end of withdrawal.
For any patient who has received IMP and withdrew prematurely from the study every effort should be made for attendance of a safety follow-up visit. The primary reason for withdrawal from the study should be documented. Patients will not be followed for any reason after consent has been withdrawn, unless a separate consent has been given for further data collection.
The investigator has the right to discontinue a patient from IMP or withdraw a patient from the study at any time.

The following study-specific clinical termination criteria are defined:
- Recurrent measurements of arterial systolic blood pressure >180mmHg, which cannot be lowered by adjusting medication
- Hypertensive emergency (hypertensive crisis (systolic blood pressure >180mmHg) with signs of organ damage)
- Decompensated heart failure (cardiac weight gain >3kg, doubling of NTproBNP in non-intensive patients*)

* ACEI / ARB are usually discontinued in patients requiring intensive care. An increase in NTproBNP usually reflects the critical condition of the patient in the context of COVID19-related organ failure

5. Study Procedures

5.1 General Study Procedures and Assessments Schedule

It is the responsibility of the investigator, or a person delegated by the investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The investigator or designee will explain the patients that they are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.
No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.
A copy of the signed informed consent form will be given to the participant. The original signed and dated form will be retained at the study site and a copy placed in the medical notes.
If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

5.2 Screening Visit (Day –3 to 0)

The screening tests can be performed for a maximum of three days before the patients are included in the clinical trial. Only patients who meet all the inclusion criteria and none of the exclusion criteria will be included.

The following information must be entered:
- Age
- Gender
- Existing therapy with a drug of the ATC groups C09A, C09B, C09C, C09D
- Proven SARS-CoV2 infection (when was a swab taken, when was the infection confirmed)

Some patients with suspected COVID-19 are released to their home environment after testing, even before the test result is received. For these patients, conditional consent can be obtained during the initial interview in case of a positive test result for participation in the study. In this case (proven SARS-CoV2 infection) the patients are contacted by the study physician by phone as soon as the test result is available and informed about the study inclusion. The study physician then discusses the further procedure with the patient regarding the study.

5.3 Visit 1 (Baseline - Day 0)

All patients who meet the inclusion and exclusion criteria are randomized 1:1 into two groups:

Group 1 (intervention): discontinuation of ACEI or ARB.
If necessary, a switch to another drug without direct effect on the RAAS system may be necessary. The decision is up to the treating physician, it must be made individually and must include the following aspects:
- Indication for chronic RAAS blockade: In case of arterial hypertension, a switch to a Ca-antagonist (e.g. amlodipine) should be considered. Patients with heart failure and normotension usually do not receive replacement therapy.
- Companion medication: The extent to which discontinuation of the investigational product can be compensated by increasing the dose of a previously prescribed product should be investigated.

Group 2 (control): no intervention, i.e., further treatment with ACEI or ARB. If discontinuation of ACEI / ARB is necessary for medical reasons (e.g., hypotension in early sepsis), this is done independently of the study.

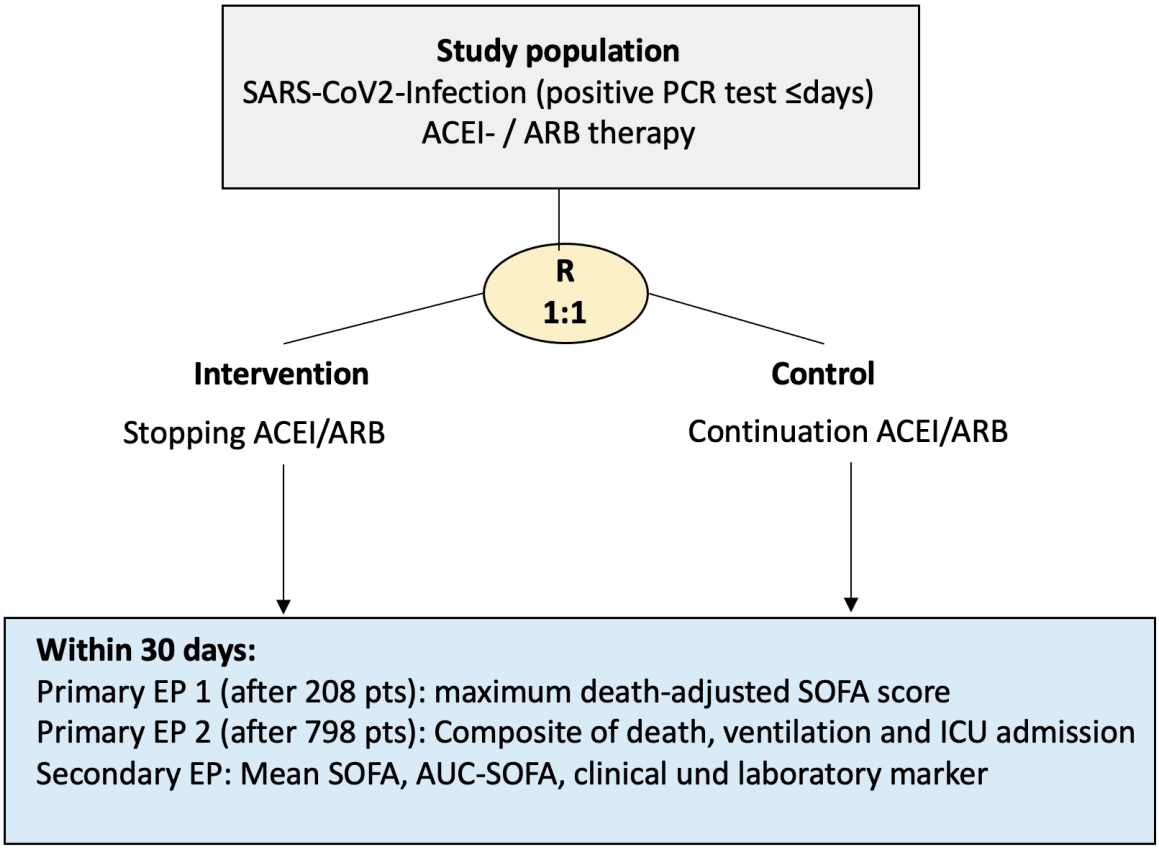


Figure Flow chart of the proposed project

The following parameters are to be recorded baseline:

- Information about other drug prescriptions

- Pre-existing conditions
o Diabetes mellitus
o Coronary heart disease
o Heart failure, if known left ventricular pump function
o Renal insufficiency
o Stroke
o Malignant disease
o Chronic obstructive pulmonary disease

- Cardiovascular risk factors
o Arterial hypertension
o Hypercholesterolemia
o Nicotine abuse
o Family disposition

- Physiological parameters
o Respiratory rate (/min)
o Heart rate (beats/min)
o Arterial blood pressure (systolic, diastolic, (mmHg))
o Oxygen saturation (SpO2) (%)
o Oxygen demand (l/min)
o Body temperature (°C)

- Symptoms
o Coughing
o Sputum
o Fever
o Dyspnoea
o Myalgia
o Fatigue
o Diarrhoea
o Nausea / vomiting

- Laboratory parameters (determined as part of the routine)
o Infectiological parameters
o Liver function parameters and coagulation diagnostics
o Renal function parameters
o Cardiac enzymes
o Blood count and differential blood count
o Thyroid parameters
o Immunoglobulins
o Iron status and metabolism
- Baseline SOFA Score and Quick SOFA (qSOFA) Score (resulting from the above parameters, see tables 1 and 2)
- In addition to routine laboratory control, optional collection of EDTA (2x10ml), serum (1x10ml) and heparin blood (1x10ml) for biomarker analysis
- Virus load COVID-19 (determined by respiratory or serum PCR) as part of routine
- Imaging (X-ray, computed tomography, magnetic resonance imaging, echocardiography) if routinely determined

5.4 Control Visits (Day 1 - 29)

1. Patients in hospital setting

Daily survey of
- SOFA (includes blood pressure)
- qSOFA
- In addition to routine laboratory control, optional collection of EDTA (1x10ml), serum (1x10ml) and heparin blood (1x10ml) for biomarker analysis
- Survey of accompanying medication and, if necessary, intensive care measures
- Virus load COVID 19 (determined by respiratory PCR) as part of routine
- Imaging (X-ray, computed tomography, magnetic resonance imaging, echocardiography) if routinely determined

2. Patients in ambulatory/home setting
Daily survey of
- Fever status, respiratory distress,
- clinical events: hospitalization or mortality
- Quality of life (EQ-5D-3L questionnaire)
- arterial blood pressure (if not available, patients are provided with a blood pressure monitor). Patients are instructed to carry out a self-measurement of their blood pressure 3 times a day.
- Body weight
- Symptoms that could indicate a hypertensive derailment (headache, nausea, double vision)

Patients who are suspected or diagnosed with a hypertensive derailment are visited by telephone or in person to adjust their treatment, through home visit or hospital presentation. If necessary, patients are provided with a blood pressure monitor at home for daily blood pressure monitoring.

A combination of outpatient and inpatient care is also possible. We assume that about 50% of patients are treated as outpatients and 50% as inpatients.

5.5 End of Treatment (Day 30)

The observation period ends on day 30 after randomisation. The final visit is carried out according to the same scheme.
During the final visit, the study physician discusses the further procedure with regard to ACE inhibitor/ARB therapy in person or during a telephone visit (for outpatients). Patients who have been discontinued for study reasons will be re-started with the investigational product after individual review of any contraindications.

5.6 Discontinuation of the Study/Premature Termination of the Trial

The trial subject can withdraw from the trial at any time, without giving reasons, and without incurring any disadvantages for further medical care.

It is up to the investigator (or, if applicable, the sponsor of this trial) to decide whether the subject's participation in the trial should be terminated prematurely. The reasons for this may be:
- The subject does not meet the requirements of the trial;
- the investigator feels that continued participation in the trial is not in the interests of the subject.
- Arterial blood pressure deterioration that cannot be controlled by adjusting drug therapy and therefore requires RAAS blockade.

5.7 Unscheduled Visits

Unscheduled visits will be documented.

5.8 Further treatment after end of treatment

After participation in the study is terminated, the treating physician decides on the further therapy. In the intervention group, the aim is to restart the previous treatment with a drug of the ATC groups C09A, C09B, C09C, C09D.

5.9 Closure of trial centres/premature termination of the clinical trial

The sponsor is entitled at any time to prematurely close a trial site that is participating in the clinical trial. The reasons may include the following:
- patient recruitment is unsatisfactory
- administrative reasons

The sponsor must inform the investigator if it has been decided to terminate the participation of a trial site.

The sponsor is entitled to terminate the trial prematurely at any time. This may be due to medical or ethical concerns, or if the trial cannot be conducted properly. The reasons for termination will be documented in detail.

All patients under treatment at the time of termination must undergo a final examination. The coordinating investigator must be informed without delay of any ethical concerns of the sponsor regarding the continuation of the trial.

Early termination of a trial is considered under the following conditions:
- the benefit-risk analysis has changed significantly for the worse for the patient

- further treatment in the control group or intervention group is ethically unacceptable
- interim results or analyses of other clinical trials show that the treatments in the clinical trial are superior or inferior to another
- the clinical trial can no longer be conducted in a meaningful way

If no significant difference between the two treatment groups is observed after evaluation of the data from the first 208 study participants, the clinical trial will be terminated prematurely. If the evaluation after 208 patients shows a trend for the superiority of one group with respect to the primary endpoint 1 ($p<0.1$), the group size may be increased in accordance with the Steering Committee and statistical advice.

The sponsor makes the decision regarding termination/continuation of the trial in consultation with the steering committee and statisticians.

If a trial is terminated prematurely, the ethics committee(s) and regulatory authority(ies) must be informed of the termination within 15 days.

5.10 Closure of the Study

The clinical trial ends when the last patient has completed the planned last visit according to protocol. The completion of the study will be reported to the ethics committee as well as to the relevant authorities.

6. Study Medication (IMP)

6.1 Name and Description of Investigational Medicinal Product (IMP)

Drugs of ATC group C09A, C09B, C09C, C09D, which act on the renin- angiotensin-aldosterone system, are being investigated. The drugs are listed in Table 2 of the Annex.

6.2 Name and Description of Placebo/Comparable Product

No comparative drugs or placebo are used.

6.3 Dosage and Administration

The dosage and treatment in the control group is carried out according to the recommendations given in the approval conditions of the respective drug.

6.4 Dose Modifications

Any change in the dose in the control group is at the discretion of the supervising physician according to the recommendations given in the approval conditions of the respective drug.

6.5 Concomitant Medication

The administration of concomitant medication is carried out according to the recommendations given in the approval conditions of the respective preparation. In the intervention group, in addition to the discontinuation of the drugs of ATC C09A, C09B, C09C, C09D without replacement, it is also possible to switch to an alternative substance group that does not affect the renin-angiotensin-aldosterone system. Whether and to which alternative substance without direct effect on the renin-angiotensin-aldosterone system is converted is at the discretion of the attending physician. Each conversion is carried out according to the recommendations given in the approval conditions of the respective alternative preparation.

6.6 Labelling

Since only approved drugs - even before inclusion in the clinical trial - are administered to patients in the control group according to the recommendations given in the approval conditions of the respective preparation, no corresponding labelling is necessary.

6.7 Handling of IMP at the Site and Drug Accountability

Since only approved drugs are administered to the patients in the control group according to the recommendations given in the approval conditions of the respective drug, it is not necessary to manufacture specialty drugs especially for this clinical trial. The dosage of the administered drug in the control group is recorded without interruption for each patient.

7. Adverse Events

7.1 Summary of known and possible Adverse Events of the IMP

Patients are already pretreated with the investigational medicinal products. Side effects of the different investigational medicinal products can be found in the respective expert information. In the study, discontinuation of the investigational products is investigated so that no investigational product-specific side effects can occur.

Withdrawal of the investigational product may increase blood pressure and possibly aggravate pre-existing heart failure. It is the responsibility of the investigator or treating physician to begin an alternative therapy.

7.2 Adverse Events

An Adverse Event (AE) is any adverse medical event occurring in a subject, user, or other person, any unintended illness or injury, or any adverse clinical diagnosis (including abnormal laboratory findings), whether or not associated with the Investigational Product. Because the trial is investigating only discontinuation of the investigational product, no investigational product-specific adverse events can occur. Therefore, only adverse events of special interest (AESI) or SAEs with a causal relationship to discontinuation of the investigational product are reported.

7.3 Serious Adverse Events

If a serious adverse event (SAE) occurs, the investigator must alert the sponsor without unjustified delay to any AE (whether causally or not) from this study that results in one of the following outcomes, or is significant for any other reason:

- death (excluding death from progressive disease)
- a life-threatening experience – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- initial hospitalization, or prolongation of existing inpatients' hospitalization
- persistent or significant disability or incapacity
- congenital anomaly or birth defect

Medical judgment should be exercised in deciding whether an AE/adverse drug reaction (ADR) is serious in other situations. Important AE/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeoparadize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Patients should be closely observed for adverse events while receiving treatment with the IMP. Further on for 12 weeks after discontinuation from study therapy in order to detect delayed toxicity. After this period, the clinical trial medical safety desk will only be alerted to serious adverse events if the investigator believes that the event may have been caused by the investigational device or by a protocol procedure.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Disease progression will not be reported as AE or SAE unless the progression is unexpected in severity or early occurrence. Progressive disease will be appropriately documented on the case report form as part of the efficacy parameters.

7.4 Adverse Drug Reaction (ADR) & Unexpected Adverse Drug Reaction

In the study, discontinuation of the investigational medicinal products is investigated. Preparations of the investigated substance classes are used to treat arterial hypertension and heart failure. Accordingly, discontinuation could lead to arterial hypertension and cardiac decompensation. These events are investigated as safety endpoints.

A resumption of therapy with the respective IMP is carried out according to the investigator's instructions and in accordance with the relevant specialist information published on the BASG homepage (https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx?_afrLoop=251816249017884&_afrWindowMode=0&_adf.ctrl-state=3pmhz6ukm_4).

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7.5 Grading of Severity of Adverse Events

Intensity of all adverse events will be graded according to the NCI common terminology criteria for adverse events (CTCAE), version 5 on a five-point scale (grade 1 to 5) and reported in detail in the CRF. Adverse events not listed in the CTCAE version 5 should be graded as follows:

CTC grade	**Equivalent to**	**Definition**
Grade 1	mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall wellbeing or symptoms of the patient.
Grade 3	severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	life-threatening /disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	death	AE resulting in death

7.6 Causality

For all, the investigator will assess the causal relationship between the IMP and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the IMP
- Is biologically implausible and does not follow known response pattern to the suspect IMP (if response pattern is previously known)
- can be explained by the known characteristics of the subject's clinical state or other modes of medication administered to the subject.

Unlikely

- There is a reasonable temporal relation between the AE and the IMP, but there is a plausible other explanation for the occurrence of the AE possibly.
- Follows a reasonable temporal sequence from administration of the IMP. The AE may equally be explained by the study subject's clinically state, environmental or toxic factors, or concomitant therapy administered to the study subject.
- The relationship between the medical device and AE may also be clinically plausible.

Probably

- Follows a reasonable temporal sequence from administration of the IMP, and plausible reasons point to a causal relation with the IMP.

Related

- Follows a reasonable temporal sequence form administration of the medical device.
- Follows a known response pattern to the medical device (if response pattern is previously known).
- No other reasonable cause is present.

Not assessable

- The causal relationship between the IMP and the AE can not be judged.

7.7 Reporting Procedures

7.7.1 Reporting Procedures for Adverse Events (AEs)

A special section is designated to adverse events in the CRF where the following details must be entered:

- type of adverse event (diagnosis or syndrome; if not known signs or symptoms)
- start (date)
- end (date)
- severity (mild, moderate, severe, life-threatening/disabling, death)
- serious (no / yes)
- unexpected (no / yes)

- outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- action taken (none, study medication dose reduced, study medication interrupted, study medication discontinued, medication therapy, surgical procedure, hospitalization, other)
- relation to study drug (possibly, probably or definitely related or unlikely, probably not related or definitely not related)

The investigator has to report immediately new significant follow-up information resulting from follow up examination to the sponsor (i.e. no more than 24 hours after becoming aware of the information).

After discontinuation of the study drug (in the intervention group), all AEs and SAEs, regardless of their relation to the discontinuation of the investigational product, will be recorded, i.e. until the initial state is restored, the patient is Lost to Follow-Up or the patient has withdrawn his or her consent.
Even after the end of the trial, the investigator should report to the sponsor any deaths, SAEs, or other AEs that the investigator deems significant and that are also believed to result from discontinuation of the investigational product.

7.7.2 Reporting Procedures for SAEs and SUSARs

Serious events require immediate notification so that the sponsor can react appropriately to new risks and make appropriate adjustments to the clinical trial. The investigator must report such events immediately to the sponsor; no more than 24 hours should elapse between the time the investigator becomes aware of the event and its report to the sponsor. The investigator must report the following events to the sponsor within 24 hours, regardless of the investigational product context:
- Serious Adverse Events (SAEs)

The investigator must report any new, significant information, e.g. from the follow-up investigation, directly to the sponsor (e.g. within 24 hours of becoming aware of it). New, significant information includes the following:
- new symptoms or a change in diagnosis
- significant new diagnostic test results
- Change of views on the cause due to new information
- Changes in the outcome of the event, including recovery
- additional information on the clinical course of the event

All AEs and SAEs must be reported until the end of active study participation, regardless of the relationship to drug administration. Even if the investigator judges the event to be stable or the patient has failed to follow up or the patient withdraws consent, this must be reported.

In the case of a serious adverse event, the investigator has to use all supportive measures for best patient treatment. The SAE form must be completed by the investigator and reported no more than 24 hours after awareness of the event.

The following details should be available with the initial report:

- patient number
- patient: date of birth, ethnic origin
- name of investigator and trial site
- period of administration
- the suspected investigational medicinal product (IMP)
- the adverse event assessed as serious
- concomitant disease and medication
- relevant medical history
- short description of the event and outcome
- description
    - onset and end (if applicable)
    - therapeutic intervention
    - causal relationship to each of the (study drugs)
    - hospitalization or prolongation of hospitalization
    - death, life-threatening, persistent or significant disability or incapacity

If applicable, the initial report should be followed by the follow-up report, indicating the outcome of the SAE.

For SAEs, SUSARs and pregnancies, the sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g. from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. A follow-up SAE form must also be completed and reported appropriately.

SUSARs will be reported to the required regulatory authorities, investigators/institutions, and ethical committees in compliance with all reporting requirements according to local regulations and good clinical practice by the sponsor and/or its designees.

Once per year, the sponsor or PCI will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent supreme and the competent authorities of all other member states of the EU or EEA where the trial is being conducted. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“

The data lock point for the patient data to be included and analyzed is XX.XX.XXXX / the day of the approval of the clinical trial.

Detailed requirements regarding form and content are covered by the ICH Guideline E2F „Development Safety Update Report – DSUR“. The DSUR presents a comprehensive analysis of the current safety profile concerning the study drug.
The sponsor or PCI will supply the report within 60 days of one year after the reference date (data-lock point).
The data lock point is the last day of the one-year reporting period following the “Development International Birth Date” (DIBD). This date is the sponsor’s first authorization to conduct a clinical trial in any country worldwide. When the DBID is not available to the sponsor, the data lock point can be defined as the first authorization to conduct a clinical trial in the EU if an adequate explanation can be provided.

8. Documentation

The conduct of the study in agreement with the GCP-guidelines and the investigational plan as well as the accuracy of all data documented in the CRF are the responsibility of the investigator. All collected data of this study have to be recorded on the CRF by appropriate authorized persons. This also includes data of patients who dropped-out of the study.
The investigator records the participation on a special identification list of patients. This list gives the possibility for a later identification of the patients and contains the patient number, full name, date of birth and the date of the enrollment into the study. The identification list of patients remains in the study center after the closure of the study. Additionally, the participation of the patient in this clinical study has to be recorded in the patient`s medical record (investigational medicinal product, number of patient or randomization, start and end of the study).
Further it has to be assured that all persons authorized for CRF entries can be identified. A list with signatures and identification codes of the persons must be archived in the ISF and TMF. Furthermore logs according to ICH E6 (e.g. Signature/Delegation/Screening/Drug Accountability log) will be implemented and maintained by the Investigator.

8.1 Data Recording

A: Study with paper-based documentation
Data of patients and investigation results should be recorded into electronic Case Report Forms (eCRF), which are especially developed for this study.
The monitor is responsible for checking the entries in the eCRF at regular intervals for plausibility and completeness. Corrections in the eCRF (electronic Case Report Form) can only be made by people authorized by the principal investigator and have to be justified. Corrections are filed in a way that previous data can be recalled. All data entries and corrections are traced with date, time and person.
It is the responsibility of the investigator to document all data of the clinical study correctly and completely into the database.

8.2 Trial Folders

The trial folders should contain the complete documentation of the trial. They should allow the evaluation of the conducted trial and data quality.

8.2.1 Trial Master File (TMF)

The TMF, established at the beginning of the trial and secured in a safe place, contains all essential documents that demonstrate that the trial is conducted in accordance with regulatory requirements and ICH GCP. All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the TMF and will be clearly labelled as outdated or will be relocated in a section for outdated documents. The TMF is archived at the end of the study for 15 years.

8.2.2 Investigator Site File (ISF)

The paper-based/electronic ISF, established at the beginning of the trial will be secured in a safe place (the file is provided to the site at the site initiation visit). It contains all essential documents maintained by the PI(s). All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the ISF and will be clearly labelled as outdated or versions will be relocated in a section for outdated documents. Within the Monitoring, the ISF will be checking regarding actuality and completeness in accordance with the formalities. After completion or discontinuation of the study this ISF has to be kept for 15 years.

8.3 Data Storage

8.3.1 Storage duties of the Sponsor

The Sponsor has to keep all study-relevant documents of the completed or discontinued clinical trial after completion or discontinuation of the study for a minimum of 15 years.

8.3.2 Storage duties of the Investigator

The Investigators have to keep all records and documents, which are related with the study or the allocation of investigational medicinal products (e.g. data entry form, consent form, list of the allocations of investigational medicinal products and further relevant documents), for a minimum of 15 years. Medical records and other original data have to be kept for 30 years.

9. Data Management

The log is reviewed from a data management perspective, taking into account the processes of data collection, data acquisition, data preparation and processing, and subsequent data analysis. The clinical

data manager must determine the variables to be collected and determine the scope of these in accordance with the visit plan.
An electronic questionnaire was created for data collection, and the instructions for filling it out are provided as a separate document to ensure that the investigators collect data with as few errors as possible.

The collected data is checked by a clinical monitor in accordance with the monitoring plan for accuracy, completeness and consistency with the original data.

The electronic questionnaires are then transferred to data management.

Any discrepancies are forwarded to the investigators for clarification or, in the case of self-explanatory discrepancies (obvious typing errors), corrected by the data management system itself.

Discrepancies that can only be clarified by the investigator are sent to the trial site using a specially prepared form (Data Clarification Form) and answered by the investigator as quickly as possible.
In cases where the discrepancies cannot be explained by the investigator, they are declared unsolvable and documented separately.

After the data validation process, the data set is finalised in consultation with the responsible statistician. As soon as all data management activities in connection with the study are completed, the data set is closed and sent to the statistician for analysis.

All work steps are carried out in compliance with national and international relevant legislation, internal SOPS and guidelines: Good Clinical Data Management Practices (GCDMP) and the Clinical Data Acquisition Standards Harmonization (CDASH) standards.

10. Protocol Deviations

All deviations to the study protocol have to be documented with an explanation. Deviations have to be reported to the sponsor, who is responsible for their valuation.
Reasons for trial termination of a patient have to be documented. In case of termination for safety reasons or insufficient effect of the IMP, the patient has to be further monitored.
Deviations have to be analyzed whether changes of the clinical investigation plan or the closure of the study are necessary.
If necessary, the ethics committee or the responsible authorities have to be informed.

11. Statistics

As described, this is a study with several endpoints. This leads to two hierarchical checks. The first test is defined by fixed design to detect differences between the groups in the maximum death- adjusted SOFA score. If it is completed with a significant result, the second test is defined by a fixed design to detect differences between the groups in a combined event endpoint.

Using a Wilcoxon rank sum test, the fixed design requires 83 patients per group to detect a difference of 3.0 ± 1.51 (X1) to 2.25 ± 1.2 (X2) in the maximum death- adjusted SOFA score on a two-sided 5% significance level with a power of 90%. Formally, this specification for the effect definition results in P(X1>X2) = 0.646. This was determined by simulation in the software R: xx.1<-rnorm(10000,3,1.5), xx.2<-rnorm(10000,2.25,1.2), mean(abs(xx.1) > abs(xx.2)). A drop-out rate of 20% results in a group size of 104 patients per group.

Using a chi-square test with continuity correction, 319 patients per group are needed to detect a difference of 18% (control group) to 10% (intervention group) on a two-sided 5% significance interval with a power of 80%. With the adjustment of the number of cases to a failure rate of 20%, 399 patients per group are needed.

Thus, the overall study could reach a maximum sample size of 2x399 = 798 patients. If the testing of the first endpoint is not significant, a total of 208 patients will be included in the study. If the evaluation after 208 patients shows a trend for the superiority of a group with respect to the primary endpoint 1 (p<0.1), the group size can be adjusted according to the Steering Committee and statistical advice. For this purpose, we use the method Niewczas J, Kunz CU, König F.

11.1 Randomization

Randomisation is only stratified by centre. The block size is chosen as 8. The additional package blockrand of the software R is used for randomization. For randomisation, an electronic distribution of closed envelopes is used. In case of exceptions (e.g. technical problems) a manual distribution of closed envelopes is allowed. The order of the blocks is assigned according to computer-generated random numbers.

11.2 Statistical Design, Methods and Analysis process

This is a non-blinded randomized, multicenter study. A linear regression analysis with random effects is used to test the association of therapy with the primary endpoint (maximum death- adjusted SOFA score), to consider stratification and to adjust for important prognostic factors. Stratification by centre uses random effects.

The test of the composite event timing is performed using logistic regression. Again, centres are modelled as random factors. The therapy and adjustment factors are entered into the model as fixed effects.

The exact elaboration of the analysis takes place in a statistical analysis plan (SAP), which will be available before the first evaluation (difference in maximum death- adjusted SOFA score).

11.2.1 Target Variable

Potentially there are two primary endpoints: 1) The maximum death- adjusted SOFA score as a continuous variable and 2) The combined event endpoint: admission to ICU, intubation and mortality. Secondary endpoints are continuous (e.g. qSOFA, viral burden, laboratory parameters, etc.) and categorical variables (e.g. death, admission to ICU, etc.). Hypertensive urgency and hospitalization due to decompensated heart failure are used as safety parameters, which are categorical variables.

11.2.2 Definition of Analysis Sets/Populations/Subgroups

All randomized patients who received their assigned treatment for at least one day constitute the primary evaluation collective (Intention-to-Treat (ITT) collective). They are evaluated according to the ITT principle. In addition, they are evaluated according to the Per Protocol Principle as a sensitivity analysis. Furthermore, the following subgroups are to be examined:

1.) Stratified by age: patients > 75 years and ≤ 75 years

2.) Stratified by baseline qSOFA: patients with high (>2) and low (≤2) baseline SOFA

3.) Stratified by baseline viral load: patients with high (>1 × 106 copies per mL) and low (≤1 × 106 copies per mL) baseline viral burden

4.) Stratification according to indication for ACEI and ARB treatment (arterial hypertension, heart failure, coronary heart disease)

11.2.3 Interim Analysis

If significant evidence of a difference in the maximum death- adjusted SOFA score is found, the second primary endpoint is further tested. The 208 patients up to the testing of the first endpoint determine the first stage of the study, after an interim analysis the second study phase will then begin.

If no significant difference between the two treatment groups is observed after evaluation of the data from the first 208 study participants, the clinical trial will be terminated prematurely. However, if the analysis after 208 patients shows a trend for the superiority of one group with respect to the primary endpoint 1 ($p<0.1$), the group size can be increased in accordance with the Steering Committee and statistical consulting.

11.2.4 Handling of missing, unused or spurious Data, including Drop-outs and Withdrawals

Missing values in the SOFA score are replaced by imputation procedures. The corresponding details are defined in SAP. Missing values in the combined event end point are evaluated as "failure".

11.2.5 Data Analysis

Regression analyses are used to test the association of therapy with the primary endpoint (maximum death- adjusted SOFA score, combined event endpoint). Centres are introduced into the corresponding models as random factors. The group indicators defined under points 1 to 4 in section 12.2.2. are used for adjustment. Within the framework of the subgroup analyses, the interaction between the therapy indicator and the group indicators is considered.

12. Quality Management

Training, monitoring and audits are performed for quality assurance within this clinical study. Monitoring and auditing procedures developed or endorsed by the sponsor will be conducted, in order to comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data.

12.1 Qualifications

The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources. Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s) (see ICH GCP E6).

12.2 Monitoring

The monitoring of the clinical trial is carried out by an independent and qualified institution.
The investigator agrees that the monitor will perform a data review at an interval specified in the monitoring plan to ensure satisfactory data collection and compliance with the clinical trial protocol.
The investigator also agrees to cooperate with the monitor and to provide the monitor with all necessary information whenever necessary. This includes access to all documents related to the trial, including original patient records relevant to the trial. The monitor is also enabled to perform data review and comparison with the relevant patient records in accordance with the sponsor's SOPs and ICH-GCP guidelines at predetermined intervals to ensure compliance with the protocol and continuous data recording. All original medical findings that are necessary as the source of the information in the eCRF are reviewed. The patient has agreed to such a review by signing the informed consent form. A report of the monitoring visit will be prepared, indicating the progress of the study and any problems encountered. All data related to the study will be kept confidential by the monitor.

12.3 Audits and Inspections

In order to guarantee that the clinical trial is conducted in accordance with GCP guidelines, internal (e.g. by the sponsor) and external (e.g. by authorities) audits can be carried out for this trial. The investigator commits himself to give the auditor access to all study relevant information and to support the sponsor

in solving possible ambiguities/problems. After each audit, the auditor will issue a confirmation to this effect. The

This must be kept in the inspection file so that it is available in case of an inspection by the authorities. The audit report is sent to the sponsor of the clinical trial. At the end of this, an audit certificate is attached to the final report.

All persons conducting audits must keep patient data and other clinical trial data confidential.

13. Reporting

For the documentation of the progress and development of the study, protocols about the meetings of the various group committees are necessary.

13.1 Final Study Report

All information relating to the clinical trial must be kept confidential. The statistical analysis and the attached final report will be prepared in accordance with ICH E6 guidelines. These must be completed within 12 months after the last examination of the last patient (Last Patient Last Visit (LPLV)). The final report is reviewed and signed by the sponsor, the coordinating investigator and all other responsible persons. All information within the report is strictly confidential.

The physician appointed by the sponsor signs the final report of the trial. By doing so, he confirms that the final report describes to the best of his knowledge the conduct and results of the trial.

13.2 Publication

The results of this clinical trial will be published. The publication or presentation of the results requires prior comment and approval by the sponsor. All data collected in connection with the clinical trial must also be treated confidentially. For all publications, the data protection for all patient data must be maintained. The clinical trial is registered in a publicly accessible database (e.g. www.clinicaltrials.gov).

14. Amendments

In order to ensure comparable conditions in all trial sites and in the interest of proper data evaluation, no changes to the agreed trial conditions laid down in the clinical trial protocol are planned.

In exceptional cases, however, changes to the conditions of the clinical trial are possible. These are only made after mutual agreement between the investigator and the sponsor. Any change to the trial procedure specified in the protocol must be made in writing, stating the reasons for the change, and signed by all parties responsible for the trial. The amendments will then be considered an integral part of the protocol.

Deviations should be reviewed to determine whether it is necessary to amend the protocol or terminate the trial.

If the change is significant and, in particular, could affect the safety of the trial subjects or influence the scientific validity of the trial, the sponsor undertakes to notify the Federal Office of Public Health and the competent Ethics Committee of the content of the change and all reasons for it.
However, if the above list of investigators and trial sites changes, it will not be formally updated each time by amendments; the sponsor will maintain an updated list, which is available on request. The final list of all trial sites and investigators will be included in the final report.

15. Ethical and Regulatory Aspects

15.1 Responsibilities of Sponsor and Investigator

The sponsor of this clinical trial will assume responsibility for inducement, organization and financing of the implementing trial according to the ICH E6. The procedures set out in this study protocol are designed to ensure that the sponsor and the Investigator comply with the principles of ICH-GCP the Declaration of Helsinki and the ICH E6 guideline concerning the conduct, evaluation and documentation of the study. The study will also be performed adhering the local legal conditions and requirements. Each Investigator has to confirm this by signing the study protocol.
Responsibilities of the sponsor:

- verification of the understanding of the investigator´s brochure or the described IMPD
- verification of the understanding of treatment schedule
- ensuring for enough time and capacity for the implementation of this study
- correct collection and documentation of data, reporting
- provision of all data to the sponsor, monitor or relevant authorities for audits or inspections
- assurance for the confidential handling of patients data and information

The principal investigator accepts the responsibility for the conduct of this clinical trial at this study site according to the ICH E6

15.2 Approval of Ethics Committee and Notification to the Authority

Prior to study start, the study protocol and/or other appropriate documents will be submitted to the relevant ECs and CAs for approval. Approval from all concerned ECs and CAs must be obtained before starting the study.

15.3 Patient Information and Consent Form

Every patient has to give his/her written consent BEFORE the participation in the clinical trial. Before the patient gives his/her written consent the patient has to be informed completely in oral and written form in an understandable manner about character, importance, relevance and consequences of the clinical trial.
The content of the consent information is documented on the patient information/ informed consent form. The patient will be notified, if essential findings about the MD appear during the study.

The informed consent of the patient about the participation in the clinical trial has to be dated and signed by the patient and the Investigator. The patient receives a copy of the signed and dated Patient information and informed consent Form. The Investigator stores the original signed and dated exemplar in the investigator site file.
It has to be explicitly pointed out, that before patient sign the informed consent form it is not allowed to perform any study specific actions with the patient.

15.4 Insurance

The sponsor will take out reasonable third-party liability insurance cover in accordance with local legal requirements. The civil liability of the investigator, all persons instructed and the hospital, practice or institute in which they are employed and the liability of the sponsor in respect of financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable local law.
The sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the study medication or by medical steps taken in the course of the study. Such insurance is taken out by the sponsor in accordance with or by way of analogy to both the Austrian and the other participating countries pharmaceutical act.

15.5 Data Protection and Confidentiality

All clinical trial findings and documents are treated confidentially and local legal requirements regarding data security are observed. The investigator or the study team may not disclose any information without the written consent of the sponsor.
Documents that list patients by name (e.g., informed consent forms, patient lists) must be kept confidential by the investigator. Patients must be informed in the patient information that all trial results will be stored electronically and kept strictly confidential.

15.6 Financing

The present clinical trial is financed from the university's own funds.

15.7 Regulatory Aspects

The processes set out in this study protocol are designed to ensure that the sponsor and the Investigator abide the principles of the ICH E6 and the Declaration of Helsinki concerning the conduct, evaluation and documentation of the study. The study will also be performed in compliance with the local legal conditions and requirements. Each investigator has to confirm this by signing the study protocol.

16. Committees

16.1 Steering Committee

The Steering Committee is responsible for monitoring of the conduction and administrative progress of the study. The committee will meet at regular intervals. In critical phases it can also be convened at short notice. Members of the Steering Committee are Axel Bauer, Steffen Massberg, Konstantinos Rizas, Herbert Tilg, Günter Weiss, Florian Kronenberg, Oliver Keppler.

16.2 Event Adjunction Committee

An Event Adjudication Committee (EAC) will be established to evaluate clinical events and clinical endpoints in the study. For this purpose, the EAC will first determine the minimum amount of data required to classify a clinical event. The EAC will then define criteria that will be used to categorize clinical events and clinical endpoints. All members of the EAC will be blinded to the primary outcomes of the study and the group membership of the study participants.

17. Appendix

Table: Medical product list

ACE-inhibitor
Cilazapril
Enalapril
Fosinopril
Imidapril
Lisinopril
Ramipril
Perindopril
Quinapril
Angiotensin-Receptor blocker
Substance
Azilsartan
Candesartan
Eprosartan
Irbesartan
Losartan
Olmesartan
Telmisartan

18. Literature

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