Clinical Trial Protocol

	Document Number:	**c32418694-02**
EudraCT No. **EU Trial No.**	2020-003211-96	
BI Trial No.	1434-0009	
BI Investigational Medicinal Product	BI 764198	
Title	BI 764198 effic**ac**y and safe**t**y in preven**tion**/progression of ARDS and ARDS-related complications sec**on**dary to **COVID-19** **(ACTION ON COVID-19)**	
Lay Title	ACTION ON COVID-19: A study to test whether BI 764198 helps lung health of people hospitalised with COVID-19	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone [redacted]	
Version and Date	Version: 2.0	Date: 08 Jan 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	18 Sep 2020
Revision date	08 Jan 2021
BI trial number	1434-0009
Title of trial	BI 764198 effic**ac**y and safe**t**y in prevent**ion**/progression of ARDS and ARDS-related complications sec**on**dary to **COVID-19 (ACTION ON COVID-19)**
Coordinating Investigator	[redacted] Phone [redacted]
Trial site(s)	Multi-centre trial
Clinical phase	Phase II
Trial rationale	TRPC6 inhibition should reduce pulmonary endothelial and epithelial cell apoptosis thereby improve lung edema and clinical outcomes in patients with severe SARS-CoV-2 infection..
Trial objective(s)	To evaluate the efficacy and safety of [redacted] BI 764198, an inhibitor of the transient receptor potential subtype C6 (TRPC6), compared to placebo in reducing risk or severity of acute respiratory distress syndrome (ARDS) in patients hospitalised for COVID-19.
Trial endpoints	Primary endpoint • Patients alive and free of mechanical ventilation at Day 29 Secondary endpoints • Patients alive and discharged free of oxygen at Day 29 • Patients with occurrence of any component of composite: In-hospital mortality or intensive care unit (ICU) admission or mechanical ventilation at Day 29 • Time to response, defined as clinical improvement of at least 2 points (from randomisation) on the World Health Organization Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (a score of 0, 1, 2, or 3 on the Clinical Progression Scale), whichever comes first, by Day 29 • Number of ventilator free days by Day 29 • Mortality at Day 15, 29, 60, and 90
Trial design	This is a multi-centre, randomised, double-blind, placebo-controlled trial of BI 764198 in the treatment of COVID-19 disease.
Total number of patients randomised	130 patients
Number of patients on each treatment	65 patients placebo and 65 patients [redacted] BI 764198
Diagnosis	Hospitalised with a diagnosis of COVID-19 at risk of developing or diagnosed with ARDS

Main in- and exclusion criteria	• Adults (≥50 years) hospitalised for SARS-CoV-2 infection confirmed by PCR or approved point-of-care test. • Women of childbearing potential (WOCBP) and men able to father a child must abstain from male female sex or must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during hospitalisation and for at least 7 days after last trial drug intake. • A score of 5 (hospitalised; oxygen by mask or nasal prongs) or 6 (hospitalised; oxygen by non-invasive ventilation or high flow) on the World Health Organization Clinical Progression Scale (no previous score of 7 or above). • Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. • No relevant end-organ failure or other medical conditions (e.g. active cancer, renal, cardiac, gastrointestinal) which based on investigator judgement would interfere with the conduct of this study. • Not previously on long-term oxygen therapy.
Test product(s)	BI 764198
dose	[redacted] per day
mode of administration	Oral (p.o.) or, only if needed, nasogastric intubation
Comparator product(s)	Placebo to BI 764198
dose	Not applicable
mode of administration	Oral (p.o.) or, only if needed, nasogastric intubation
Duration of treatment	Up to 28 days
Statistical methods	The primary endpoint will be analysed with a logistic regression model using covariates of treatment, severity grade at baseline, age, creatinine at baseline, and duration of symptoms before hospitalisation, to evaluate the absolute difference in proportions of patients alive and free of mechanical ventilation at Day 29 with BI 764198 and placebo. Patients who terminate the study medication prematurely will be followed and the events which occur after premature discontinuation of medication and before the time point of interest will be included in the analysis using the Full Analysis Set (FAS). The logistic regression for the primary endpoint analysis will be used for other binary endpoint(s) and time-to-event endpoints will be analysed using Cox regression including covariates used for the primary analysis. Ventilator free days will be analysed using ANCOVA including the same covariates as in the primary analysis.

FLOW CHART

Trial Periods	Screening	Treatment			Follow-up (telephone visits only[b])		
Visit	**1**	**2**	**3 through 29**	**EOT[a]**	**FUP[b] 1**	**FUP[b] 2, 3, 4**	**EOS[b]**
Day	**-1**	**1**	**Daily Day 2 through discharge -1 day (maximum Day 28)**	**dis-charge/ day after last dose**	**EOT +4 days**	**15, 29, 60 (from Day 1)**	**90 (from Day 1)**
Time window for visits (days)	**-3 to 1[c]**				**+2**	**±3**	**±6**
Informed Consent	X						
Demographics	X						
Medical History	X						
Baseline Conditions	X						
Clinical Frailty Scale (CFS)	X						
SARS-CoV-2 PCR test [c,h]	X						
Review of inclusion/exclusion criteria[c]	X	X					
Randomisation		X					
Concomitant Therapy and Procedures	X	X	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X	X
Hospitalisation Status	X	X	X	X	X	X	X
World Health Organization (WHO) Clinical Progression Scale	X	X	X	X	X[f]	X[f]	
Ventilation and oxygen parameters; respiratory rate, FiO_2, SpO_2	X	X	X	X	X[f]	X[f]	
Vital signs (refer to Section 5.2.2)	X	X	X	X			
Blood Gases/PaO_2 data capture if performed as part of routine care	X	X	X	X			
12-lead ECG[c,g]	X	X (+1 day)	Day 3,7,14,21 (±1 day)	X			
Physical Exam (refer to Section 5.2.1)	X	X (±1 day)	Day 3,7,14,21 (±1 day)	X			
Safety Laboratory Samples (refer to Section 5.2.3)[c,d]	X	X (±1 day)	Day 3,7,14,21 (±1 day)	X			
Pregnancy test (blood) for WOCBP[c,d]	X		Day 7,14 (±1 day)	X			
Administration of trial medication[e]		X	X	X[i]			
Termination of trial medication				X			
Trial Completion							X
Vital Status					X	X	X

EOT=End of Treatment; EOS=End of Study; FiO_2=fraction of inspired oxygen; FUP=Follow-up; PCR=polymerase chain reaction; PO_2=partial pressure of oxygen; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.

Footnotes:

[a] EOT visit should be completed the day after the last dose of study drug is administered for all patients. EOT visit should occur no later than Day 29.

[b] FUP 1 should be performed 4 days after EOT visit for all patients. FUP 2 and FUP 3 which correspond to study Day 15 and Day 29 after start of therapy, should be performed *if the time point is applicable after drug discontinuation.* FUP 2 and FUP 3 visits should not be conducted within +/- 2 days of EOT or FUP 1. FUP 4 and EOS which correspond to study Day 60 and Day 90 will be performed for all patients. If a patient remains hospitalized after EOT visit, applicable FUP visits and

the EOS visit will be conducted in hospital until discharge and thereafter by telephone. Refer to Section 6.2.3.

[c] Laboratory tests and ECG performed up to 72 hours prior to enrolment will be accepted for determination of eligibility and the screening visit date may be the same day as Visit 2 or up to 3 days prior to Visit 2.

[d] Results from laboratory tests performed as part of routine clinical care within the specified visit window may be used.

[e] Interactive Response Technology (IRT) will be used to allocate a 10 day supply of study drug at Visit 2 (or at the conclusion of Visit 1 after all eligibility criteria are confirmed to be met to allow time to prepare the study drug prior to day of randomization (first administration of study drug) and, if applicable per an individual patient's treatment duration, at Visit 12 and Visit 22.

[f] If the patient discontinues treatment and is not discharged prior to Day 29, collect ventilation and oxygen parameters daily up to Day 29, respiratory rate, FiO_2, SpO_2, if applicable, at Day 29, and WHO Clinical Progression Scale score at Day 29. If patient is on oxygen therapy at discharge, collect end date of that oxygen therapy when available during the Follow-up visit telephone call(s).

[g] ECG should be performed 0.5-4 hours after drug administration.

[h] SARS-CoV-2 PCR test to be performed as visit procedure and an approved SARS-CoV-2 point-of-care test may be used to evaluate inclusion criterion 2, refer to Section 3.3.2.

[i] Dosing should be stopped the day prior to EOT. However, if it is uncertain whether a patient is fit for discharge, and the patient has not yet completed the allowed treatment duration of 28 days, administer study drug and perform all study procedures per the planned treatment period visit. If later that day the PI makes the decision that patient will discharge, perform any additional EOT visit procedures, if applicable, per Flow Chart and record visit in the eCRF as EOT visit.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
Ca^{2+}	Calcium
CFS	Clinical Frailty Scale
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	Maximum Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ECMO	Extracorporeal Membrane Oxygenation
EOS	End of Study
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	Fraction of inspired Oxygen

FUP	Follow-up
GCP	Good Clinical Practice
gRT	Global Randomization Team
GMP	Good Manufacturing Practice
HA	Health Authority
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
iSTAT	Independent Statistician
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLVPE	Last Patient Last Visit Primary Endpoint
LPLT	Last Patient Last Treatment
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Drug Regulatory Activities
MPC	Mutant Prevention Concentration
NOAEL	No-Observable-Adverse-Effect-Level
OPU	Operative Unit
PaO_2	Partial pressure of Oxygen
PCR	Polymerase Chain Reaction
p.o.	per os (oral)
q.d.	quaque die (once a day)
RA	Regulatory Authority
RNA	Ribonucleic Acid
REP	Residual Effect Period
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SoC	Standard of Care

SpO_2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TRPC6	Transient Receptor Potential subtype C6
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
VFD	Ventilator Free Days
WHO	World Health Organization
WOCBP	Woman Of Child Bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Coronaviruses are single-stranded ribonucleic acid (RNA) viruses. In humans, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to the syndrome known as COVID-19 which is associated with a wide spectrum of symptoms and symptom severities. The respiratory system is a key organ affected.

Many individuals, in particular younger patients, with COVID-19 experience only mild upper respiratory tract symptoms. Severe illness occurs more frequently in people over the age of 60 years and in those with co-morbidities. In some cases, dyspnoea and progressive hypoxemia may necessitate the use of mechanical ventilation. Upwards of 15% of patients with SARS-CoV-2 require hospitalisation and many of these patients need some form of oxygen support.

Many of the COVID-19 cases which require hospitalisation are complicated by acute respiratory distress syndrome (ARDS), an injurious and potentially fatal lung condition [R20-1310, R20-1309]. ARDS has no effective specific treatment besides supportive care, which includes conservative fluid strategies, early empirical antibiotics for suspected bacterial co-infection, and importantly the use of ventilation strategies, and prone positioning in severe disease. The mortality rate for severely affected patients with ARDS is between 25% and 60% with the current standard of care [R20-1652]. Histological hallmarks in the early stages of ARDS include diffuse alveolar damage followed by oedema, haemorrhage, and subsequent intra-alveolar fibrin deposition [R20-1812]. Thus, preventing or reducing the severity of the ‘exudative’ phase of ARDS may delay the onset and/or severity of the injurious ‘proliferative’ and potentially the ‘fibrotic’ stages of disease in some patients [R20-1815].

Transient Receptor Potential (TRP) channels have been shown to act as chemosensors in stress-induced signal transduction cascades [P20-05219]. In the human lung, TRPC6 is the most abundantly expressed TRP channel. It is highly expressed on bronchial epithelial cells, alveolar type II cells, and endothelial cells. There is evidence that TRPC6 channels are indirectly activated by hypoxia and reactive oxygen species, resulting in channel-induced Ca^{2+}-influx. Increased calcium influx in smooth muscle cells causes cellular contraction and increased epithelial and endothelial cell damage which lead to increased endothelial permeability and lung oedema in pathological conditions. Pharmacological inhibition of TRPC6 in mouse models of lung injury has been shown to markedly reduce alveolar leakage, endothelial cellular damage and cell death.

Due to the rapid global spread of SARS-CoV-2, there is an urgent need to develop efficacious treatments for the disease and its complications. While the investigation of anti-viral treatment strategies for COVID-19 continues, and in anticipation of a potential future safe and effective vaccine, therapies aimed at preventing or slowing down the progression and/or intensity of the exudative phase of ARDS secondary to COVID-19 may provide a complementary means of reducing morbidity and mortality in patients with lung

complications. Targeted inhibition of TRPC6 in this context might therefore be of benefit to patients with SARS-CoV-2 at risk of lung complications.

1.2 DRUG PROFILE

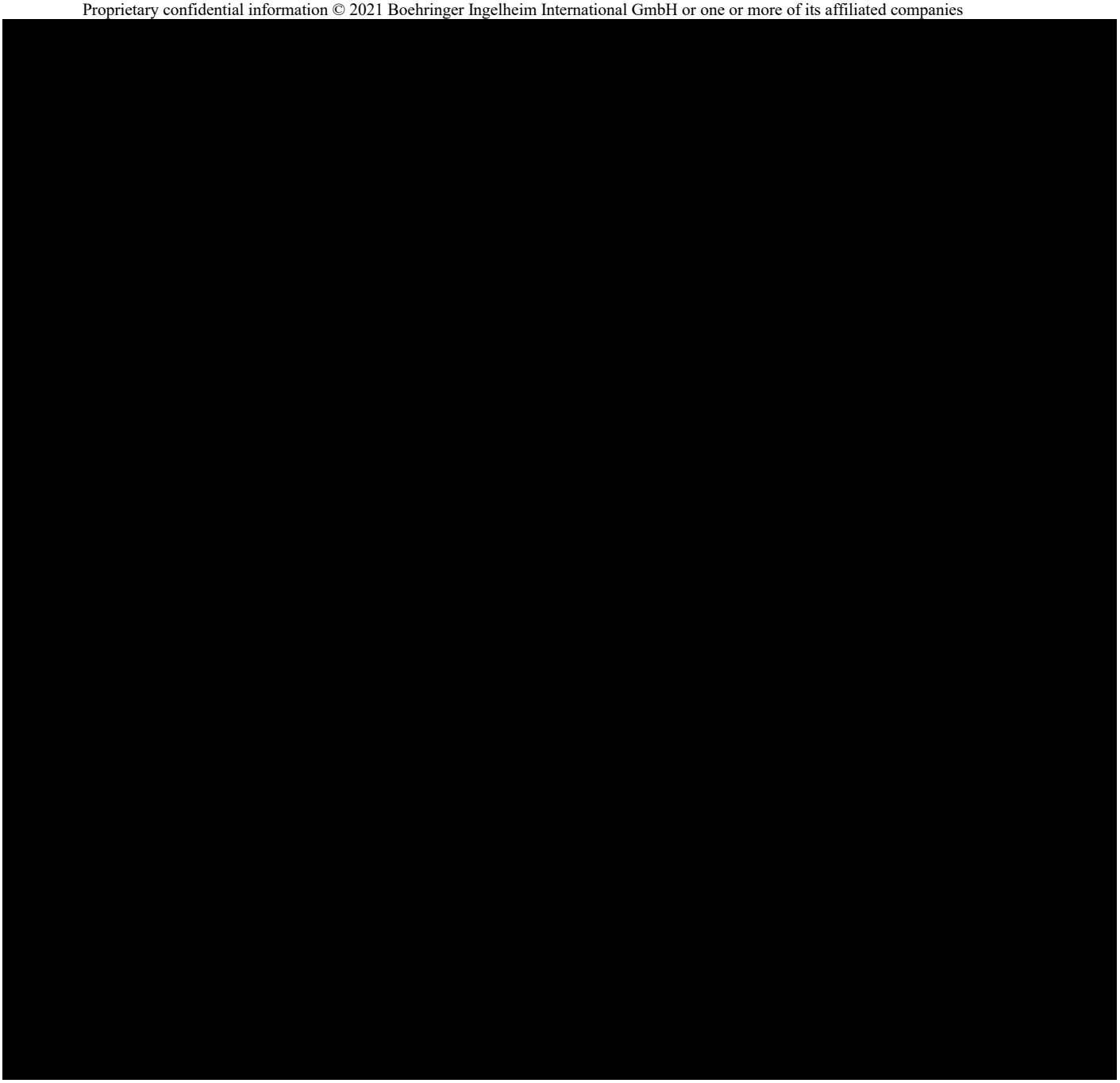
BI 764198 is an oral, small-molecule inhibitor of TRPC6. It is being developed for the treatment of advanced chronic kidney disease on top of standard of care. Because of the potential effect of TRPC6 inhibition in the lungs with regard to formation of lung edema and endothelial and epithelial cell apoptosis, BI 764198 is also being investigated for the treatment of patients hospitalised for COVID-19.

Mode of action
BI 764198 is a potent inhibitor of human TRPC6 [redacted], rat TRPC6 [redacted], mouse [redacted] dog TRPC6 [redacted] and cynomolgus monkey [redacted] in *in vitro* manual patch clamp assays using human HEK293 cells with inducible TRPC6 expression.

Inhibition of channel-induced Ca2+-influx is believed to prevent smooth muscle cell contraction and reduce endothelial cell permeability and damage. [redacted]

Drug interactions
To date, no human drug-drug interaction studies have been conducted.

[redacted]



1.3 RATIONALE FOR PERFORMING THE TRIAL

TRPC6 inhibition should slow or prevent the progression of pulmonary endothelial and epithelial cell apoptosis and lung edema in patients with SARS-CoV-2 infection, improving the outcome for patients. There is an urgent public health need for rapid development of interventions to treat COVID-19 and its complications. Patients to be included in this trial will be hospitalised and may require either supplemental oxygen, non-invasive ventilation or high-flow oxygen devices. The trial will investigate the efficacy and safety of BI 764198 in patients with SARS-CoV-2.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

The TRPC6 channel is the most abundantly expressed member of the TRP family on human lung cells. In pulmonary endothelial cells, calcium (Ca^{2+}) influx through TRPC6 increases cellular permeability induced by hypoxia/reactive oxygen species generation. Therefore, inhibition of channel-induced Ca^{2+}-influx in this context may prevent smooth muscle cell contraction and reduce endothelial cell permeability and damage. These dysregulated pathophysiological events are postulated to contribute to COVID-19 induced lung injury/ARDS. [redacted]

The intended target indication for BI 764198 is the reduction of ARDS risk or severity in hospitalised patients with SARS-CoV-2 infection. TRPC6 inhibition in this patient population is expected to improve lung associated morbidity and mortality on top of supportive standard of care oxygen therapy, antiviral therapy, or anti-inflammatory therapies. The medication is to be administered orally or via nasogastric tube as needed. [redacted]

[redacted] Risks

Procedure-related risks
The use of an indwelling venous catheter for blood sampling may be accompanied by mild bruising and in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

In most cases, the total volume of blood withdrawn during the entire study per subject will likely not exceed the volume of a normal blood donation (500 mL).

Drug-related risks and measures
Non-clinical safety data is summarized in Section 1.2 above. [redacted]

[redacted]

[redacted]

Taken together, no specific drug-related risks are anticipated. Nevertheless, the following safety measures in this study will minimize the risk for the participating patients:

- As all patients in the study are hospitalised, they will undergo close medical surveillance

- Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.6.1.4, adverse events of special interest (AESI).

1.4.3 Discussion

BI 764198 has the potential to become an oral treatment for patients hospitalised with SARS-CoV-2 at risk of respiratory complications, an area of urgent unmet medical need. Based upon preclinical and first clinical data for BI 764198, as well as the close medical monitoring in this study, medical risks are minimized in relation to the important information expected to be gained from this trial. Considering the medical need for effective treatments in patients hospitalised for COVID-19, the sponsor considers that the potential benefits of therapy in this context will outweigh potential risks, which justifies the treatment of patients with BI 764198 who are hospitalized with severe SARS-CoV-2 and are at high risk of lung complications.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

To evaluate the efficacy and safety of [redacted] BI 764198, an inhibitor of the transient receptor potential subtype C6 (TRPC6), compared to placebo in hospitalised patients at risk of developing ARDS or diagnosed with ARDS secondary to COVID-19 infection.

The primary comparison of interest is the absolute difference in proportion of patients alive and free of mechanical ventilation by Day 29. The primary trial objective is to estimate the treatment effect between BI 764198 and placebo. The primary comparison will be made as randomised, without regard to any treatment changes.

2.1.2 Primary endpoint(s)

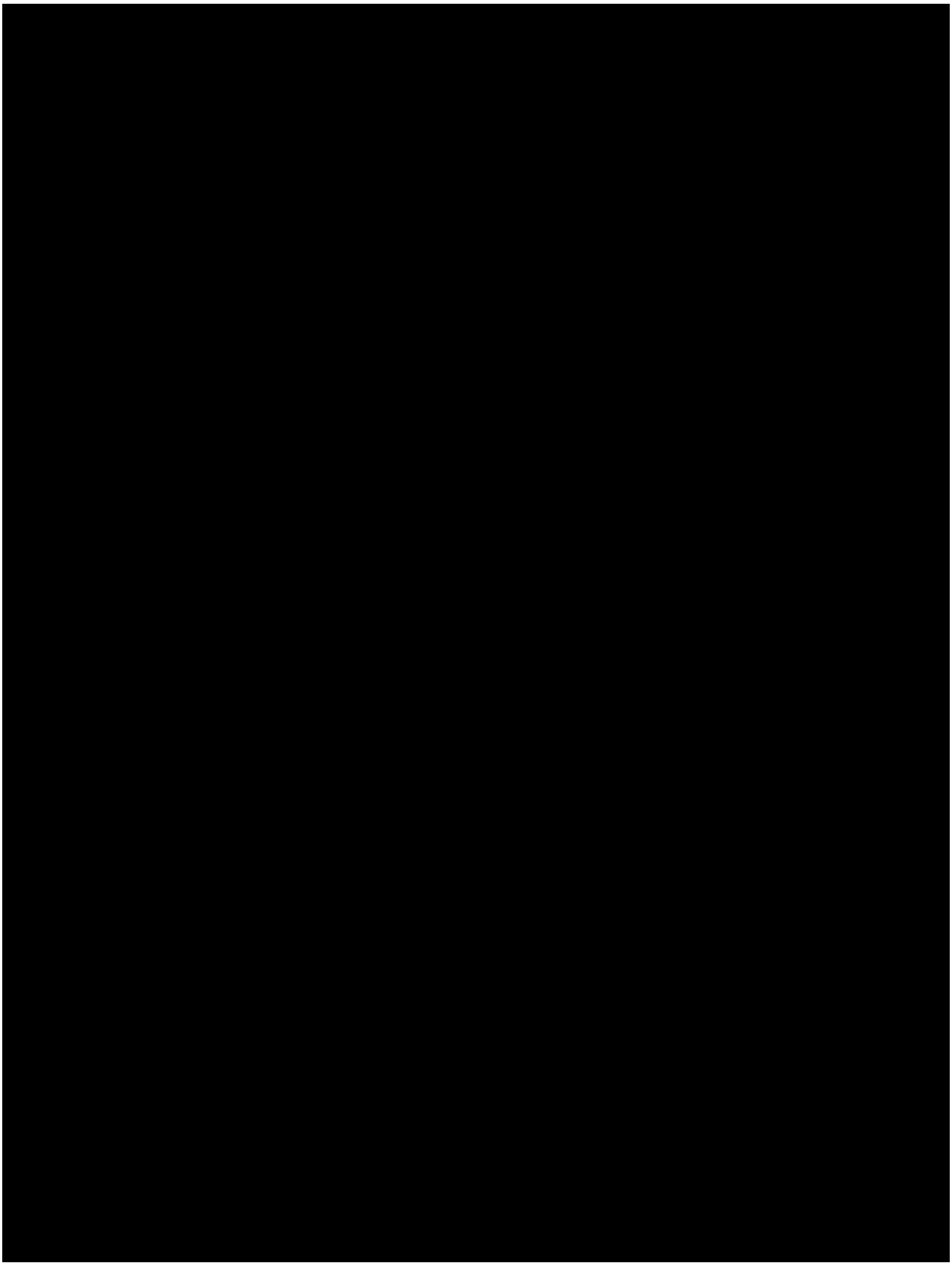
- Patients alive and free of mechanical ventilation at Day 29

2.1.3 Secondary endpoints

- Patients alive and discharged free of oxygen at Day 29
- Patients with occurrence of any component of composite: In-hospital mortality or intensive care unit (ICU) admission or mechanical ventilation at Day 29
- Time to response, defined as clinical improvement of at least 2 points (from randomisation) on the World Health Organization Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (a score of 0, 1, 2, or 3 on the Clinical Progression Scale), whichever comes first, by Day 29

  World Health Organization (WHO) Clinical Progression Scale [R20-2002]:
  0. Uninfected; no viral RNA detected
  1. Asymptomatic; viral RNA detected
  2. Symptomatic; independent
  3. Symptomatic; assistance needed
  4. Hospitalised; no oxygen therapy
  5. Hospitalised; oxygen by mask or nasal prongs
  6. Hospitalised; oxygen by non-invasive ventilation or high flow
  7. Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
  8. Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
  9. Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO)
  10. Death

- Number of ventilator free days by Day 29
- Mortality at Day 15, 29, 60, and 90



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-centre, randomised, double-blind, placebo-controlled trial of BI 764198 in the treatment of COVID-19.

The study will include adult patients (≥50 years) who are hospitalised for infection with SARS-CoV-2, the virus that causes COVID-19, as confirmed by PCR (approved point-of-care test may be used to evaluate inclusion criterion 2 (Section 3.3.2). For inclusion, patients will need to have clinical status of Grade 5 (hospitalised; oxygen by mask or nasal prongs) or Grade 6 (hospitalised; oxygen by non-invasive ventilation or high flow), as defined by the WHO Clinical Progression Scale (Section 2.1.3).

Patients will be enrolled (screened) in the trial once the appropriate informed consent has been obtained. Patients who successfully complete screening and still meet the inclusion/exclusion will be randomised in a 1:1 ratio to receive either placebo or [redacted] BI 764198 per day stratified by baseline severity grade. Dosing with study medication will commence on Day 1. The treatment duration is anticipated to last up to 28 days. Refer to Flow Chart for EOT, FUP, and EOS visit schedule. The study schematic is shown in Figure 3.1: 1 below.

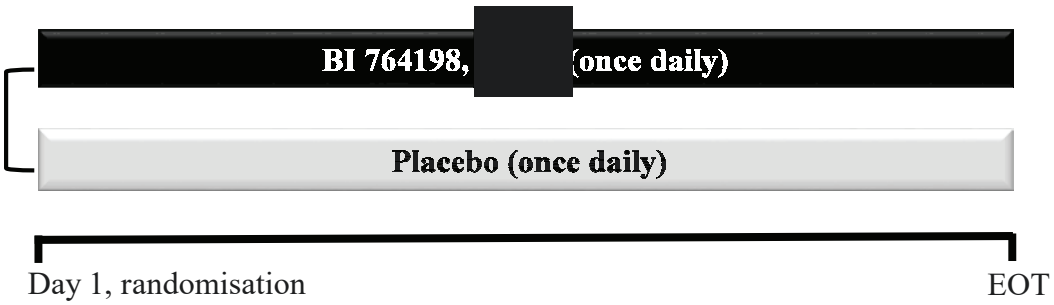


Figure 3.1: 1 Study schematic

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

There is an urgent public health need for development of treatments for COVID-19. This trial is designed to assess BI 764198 as a potential treatment for respiratory disease associated with COVID-19. Patients to be initiated in the study will be those hospitalised for COVID-19, but not yet needing tracheal intubation and mechanical ventilation.

The primary endpoint (patients alive and free of mechanical ventilation at Day 29) is a clinically meaningful outcome measure for an acute condition in which most patients will either die or substantially recover within a short time period.

The secondary endpoint of improvement on the WHO Clinical Progression Scale is an internationally recommended endpoint for assessing the efficacy of new treatments for patients with SARS-CoV-2 [R20-2002]. As patients may continue to worsen despite therapy, the study will also capture disease worsening prior to, or in the absence of, disease improvement.

A parallel group, randomized, double-blind, placebo-controlled trial is considered the most appropriate design to assess the efficacy and safety BI 764198. Therapy will be on top of usual care for COVID-19, so all patients will receive usual care.

A Data Monitoring Committee (DMC), which is independent of the sponsor except for the iSTAT, will be established for this study to assess safety on an ongoing basis throughout the study (see Section 8.7). The DMC members will perform ongoing safety surveillance and provide recommendations to the sponsor regarding study conduct. Further details are provided in the DMC charter.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

Patients over the age of 50 years are included as these patients have higher risk of developing severe lung complications or potentially dying as result of SARS-CoV-2 infection. Hence, the evaluation of the potential beneficial effects of TRPC6 inhibition in this high risk population would expose a smaller number of patients to this investigational compound in this clinical proof of concept study.

Patients are selected because they have been hospitalised for COVID-19 and are at risk of developing ARDS. Efforts should be made to minimize the time from patient identification to treatment, as TRPC6 inhibition is expected to provide benefit early in the course of disease. Patients that do not have the potential for key outcomes or are already improving should not be included.

A sufficient number of patients hospitalised for COVID-19 will be screened in multiple countries from approximately 40 trial sites to ensure the randomisation of approximately 130 eligible patients.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Adult patients (≥50 years) hospitalised for COVID-19 requiring non-mechanical (ventilator) oxygen therapy and who comply with eligibility requirements may qualify for participation in this trial.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Age ≥50 years
2. SARS-CoV-2 infection positive confirmed by PCR or approved point-of-care test.
3. A score of 5 (hospitalised; oxygen by mask or nasal prongs) or 6 (hospitalised; oxygen by non-invasive ventilation or high flow), but not previously ≥7, on the WHO Clinical Progression Scale.
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
5. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must abstain from male female sex or must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during hospitalisation for at least 7 days after last trial drug intake. A list of contraception methods meeting these criteria is provided in Section 4.2.2.3.

3.3.3 Exclusion criteria

1. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 × the upper limit of normal (ULN).
2. Known active infection with HIV or hepatitis B or C.
3. Pulmonary oedema/respiratory failure due to cardiogenic insult.
4. Long-term oxygen therapy prior to current hospitalisation.
5. A confirmed baseline prolongation of QTc interval to greater than 450 ms in males or 470 ms in females, or any other relevant ECG finding at screening, or continued use of agents known to prolong the QT interval (refer to listing provided in ISF).
6. Stage 4 kidney disease or requiring dialysis (i.e., eGFR <30 mL/min/1.73 m^2).
7. History of the following cardiac conditions:
   a) Myocardial infarction within 3 months prior to the first dose

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 2 years without an alternative medical cause.

b) Unstable angina
c) Clinically significant long QT features on electrocardiogram (ECG) or history of familial long QT

8. Anticipated transfer/discharge to another hospital or care facility other than their place of residence.
9. Not committed to full support or intubation (do not resuscitate/do not intubate wishes)
10. Allergy to study medication.
11. Relevant end-organ failure or other medical conditions (e.g. active cancer, cardiac, gastrointestinal) which based on investigator judgement would interfere with the conduct of this study.
12. Experimental, or off-label usage of medicinal products as specific treatments for COVID-19.
13. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5 half-lives (whichever is shorter) since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
14. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Section 3.3.4.1 and Section 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

- The patient experiences renal impairment based on clinical judgement (e.g. sustained eGFR <30 mL/min/1.73 m^2).
- The patient experiences hepatic impairment based on clinical judgement (e.g. ALT/AST >5 × ULN.
- The patient experiences QT prolongation of the QTc interval of either >60 ms change from baseline or greater than 500 ms during the study.

Should a patient become pregnant during the trial, study medication will be stopped and the patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected until Last Patient Completed and reported in the clinical trial report. Any events thereafter will be reported in the BI Pharmacovigilance database. For further details on pregnancy reporting, refer to Section 5.2.6.2.3.
If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.
Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation, follow-up, and vital status collection as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 764198 and placebo to match BI 764198

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	BI 764198
Pharmaceutical formulation:	Capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	[redacted]
Posology	q.d.
Route of administration:	Oral (p.o.) or, only if needed, nasogastric intubation

Table 4.1.1: 2 Test product 2

Substance:	Placebo to match BI 764198
Pharmaceutical formulation:	Capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Not applicable
Posology	q.d.
Route of administration:	Oral (p.o.) or, only if needed, nasogastric intubation

4.1.2 Selection of doses in the trial and dose modifications

The proposed therapeutic dose in patients hospitalised with COVID-19 is [redacted] once daily; a dose expected to achieve maximal therapeutic benefits. The rationale for the selection of this dose is based on the following considerations (refer to Section 1.2):

[redacted]

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 1:1 ratio at Visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

Study medication will be administered, according to the Flow Chart, by a member of the site staff that is qualified and licensed to administer the study drug. During the treatment period, patients are hospitalised and study medication will be administered once daily after the other visit procedures have been performed. Study drug should be administered after at least 6 hours fasting (no food, water is allowed). Patients should remain fasted for 1.5 hours after study drug administration. Therefore, it is recommended to dose patients after overnight fast, 1.5 hours prior to breakfast meal intake.

For administration of study medication on Day 1, the following guidance may be followed to allow flexibility in the emergency care setting to begin treatment as soon as feasibility after study qualification:

- While 6 hours of fasting is preferred, a minimum of 2 hours is allowed in order to dose an eligible patient as soon as feasible following completion of screening
- It would be preferred to maintain a 12-18 hour interval between the doses
- If the patient is dosed before 18:00, the next dose should be a morning fasted dose the next day (followed by morning dosing thereafter)
- If the patient is dosed before midnight, the next dose should be at about noon the next day (followed by morning dosing thereafter)

The route of administration is oral (p.o.) or, only if needed, nasogastric intubation (refer to investigator site file (ISF) for dissolution preparation and administration instructions). If a patient is on continuous nasogastric feeding, the need to meet caloric requirements should be prioritized and it is recommended that feeding only be interrupted for the duration needed to administer the drug.

Trial treatment may be restarted after a temporary reason for treatment discontinuation. Dose reductions or down-titrations are not allowed.

Patients will be administered one capsule per day from Visit 2 until the visit prior to EOT Visit. Patients may receive treatment with study drug for up to 28 days. In Table 4.1.4: 1, the medication schedule for each treatment group is listed.

Table 4.1.4: 1 Dosage and treatment schedule

	[redacted] or matching placebo capsule
[redacted] treatment group	1 active
Placebo group	1 placebo

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until a snapshot after Last Patient Last Visit Primary Endpoint is taken. This snapshot will be taken after the last patient completes the EOT Visit, and will be used to obtain efficacy results, to guide further development plans for BI 764198. At the timepoint of unblinding of this snapshot, patients and investigators will continue to be blinded and will remain so until after database lock after Last Patient Completed.

The access to the randomisation codes will be kept restricted by the global Randomization Team (gRT) until the last patient has completed their End of Treatment (EOT) visit and all data up until that time point should be entered and cleaned and in preparation for unblinding according to the sponsor's Standard Operating Procedures (SOPs).

To ensure that all members of the Trial Team remain blinded, a trial independent statistician (iSTAT) will be appointed for the DMC. The iSTAT is involved neither in the conduct of the trial(s) the DMC Charter refers to, nor in any other project activities. The iSTAT is not allowed to disclose any unblinded trial data to anyone else other than the DMC members and is also not allowed to disclose any of the proceedings of the closed DMC session to non-DMC members. In order to unblind the data for the DMC, the randomization codes will be submitted to the iSTAT by the gRT according to the sponsor's SOPs.

Refer to Section 4.1.5.2 for rules of breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator

in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from [redacted] to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated clinical research organization (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. Where necessary, a temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (for US sites).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use for each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were administered the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.
Study medication will be administered as an add-on to standard of care (SoC). The SoC will be based on appropriate guidelines in place at the time of treatment and may change during the course of the study as new information becomes available about treating COVID-19.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications listed under the exclusion criteria (Section 3.3.3), are restricted during the trial (refer to ISF for further details).

[redacted]

4.2.2.2 Restrictions on diet and life style

Patients are hospitalised during the treatment period and study drug should be administered after at least 6 hours fasting (no food, water allowed). Patients should remain fasted for 1.5 hours after study drug administration.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.3) and men able to father a child must abstain from male-female sex or must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during hopsitalisation and for a period of at least 7 days after last trial drug intake.

Men (trial participant or partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP.
WOCBP (trial participant or partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Or WOCBP and men able to father a child must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient or, per investigator judgement, relevant to the patient during hospitalisation through 7 days after last trial drug intake. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

For each dose of study medication administered, the date, time, and route will be entered into the electronic case report forms (eCRFs). Any missed doses must be recorded in the eCRFs.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Proportion of patients alive and free of mechanical ventilation at Day 29

Patients who are alive and free of mechanical ventilation at Day 29 is defined as those who have not died at Day 29 and those who do not depend on mechanical ventilation for breathing at Day 29.

5.1.2 Improvements on the WHO Clinical Progression Scale

The condition of each potential participant in the study will be assessed using the WHO Clinical Progression Scale at the time points specified in the Flow Chart, prior to study drug administration as applicable.

WHO Clinical Progression Scale [R20-2002]:

0. Uninfected; no viral RNA detected
1. Asymptomatic; viral RNA detected
2. Symptomatic; independent
3. Symptomatic; assistance needed
4. Hospitalised; no oxygen therapy
5. Hospitalised; oxygen by mask or nasal prongs
6. Hospitalised; oxygen by non-invasive ventilation or high flow
7. Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
8. Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
9. Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO)
10. Death

To be considered for inclusion in the study, patients must be Grade 5 or 6 on this scale.

To be considered a “responder” to treatment with a target candidate, a patient needs to show a response defined by time to an improvement of at least 2 points (from randomisation) on this scale by Day 29. For example, a patient who is Grade 5 (hospitalised; oxygen by mask or nasal prongs) at randomisation but improves to Grade 3 (symptomatic; assistance needed) would be considered to be a responder. A patient with a discharge from hospital or who is considered fit for discharge (a score of 0, 1, or 2 on the Clinical Progression Scale) by Day 29 will also be considered to be a responder.

5.1.3 Other efficacy assessments

The duration of, and time to, ICU admission, the number of ventilator-free and oxygen-free days, the initiation of new ventilation use, and duration of hospitalisation will be derived from source documents. The date of discharge from hospital and/or death will be recorded on the eCRF.

The Clinical Frailty Scale (CFS) [R20-2080] will be determined at the time point indicated on the Flow Chart. The CFS is a means of summarising the overall level of fitness or frailty of an individual. It comprises a 9-point scale with categories ranging from 1 (very fit) to 9 (terminally ill).

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination, including an assessment of presenting symptoms, will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Height and weight will be recorded at screening.

The results must be included in the source documents available at the site.

5.2.2 Vital signs and blood gases

Vital signs and blood gases will be evaluated at the time points specified in the Flow Chart, prior to study drug administration as applicable.

Temperature, pulse rate, blood pressure, and respiratory rate will be assessed. SpO_2 will also be assessed. The results must be included in the source documents available at the site.

Blood gases (oxygen and carbon dioxide), when available as part of routine care, and respiratory support will be recorded. FiO_2 will also be recorded.

Measurements will be taken in line with standard practices for the study centre.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart. All analyses will be performed by a local hospital laboratory, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

It is the responsibility of the investigator to evaluate the local laboratory results. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula will be used to estimate eGFR (R12-1392) using serum creatinine in mg/dL (Conventional Unit)* [R12-1392]:

$$\left(\text{eGFR} = 141 \times \min\left(S_{C_r}/\kappa, 1\right)^{\alpha} \times \max\left(S_{C_r}/\kappa, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female] x } 1.159 \text{ [if Black]}\right),$$

where:
S_{C_r} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{C_r}/κ or 1, and
max indicates the maximum of S_{C_r}/κ or 1

The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

Note * when serum creatinine is reported in SI unit (µmol/L), the value must be multiplied by 0.0113 to obtain the value in Conventional Unit (mg/dL).

Table 5.2.3: 1 Safety laboratory tests

Laboratory Assessments	Parameters
Haematology	Blood Typing (only at screening) Reticulocyte Count (absolute) Complete blood count: Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential Platelet count
Coagulation	D-dimer test Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International Normalised Ratio (INR) Protein C (activity as well as antigen, if available) Plasminogen activator inhibitor-1 (PAI-1) (activity)
Clinical Chemistry	Potassium Sodium Calcium Magnesium Phosphate Alkaline phosphatase Bicarbonate Creatinine Creatine kinase (MB fraction) eGFR (estimated by the CKD-EPI formula) Glucose Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) C-reactive protein (regular test) Ferritin Triglycerides Lactate dehydrogenase (LDH) Troponin (I)

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. ECGs should be performed 0.5-4 hours after drug administration. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for safety evaluation.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record. The aggregate PR, QRS, QT, RR, QTcF, and QTcB interval data, as available, from the local ECG readout will be recorded in the eCRF for safety evaluation.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

Refer to Section 3.3.4.1 for treatment discontinuation criteria regarding QT prolongation.

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the electronic data capture system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate:	Sufficient discomfort to cause interference with usual activity.
Severe:	Incapacitating or causing inability to work or to perform usual activities.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks

of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the follow-up Visit 1: all AEs (non-serious and serious) and all AESIs.
- After follow-up Visit 1 until the individual patient's end of trial: cancers of new histology and exacerbations of existing cancers, all trial treatment related SAEs and all trial treatment related AESIs.
- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

Vital Status Data Collection
Patients who discontinue trial medication prematurely, who agree to be contacted further, but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs (including "Always serious" events, even though they may not have met the criteria of an SAE), AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable

5.4 ASSESSMENT OF BIOMARKER(S)

No exploratory biomarkers are planned. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

5.5 BIOBANKING

Not applicable

5.6 OTHER ASSESSMENTS

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint measurements will be consistent with the recognized standard for patients hospitalised with SARS-CoV-2.

All other measurements performed during this trial are standard measurements and will be performed in order to determine the efficacy and safety in an appropriate way.

Therefore, all measurements performed in this trial are considered by the sponsor to be appropriate.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The visit schedule is to be adhered to as specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1.

If any visits cannot be performed while the patient is hospitalised, subsequent visits should follow the original visit date schedule. Blood sampling for safety laboratories and pregnancy testing is marked with a window of +/- 1 day in the Flow Chart and should be performed accordingly when a daily visit cannot be done.

If any Follow-up (FUP) visits have to be rescheduled, subsequent visits should follow the original visit date schedule.

Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and explanations provided in Section 5. Additional details on procedures at selected visits are provided below.

At all applicable visits vital signs, blood gases and WHO Clinical Progression Scale assessment should be done prior to study drug administration.

6.2.1 Screening and run-in period(s)

Screening Period
The Screening period is defined as the period from the screening visit to randomization (first study drug administration).

All patients (or the patient's legally accepted representative) must sign an Informed Consent consistent with ICH-GCP guidelines and the local legislation prior to any study specific procedures (refer to Section 8.1). Once consented, the patient is considered to be enrolled in the trial and have started screening. The patient should be recorded on the enrolment log and registered in IRT as a screened patient. Patients will be assigned a patient number and enrolment must be recorded in eCRF pages.

Patients who do not meet eligibility criteria should be documented as a screen failure. Re-screening will not be permitted. Procedures can be retested as necessary per investigator judgement to confirm eligibility prior to randomization.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

Medical History:
Medical history includes estimated date and time of first SARS-CoV-2 infection symptoms as well as symptom details.

Baseline Conditions:
Baseline conditions include number of co-morbidities (e.g., respiratory, cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, and renal).

6.2.2 Treatment period(s)

The treatment period starts with Visit 2 (Day 1, randomization) and ends with the EOT visit (possible Day 2 through Day 29). Patients will remain hospitalised during the treatment period and daily protocol visits will be conducted to complete procedures according the Flow Chart. Patients may receive treatment with study drug for up to 28 days, however if a patient is well enough to be discharged, then study drug may be stopped before the maximum treatment duration (i.e. 28 days).

EOT visit should be completed the day after the last dose of study drug is administered for all patients regardless of discharge status. EOT visit is expected to align with day of discharge, unless it is planned for a patient to remain hospitalised after treatment with study drug is stopped. EOT visit should occur no later than Day 29.

6.2.3 Follow-up period and trial completion

For all randomised patients, termination of trial medication and trial completion must be recorded on the corresponding eCRFs.

Applicable FUP visits and EOS visits will be conducted remotely by a phone contact for all patients that have completed treatment, EOT visit, and discharge. Each of these visits includes vital status.

FUP visits should be conducted as follows:

- FUP 1 should be performed 4 days after EOT visit for all patients.
- FUP 2 and FUP 3 which correspond to study Day 15 and Day 29 after start of therapy, should be performed *if the time point is applicable after drug discontinuation.* FUP 2 and FUP 3 visits should not be conducted within +/- 2 days of EOT or FUP 1.
- FUP 4 and EOS which correspond to study Day 60 and Day 90 will be performed for all patients.

If a patient remains hospitalized after EOT visit, applicable FUP visits and the EOS visit will be conducted in hospital until discharge and thereafter by telephone.

If a patient withdraws participation from the study, it may be agreed to collect vital status per the remaining originally planned visit schedule according to the Flow Chart.

Trial completion is defined as patients completing the FUP and EOS visits according to the Flow Chart.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a randomized, double-blind, placebo-controlled, parallel group trial with an anticipated treatment period of 4 week and a follow up period of up to 90 days from randomisation. BI 764198 will be compared to placebo in hospitalised patients at risk of developing ARDS or diagnosed with ARDS secondary to COVID-19 infection.

The primary endpoint is patients alive and free of mechanical ventilation at Day 29 and will be analysed using a logistic regression model to compare the absolute difference in proportions of patients alive and free of mechanical ventilation at Day 29 with BI 764198 and placebo. Detailed specifications are provided in Section 7.2.2.

The primary endpoint and secondary endpoints are defined in Section 2.1.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No formal testing will be performed and hence no null and alternative hypotheses are defined since this is an exploratory study.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The efficacy analysis will be performed in all randomized patients who documented to have received at least one dose of trial medication. This set will be called Full Analysis Set (FAS).

Patients will be analysed as randomised, without regard to any treatment changes. The intent-to-treat (ITT) principle will be applied to the randomized set including all observed data in the primary analysis regardless of treatment discontinuation. Baseline refers to the last measurement prior to randomisation.

7.2.2 Primary endpoint analyses

To evaluate the difference in proportions of patients alive and free of mechanical ventilation at Day 29 with BI 764198 and placebo, the analysis of the primary endpoint will be performed with a logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and duration of symptoms before hospitalisation. The point estimates, standard errors and confidence intervals for the difference in proportions will be derived based on the estimates from the logistic regression model. Patients who terminate the study medication prematurely will be followed and the events which occur after premature discontinuation of medication and before the time point of interest will be included in the analysis using Full Analysis Set (FAS). Patients will be analysed according to their assessed severity grade on the WHO Clinical Progression Scale recorded at baseline (last assessment prior to administration of study drug).

A sensitivity analysis will be conducted with a logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, D-dimer at baseline, and duration of symptoms before hospitalisation with patients who don't miss D-dimer at baseline. Details will be defined in TSAP.

Subgroup analysis will be performed using descriptive statistics/figures by subgroup e.g., age category, race, baseline severity grade, categorized duration of symptoms before hospitalisation, etc. Details will be defined in TSAP.

7.2.3 Secondary endpoint analyses

Analysis of patients alive and discharged free of oxygen at Day 29 and mortality at Day 15, 29, 60, and 90 will be conducted using the same model used for the primary endpoint, to assess the difference in proportions of patients with BI 764198 and placebo .

The difference of ventilator free days between BI 764198 and placebo group will be analysed using an ANCOVA model including treatment, age, creatinine at baseline, and duration of symptoms before hospitalisation.

Time to response, defined as clinical improvement of at least 2 points (from randomisation) on the World Health Organization Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (a score of 0, 1, 2, or 3 on the Clinical Progression Scale), whichever comes first, by Day 29, will be analysed using a Cox proportional-hazards model including covariates of treatment, age, creatinine at baseline, and duration of symptoms before hospitalisation will be performed. Hazard ratio and Kaplan-Meier curves will be provided. Patients who do not respond will be censored at Day 29.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. [redacted]

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.2.6 Interim Analyses

No interim analysis is planned, but a Data Monitoring Committee (DMC) will be in place with tasks as described in Section 8.7.

7.3 HANDLING OF MISSING DATA

All attempt will be made to collect all data per protocol.

For patients who miss Clinical Progression Scales, imputation will be performed using data from other sources if available, e.g., oxygen use, ventilation use, etc.

For patients who miss start date and/or end data of hospitalisation, ventilator use and oxygen use, data will be imputed based on available Clinical Progression Scales. If a patient dies while hospitalised, the number of days of hospitalisation will be imputed as 28 days.

Further details will be specified in the TSAP.

7.4 RANDOMISATION

Patients will be randomised in blocks at a 1:1 ratio to double-blind treatment stratified by baseline disease severity based on scores in the Clinical Progression Scale (5 vs. 6). Approximately equal numbers of patients will be randomised to each treatment group.

BI will arrange for the randomisation, packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history

- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site

as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection and future use of biological samples and clinical data, in particular

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The **"Last Patient Last Visit Primary Endpoint"** is defined as the date at which the last patient in the whole trial is examined for the purpose of final collection of data for the primary endpoint.
The **"Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate safety data and efficacy data. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

An IRT vendor will be used in this trial. Details will be provided in the IRT Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R20-2002 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infectious Diseases, Published Online June 12, 2020, doi: 10.1016/S1473-3099(20)30483-7; 2020.

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9.2 UNPUBLISHED REFERENCES

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c32296993 Investigator's Brochure BI 764198 for the treatment of COVID-19 related ARDS.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		08 Jan 2021
EudraCT number **EU number**		2020-003211-96
BI Trial number		1434-0009
BI Investigational Medicinal Product		BI 764198
Title of protocol		BI 764198 effic**ac**y and safe**t**y in prevent**ion**/progression of ARDS and ARDS-related complications sec**on**dary to **COVID-19 (ACTION ON COVID-19)**
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Synopsis, Flow Chart, 3.1, 3.3.2,
Description of change		Addition of point-of-care SARS-CoV-2 testing.
Rationale for change		To allow use of point-of-care testing to evaluate inclusion criterion 2.
Section to be changed		Flow Chart
Description of change		Specified allowed time window for screening ECG, Visit 2 safety laboratories, and physical examinations. Addition to footnote "f" to collect oxygen therapy end date during Follow-up, if unknown at discharge. Clarified IRT randomisation call timing. Added footnote "i" to cover potential dosing on EOT Visit, if treatment is less than 28 days.
Rationale for change		To add further instructions to Flow Chart procedures.
Section to be changed		Flow Chart, 5.2.4
Description of change		[redacted]
[redacted]		[redacted]

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.3
Description of change		Addition of paragraph to guide patient selection and timing of trial entry.
Rationale for change		To message on selection of patients that will help better evaluate the study drug and trial endpoints.
Section to be changed		3.3.3
Description of change		Removed “renal” from exclusion criterion 11. Rephrased exclusion criterion 4.
Rationale for change		To eliminate redundancy, as already covered by exclusion criterion 6. To clarify exclusion criterion 4.
Section to be changed		3.3.3, 3.3.4.1, 4.2.2.1: 1, 5.2.4
Description of change		[redacted]
Rationale for change		
Section to be changed		4.1.4
Description of change		Addition of guidance for the administration of the first dose of study drug and continuous nasogastric feeding.
Rationale for change		To provide study drug administration instructions around scenarios that may arise during emergency care.
Section to be changed		4.2.2.1, 4.2.2.1: 1
Description of change		[redacted]

		[redacted]
Rationale for change		[redacted]
Section to be changed		5.1.2, 6.2
Description of change		Specified that WHO Clinical Progression Scale should be performed prior to dosing.
Rationale for change		To clarify time point of assessment.
Section to be changed		5.2.2, 6.2, 6.2.2
Description of change		Updated text for requirement of vital signs and blood gases to be done prior to dosing and removed text stating that dosing must be last.
Rationale for change		To remove unnecessary ordering of procedures for an inpatient study and clarify that vital signs and blood gases, if applicable, are to be assessed for eCRF data entry once pre-dose.
Section to be changed		5.2.3, 9.1
Description of change		Addition of CKD-EPI formula and the associated reference
Rationale for change		Formula needed for site calculation.
Section to be changed		5.2.3: 1
Description of change		Clarified safety laboratory parameters.
Rationale for change		To provide sites a clearer description of local laboratory assessments.
Section to be changed		5.2.6.2.2
Description of change		Addition of “The investigator must report SAEs (including “Always serious” events, even though they may not have met the criteria of an SAE)…”
Rationale for change		To clarify SAE reporting requirements for “Always serious” events.
Section to be changed		7.2.2
Description of change		Addition of text to define that patients will be analysed according to their assessed severity grade on the WHO Clinical Progression Scale recorded at baseline. Addition of race as a subgroup analysis.
Rationale for change		To specify analysis rules and provide a rationale for collection of race data in eCRF.

Section to be changed		7.2.3
Description of change		Removed further endpoint mistakenly placed in this section.
Rationale for change		To correct the section to contain secondary endpoints only.
Section to be changed		7.5, 3.3, Synopsis
Description of change		Updated sample size and probabilities for decision making
Rationale for change		To increase sample size and give additional information on the rationale used for the calculation.
Section to be changed		Synopsis, Flow Chart, 1.1, 1.4.1, 2.2.2, 3.3, 3.3.3, 4.1.4
Description of change		Minor formatting and editorial corrections.
Rationale for change		To improve readability.

APPROVAL / SIGNATURE PAGE

Document Number: c32418694 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-revision-01

Title: BI 764198 efficacy and safety in prevention/progression of ARDS and ARDS-related complications secondary to COVID-19 (ACTION ON COVID-19)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	11 Jan 2021 09:49 CET
Author-Trial Statistician		11 Jan 2021 15:18 CET
Approval-Team Member Medicine		11 Jan 2021 15:23 CET
Author-Clinical Trial Leader		11 Jan 2021 18:04 CET
Verification-Paper Signature Completion		11 Jan 2021 19:08 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed