Clinical Trial Protocol

	Document Number: **c33563257-02**
EudraCT No. **EU Trial No.**	2020-005588-29
BI Trial No.	1487-0001
BI Investigational Medicinal Product(s)	BI 767551 (formerly EX 14870 or DZIF-10c)
Title	A Phase II/III seamless, randomised, double-blind, placebo-controlled, parallel-group, group-sequential study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.
Lay Title	A study to test BI 767551 in people with mild to moderate symptoms of COVID-19.
Clinical Phase	II/III
Clinical Trial Leader	[redacted] Phone: [redacted]
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Current Version and Date	Version 2.0 Date: 20 April 2021
Original Protocol Date	11 Feb 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim (BI)
Original Protocol date	11 Feb 2021
Revision date	20 April 2021
BI trial number	1487-0001
Title of trial	A Phase II/III seamless, randomised, double-blind, placebo-controlled, parallel-group, group-sequential study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.
Coordinating Investigator	[redacted] Phone: [redacted]; Fax: [redacted]
Trial site(s)	Multi-centre trial conducted in approximately 20 countries.
Clinical Phase	II/III
Trial rationale	This study will be conducted in SARS-CoV-2 positive symptomatic, non-hospitalized patients. The trial will be conducted in two parts. Phase II part will assess viral load measures of SARS-CoV-2 RNA by nasopharyngeal (NP) swab. The Phase II part will confirm the neutralizing mode of action (MoA) of BI 767551 which in combination with safety data may support progression to the Phase III part. The Phase III part is designed to include the lowest efficacious and safe dose group from Phase II and will assess clinical outcomes. The patients will be followed for a 90 day observation period to assess any long-term outcomes from patients.
Trial objective(s)	To evaluate the concept of pharmacological activity of BI 767551 in non-hospitalized patients with mild to moderate COVID-19 symptoms and to identify an efficacious and safe dose regimen from Phase II part to take into the Phase III part. To evaluate the efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.
Trial endpoints	Exploratory Phase II, as follows: o **Primary endpoint:** o Time-weighted change from baseline in viral shedding in nasopharyngeal swabs by RT-qPCR over 8 days o **Secondary endpoints:**

	○ Time-weighted change from baseline in viral shedding in nasopharyngeal (NP) swabs by RT-qPCR over 29 days ○ Loss of detection of SARS-CoV-2 RNA by NP swab at Days 4, 8, 15, 22 and 29 Confirmatory Phase III, as follows: ○ **Primary endpoint:** ○ Hospitalization or death from any cause by Day 29 ○ **Secondary endpoints:** ○ Time to death over 29 days ○ Hospitalization by Day 29 ○ Hypoxia or hospitalization or death from any cause by Day 29 ○ Hypoxia by Day 29 ○ Time to clinical improvement over 29 days ○ Time to loss of detection of SARS-CoV-2 RNA by site collected nasopharyngeal (NP) swabs over 29 days
Trial design	**Exploratory Phase II:** Exploratory, randomised, double-blind, placebo controlled, double-dummy, Phase II, parallel group design comparing different doses and modes of administration (i.v and inhaled) of BI 767551 to placebo. At the start of the trial, patients will be randomised in a 2:2:2:1 ratio to receive a single dose of either Placebo i.v. + Placebo inhaled, BI 767551 i.v. 10 mg/kg dose + Placebo inhaled, BI 767551 i.v. 40 mg/kg + Placebo inhaled, or Placebo i.v. + BI 767551 250 mg inhaled, respectively, followed by 90 days follow up. Following Clinical Trial Protocol (CTP) amendment 1, it is planned to include patients in an equal allocation ratio to each treatment arm. Therefore, patients will be randomised in a 1:1:1:2 ratio to receive a single dose of either Placebo i.v. + Placebo inhaled, BI 767551 i.v. 10 mg/kg dose + Placebo inhaled, BI 767551 i.v. 40 mg/kg + Placebo inhaled, or Placebo i.v. + BI 767551 250 mg inhaled, respectively, once approximately 112 patients have been randomised using the initial randomisation ratio. When approximately 112 patients have been randomised, the randomisation scheme will be implemented in sites or countries with approval for CTP amendment 1. At the time of implementation of the revised scheme, sites or countries may be placed on hold for recruitment until approval of CTP amendment 1 is granted. BI will conduct unblinded interim analysis after patients have completed one week of follow-up. The results from this analysis will also be shared with a Data Monitoring Committee (DMC) for review of safety and efficacy data and to provide recommendation how to move forward with the trial. Data from patients included in the Phase II part of the trial will not be included in the confirmatory analyses.

	Confirmatory Phase III: Confirmatory, randomised, double-blind, placebo-controlled, parallel group, Phase III comparing BI 767551 to placebo. Patients will be randomised in a 1:1 ratio to receive a single i.v. or inhaled dose of study treatment or placebo followed for 90 days of follow up. In addition, randomisation will be stratified by "high" versus "low" risk of progresson to COVID-19 to ensure equal distribution between treatment arms. The study will have a group-sequential design including two interim analyses that will be performed by the DMC. These analyses encompass futility and efficacy. Only the DMC will have access to unblinded data during this portion of the study.
Total number of patients randomised	Phase II: approximately 200 patients to be randomised. Phase III: approximately 1300 patients to be randomised.
Number of patients per treatment group	**Phase II approximately**: • Placebo i.v. + Placebo inhaled: 50 patients • BI 767551 i.v. 10 mg/kg + Placebo inhaled: 50 patients • BI 767551 i.v. 40 mg/kg + Placebo inhaled: 50 patients • Placebo i.v. + BI 767551 inhaled: 50 patients **Phase III approximately:** • BI 767551 i.v. 700 mg or 2800 mg: 650 patients or • BI 76551 250 mg inhaled and • Placebo: 650 patients
Diagnosis	COVID-19 detected by SARS-CoV-2 positive test confirmed by RT-qPCR or antigen test.
Main inclusion and exclusion criteria	Eligibility criteria for Phases II and III are identical. Patients participating in Phase II are not eligible for Phase III. **Main criteria for inclusion:** 1. Age ≥ 18 years old, males and females. 2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. 3. Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (NP or nasal swab or saliva) collected no more than 72 hours prior to start of treatment. 4. Patients experienced mild to moderate COVID-19-related symptoms or measured fever for no more than 5 days prior to

	start of treatment where symptoms are defined by fever, feeling feverish, fatigue, cough, shortness of breath at rest or during activity, sore throat, body pain or muscle pain/ aches, chills, headache, nasal obstruction or congestion, loss of smell or taste, nausea, diarrhea, vomiting, or dysgeusia. 5. One or more of the following COVID-19-related signs/symptoms present on day of start of treatment: fever, feeling feverish, fatigue, cough, shortness of breath at rest or during activity, sore throat, body pain or muscle pain/ aches, chills, headache, nasal obstruction or congestion, loss of smell or taste, nausea, diarrhea, vomiting, or dysgeusia. **Main criteria for exclusion:** 1. Severe or critical COVID-19 including at least one of: • Oxygen saturation (SpO2) ≤ 93% on room air or on their usual level of oxygen supplementation in case of chronic oxygen use • Ratio of arterial oxygen partial pressure (PaO2 in millimeters of mercury) to fractional inspired oxygen (FiO2) < 300 (in case arterial blood sample was taken) • Respiratory rate ≥ 30/min or heart rate ≥ 125/min • History of hospitalization for COVID-19 • Current or imminent need of hospitalization or immediate medical attention. Does not include patients hospitalized for isolation only. 2. Receipt of intraveneous immunoglobulin (IVIG) within 12 weeks prior to Visit 2. 3. Receipt of COVID-19 convalescent plasma or SARS-CoV-2 monoclonal antibody treatment at <u>any</u> time prior to Visit 2. 4. Receipt of SARS-CoV-2 vaccine at any time prior to Visit 2. 5. Receipt of an investigational product for COVID-19 within 5 half-lives prior to Visit 2. 6. Body weight of less than 40 kg.
Test product(s)	BI 767551
Dose	**Phase II :** 1. Single 10 mg/kg or 40 mg/kg i.v. infusion 2. Single 250 mg inhalation (nebulized)

	Phase III: 1. Single 700 mg or 2800 mg i.v. infusion or Single 250 mg inhalation (nebulized)
Mode of administration	**Phase II:** Weight based i.v or fixed dose inhalation (nebulized) **Phase III:** Fixed dose i.v. or inhalation
Comparator product(s)	Placebo
Dose	Not applicable
Mode of administration	**Phase II:** Intravenous infusion (i.v.) / inhalation (nebulized) **Phase III:** Intravenous infusion (i.v.) or inhalation (nebulized)
Duration of treatment	Single dose followed by 90 days follow-up
Statistical methods	**Phase II – Exploratory:** All analyses will be exploratory. An analysis of covariance (ANCOVA) model with baseline viral load as covariate will be used to analyse the primary endpoint of the Phase II part. **Phase III – Confirmatory:** The cumulative proportion of patients who were hospitalized or who died over 29 days will be estimated for each randomised group using Kaplan-Meier methods to take account of losses to follow-up. The difference between randomised groups in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. To account for the planned interim analyses, the local nominal alpha-level will follow an O`Brien and Fleming spending function to preserve the global alpha of 0.025 (one-sided). One sided p-values will be derived from the z-test. Two unblinded interim analyses are planned once 33% and 67% of patients have been followed up over 29 days, respectively. The futility boundary is defined as a relative reduction of 5% at the first interim analysis and as a relative reduction of 10% at the second one. Efficacy boundaries are derived using O'Brien-Fleming like boundaries. The interim analyses in this phase of the trial will be performed by the DMC and only the DMC will get access to unblinded data. Safety will be assessed based on adverse events, laboratory parameters and vital signs. Only descriptive analyses are planned.

FLOW CHART

Trial Periods	Screening	Randomisation	Follow-up								Prematurely discontinued (Before Day 29)	Prematurely discontinued (After Day 29)
Visit	**1**[1]	**2**	**3**	**4**[3]	**5**	**6**[4]	**7**	**8**[2]	**9**	**EOS**		
Visit Location: C=in clinic visit; R=remote visit[2]	**C**	**C**	**R**	**C**	**C**	**R**	**C**	**C/R**	**C**	**C**	**C**	**C**
Week			**Wk 1**			**Wk 2**		**Wk 3**	**Wk 4**	**Wk 12**		
Days	**0**	**1**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**91**		
Time window for visits	**-2 to 1 days**		**±1 day**			**±2 days**		**±4 days**		**+14 days**		
Informed consent	X											
Demographics	X											
Review of in-/exclusion criteria[5]	X	X[5]										
SARS-CoV-2 test[6]	X											
Medical history[5]	X	X[5]										
Smoking status	X											
All AEs/SAEs/AESIs[5,7]	X	X[5]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy[5]	X	X[5]	X	X	X	X	X	X	X	X	X	X
COVID-19 symptom screen	X	X[5]										
11-point WHO Clinical Progression Scale (see Section 5.1.2) [5,8]	X	X[5]	X	X	X		X	X	X	X	X	X
Collect/update secondary contacts[20]		X	X	X	X		X	X	X	X		
Vital signs[9] (refer to Section 5.2.2)	X	X		X	X		X		X	X	X	X
Physical Exam (refer to Section 5.2.1) [5,10]	X	X[5]			X[21]		X[21]		X	X	X	X
Weight		X							X	X	X	X
Height	X											
Participant completed study diary including temperature and oxygen saturation[11]		Days 1-29										
Study diary reminder[11]		X	X	X	X	X	X	X	X			
Staff review of patient diary[12]			X	X	X		X	X	X		X	
Review by e.g. phone and retrieval of study diary									X		X	
Staff-collected nasopharyngeal swab [13]		X		X	X		X	X	X		X	

FLOW CHART (continued)

Trial Periods	**Screening**	**Randomisation**	**Follow-up**								**Prematurely discontinued (Before Day 29)**	**Prematurely discontinued (After Day 29)**
Visit	**1[1]**	**2**	**3**	**4[3]**	**5**	**6[4]**	**7**	**8[2]**	**9**	**EOS**		
Visit Location: C=in clinic visit; R=remote visit[2]	**C**	**C**	**R**	**C**	**C**	**R**	**C**	**C/R**	**C**	**C**	**C**	**C**
Week		**Wk 1**				**Wk 2**		**Wk 3**	**Wk 4**	**Wk 12**		
Days	**0**	**1**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**91**		
Time window for visits	**-2 to 1[1] days**		**±1 day**			**±2 days**		**±4 day**		**+14 day**		
[redacted]												
SARS-CoV-2 Antibody Serology		X										
Haematology[16]		X			X		X		X	X	X	X
Chemistry[16]		X			X		X		X	X	X	X
Urinalysis[16]		X			X		X		X	X	X	X
Coagulation and Inflammation markers[16]		X			X		X		X	X	X	X
Pregnancy testing[17]	X[17]	X[17]			X[U, (S)]		X[U, (S)]		X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]
IRT call[18]	X	X										
Prepare and administer trial drugs		X										
Completion of patient participation[19]										X		X
Vital status data[19]										X	X	X

Wk = Week; EOS = End of Study; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

1 Visit 1 and Visit 2 can be on the same day if required (see also footnote 5). Initiation of randomised treatment at Visit 2 can only begin if the patient meets the criteria for Initiation of Treatment.

2 For any given day of an in clinic visit (except Visit 2), if the patient cannot return to the clinic, the visit may occur remotely as a home-based visit (defined as home visits by healthcare nurses or site staff), or by phone. Visit 2 must be completed in clinic. For visits occurring remotely, every effort should be made to

complete as home-based visit (by a home healthcare nurse or site staff). Remote visits can be completed as a home-based visit or by phone.

3 Visit 4 is a clinic visit for Phase II only. Remote visit for Phase III.

4 Visit 6 must be completed at least 2 days after Visit 5.

5 The procedures do not need to be be repeated/performed when V1 and V2 are performed on the same day.

6 SARS-CoV-2 laboratory confirmation (antigen or nucleic acid) as a pre-requisite before or at screening (collection within 72 hrs of treatment). The test can be completed via local lab or rapid Point-of-Care device. Result confirmation must be documented and filed in patient records.

7 After the individual patient's end of the trial the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.2.

8 For remote visits, 11-point WHO Clinical Progression Scale (Section 5.1.2) must be collected by home healthcare nurse or site staff.

9 Vital signs measurement shall include BP measurement, body temperature, respiratory rate, pulse rate and resting peripheral oxygen saturation. At screening only respiratory rate, pulse rate and resting peripheral oxygen saturation should be taken to confirm eligibility. Confirmation of PaO2/FiO2 ratio <300 only required in case arterial blood sample was previously taken. At Visit 2, measurements of vital signs should be taken pre-dose, at end of the infusion and 2 hours post study drug administration and precede blood sampling (see Section 5.2.2).

10 Complete Physical exam at Visit 1. Complete physical exam includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Symptom directed exam at all clinic visits after screening.

11 At Visit 2 Site staff will provide a thermometer and pulse oximeter to the participant as well as present and review the study diary. Participants will complete the diary with site staff prior to administration of study drug. On subsequent days with a clinic or remote visit, patients will be reminded to record their temperature, oxygen saturation, and complete all entries every day (preferably the same time every day). Participants will be reminded to bring their diary with them to the next clinic visit. Clinic visit day entry may also be completed at the clinic.

12 At clinic visits and remote visits if completed by home healthcare nurse or site staff. If visit is completed by phone, patient will be reminded to complete diary entry for that day. Study staff will enter the participant's answers on the study diary into the electronic case report forms (eCRFs) following each visit. In case of remote visits, every effort should be made to retrieve the study diary answers (or a copy of the answers if paper) for entry into the eCRFs, otherwise entery into the eCRF will be completed at the next clinic visit.

13 If V2 occurs on the same day as V1 and the sample collected for screening was NP or nasal, the V2 NP sample should preferably be taken from the other nostril. In this case care must be taken to ensure one (1) sample is taken at screening for eligibility and the second sample is taken as part of V2 procedures. On Day 1, NP [redacted] swabs should be collected prior to the intravenous and inhaled dose of investigational agent. For home-based visits, the swab will be collected by the home healthcare nurse or site staff.

14 [redacted]

15 [redacted]

16 Tests at Visit 2 and subsequent trial visits will be performed centrally. If Visit 1 and Visit 2 done on the same day, samples should be collected after eligibility has been confirmed. Blood samples will be collected prior to administration of study drug.

17 Women of childbearing potential only. Negative urine pregnancy test must be confirmed prior to study drug administration. Serum test required at Visit 2 together with blood sample collection. U-urine pregnancy test performed at all visits after Visit 2 as indicated in the Flow Chart. (S) - in case of a positive urine pregnancy

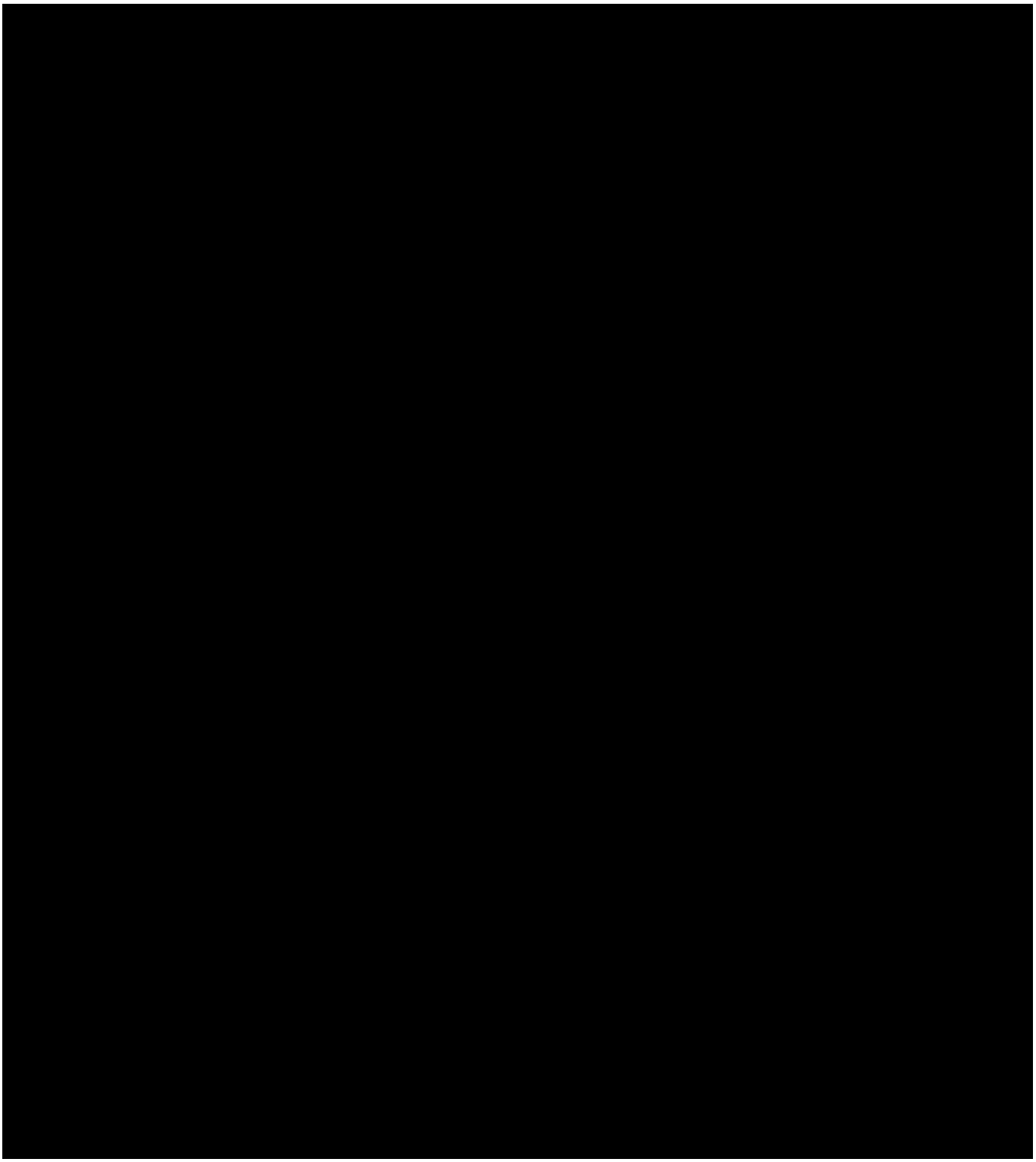
test, a serum pregnancy test will be done. In case of remote visits, clinical site may provide subjects with at-home urine pregnancy test kits (may be sponsor-provided)

18 Phase II: weight needed in IRT at randomization for body-weight based dosing.

19 Should a patient prematurely discontinue before their scheduled EOS visit, every effort should be made to keep the patient in the trial and complete all of the remaining study visits if possible. At the very least, vital status and information on whether the patient has been hospitalized shall be collected at planned completion date of each individual patient, please see Section 3.3.4. Any locally approved way of obtaining vital status information is accepted.

20 Details can be entered in site source not CRF

21 Physical examination at Visit 5 and 7 performed only if clinic visit



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ABBREVIATIONS AND DEFINITIONS

ADA	Anti Drug Antibody
ADE	Antibody-dependent enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CI	Confidence Interval
[redacted]	
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DAIDS	Division of AIDS
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ELF	Epithelial Lining Fluid

EoS	End of Study
ePRO	Electronic Patient Reported Outcome
EoT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HA	Health Authority
i.v.	Intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVIG	Intravenous immunoglobulin
LPLT	Last patient last treatment
LPLV	Last patient last visit
LPLV PE	Last Patient Last Visit Primary Endpoint
MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mode of action
[redacted]	
NIAID	National Institutes of Allergy and Infectious Diseases
NP	Nasopharyngeal
OP	Oropharyngeal
OPU	Operative Unit

[redacted]

PD	Pharmacodynamics
PFU	Plaque forming units
PK	Pharmacokinetics
RA	Regulatory Authority
RBD	Receptor Binding Domain
REP	Residual effect period
RM	Risk Management
RT-qPCR	Quantitative Reverse Transcription Polymerase chain reaction
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions

[redacted]

TSAP	Trial Statistical Analysis Plan

[redacted]

ULN	Upper Level of Normal
VoC	Variant of Concern
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

After emerging at the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread across the globe. By January 2021, over 99 million confirmed cases of SARS-CoV-2 infection and more than 2.1 million coronavirus disease 2019 (COVID-19) associated deaths have been reported (WHO Coronavirus Disease Dashboard; https://covid19.who.int). The development of safe and effective options for treatment and prevention of SARS-CoV-2 infection is therefore of urgent concern for global public health.

SARS-CoV-2 is an enveloped positive-sense single-stranded ribonucleic acid RNA Betacoronavirus of the subgenus Sarbecovirus. It is related to SARS-CoV, the causative agent of the 2002/2003 SARS outbreak, and to coronaviruses circulating in bat populations. Although a definitive animal reservoir has not yet been identified, SARS-CoV-2 is likely of zoonotic origin[R20-4053].

Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets and aerosols[R20-4052]. It is notable for the occurrence of superspreading events, in which a limited number of index cases results in the infection of a large number of contacts. Importantly, asymptomatic and presymptomatic individuals shedding the virus at high concentrations create a challenge to identify origins of transmission chains[R20-4051]. In addition to the respiratory route, transmission of SARS-CoV-2 by fomites has been suggested as plausible[R20-4050].

Following exposure, symptoms typically manifest after a median of 5-6 days, although this period can range from 1 to more than 14 days. In addition, a sizeable fraction of infected individuals appears not to develop clinically apparent signs. A majority of infections (approximately 80%) results in mild to moderately severe courses of disease that are characterized by symptoms of upper respiratory tract infections (e.g., cough, fever, rhinorrhea, coarse throat, or disturbances of smell or taste). More severe cases of COVID-19 primarily demonstrate signs of lower respiratory tract infection (e.g., dyspnea, pneumonia) and can result in respiratory failure with a need for mechanical ventilation or extracorporeal oxygenation of the blood. Beyond respiratory symptoms, an increasing number of additional manifestations have been associated with SARS-CoV-2 infection, including thromboembolic events, cardiac or systemic inflammation, and renal failure[P20-10977].

A number of investigational and approved drugs that were developed for the use in other indications are under evaluation for their potential use in the treatment of SARS-CoV-2 infection. For example, remdesivir is a nucleoside analogue prodrug that acts as an inhibitor of viral RNA polymerase following intracellular biotransformation. Based on its demonstrated *in vitro* activity against human coronaviruses, including SARS-CoV-2, clinical investigation of remdesivir for SARS-CoV-2 infection was rapidly initiated. In hospitalized adults with COVID-19, administration of remdesivir resulted in a significantly reduced time to recovery compared to

placebo[R20-3802]. Based on these observations, remdesivir has received full or conditional approval (e.g., by the FDA and EMA) for use in SARS-CoV-2 infected individuals requiring supplemental oxygen therapy. However, remdesivir requires a 5-to-10-day intravenous treatment course and its efficacy in prevention of SARS-CoV-2 infection has not been demonstrated yet. In addition to antiviral compounds, agents aimed at modulating immune-mediated organ injury are under investigation for their efficacy in COVID-19. Importantly, in hospitalized patients with COVID-19 requiring oxygen therapy, the anti-inflammatory corticosteroid dexamethasone has resulted in reduced 28-day mortality[R20-4049]. However, no effects in mortality were noted in individuals not receiving respiratory support [R20-4049].

As of November 21, 2020, two neutralizing antibody (nAb) products (bamlanivimab [redacted], casirivimab and imdevimab [redacted]) received EUA for treatment of mild-to-moderate COVID-19 in patients who are 12 years of age or older weighing at least 40 kg and who are at high risk for progressing to severe COVID-19 and/or hospitalization who are not yet hospitalized or on supplementary oxygen for COVID-19. This includes those who are 65 years or age or older or who have certain chronic medical conditions. The current EUA-issued monoclonal antibodies are administered as a single dose IV infusion. Results from the interim analyses of these studies in outpatients showed that bamlanivimab (LY-CoV555) reduced the patients' symptoms at earlier timepoints during treatment (Day 3) when compared to placebo with no difference between the three dose arms. In addition, the frequency of hospitalization was reduced for all treatment arms (1.6%) versus 6.3% in the placebo group. The reduction in hospitalization was most promounced in the high-risk subgroups approved as part of the EUA (4.2% in LY-CoV555 group compared to 14.2% in the placebo group) [R20-4045]

Similar effects were observed in REGN-COV2 study in ambulatory patients. The interim analysis from 275 patients showed an enhanced clearance of the virus in patients who were seronegative or those with with high viral loads (>10^6 copies/ml) at baseline. A numerical difference in the number of medically attended visits were also observed for all treatment arms (3%) when compared to placebo (6%). This relative reduction of 49% was increased to 59% when the subgroup of seronegative patients was analysed. [R21-0329]

These interim reports suggest that treatment with neutralizing antibodies against SARS-CoV-2 can provide an effective antiviral therapy to enhance viral clearance and lead to improved clincial outcomes or prevention of hospitalization particularly in those patients at highest risk. These studies will complete the Phase III portions and final readouts should provide additional information on the benefits of this therapy. These nAbs are also under evaluation in a subset of hospitalized patients and in post-exposure prevention settings.

As of the end of 2020, several SARS-CoV-2 variants began to emerge with unusually large numbers of mutations which may impact the transmission rates and effectiveness of therapies such as neutralizing antibodies and vaccines. Investigation are ongoing to understand the virologic, epidemiologic and clinical impact of these rapidly evolving variants of SARS-CoV-2. At the time of the finalization of the protocol, in vitro assessments of the impact of the most prevalent variants (B.1.1.7 (UK), B.1.351 and P.1 (Brazil)) on the effectiveness of BI 767551

was ongoing in the Sponsor's laboratories and in collaboration with academic centers as well as with National Institutes of Health and National Institutes of Allergy and Infectious Diseases (NIAID).

SARS-CoV-2 infection of target cells occurs through the interaction of the receptor-binding domain (RBD) of the homotrimeric spike (S) protein on the viral surface with its host target cell receptor ACE2 [R20-3952, R20-3955]. Moreover, SARS-CoV-2-infected cells can be identified through the expression on the SARS-CoV-2 S protein on the cellular surface [R20-4048]. Thus, strategies that target the S protein are of potential interest both for the treatment and prevention of SARS-CoV-2 infection.

1.2 DRUG PROFILE

BI 767551 is a potent human SARS-CoV-2-neutralizing antibody that was identified from a blood sample of a COVID-19-convalescent patient obtained 35 days after diagnosis of infection [R20-2985]. To isolate SARS-CoV-2-neutralizing antibodies from this and 11 additional patients, single memory B cells reactive to the SARS-CoV-2 spike protein were sorted using flow cytometry. Antibody heavy and light chain sequences were subsequently amplified from individually lysed cells using specific reverse transcription polymerase chain reaction (RT-qPCR) and sequenced, facilitating the recombinant production of exact antibody replicates[R20-4047]. Using this approach, the human monoclonal antibody HbnC3t1p1_F4 was identified and later modified by eliminating the heavy chain C-terminal lysine to reduce potential charge heterogeneity, resulting in antibody BI 767551. BI 767551 is a monoclonal antibody of the IgG1 kappa isotype with low somatic hypermutation compared to its germline sequence (% germline nucleotide identity of 93.2% and 96.1% for the heavy chain and light chain variable genes, respectively) [R20-2985].

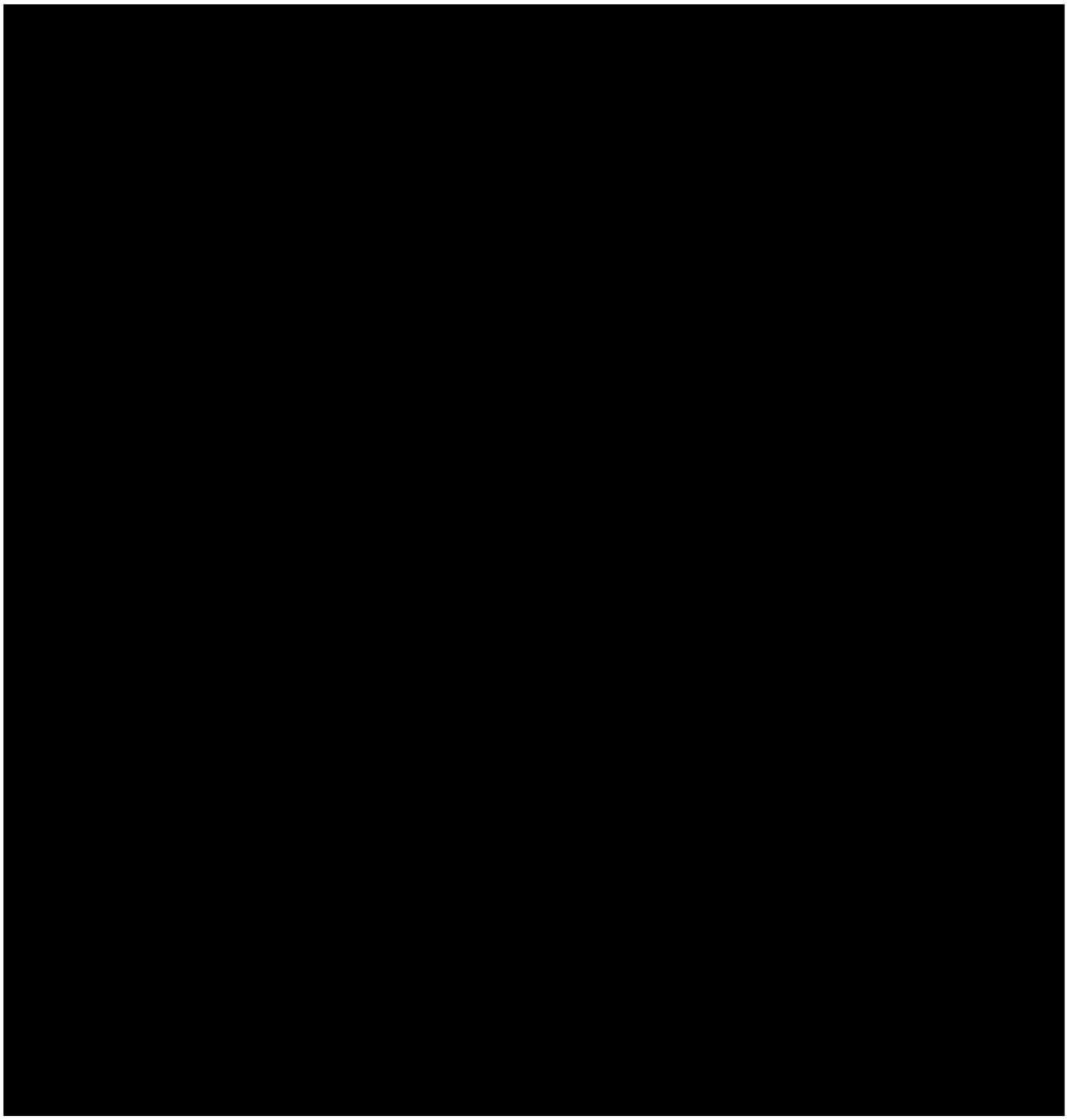
1.2.1 Mode of action

BI 767551 targets the receptor binding domain (RBD) of the SARS-CoV-2 spike protein with high affinity. When tested *in vitro*, BI 767551 demonstrates potent neutralizing activity both against authentic SARS-CoV-2 as well as SARS-CoV-2 spike-typed pseudoviruses[R20-2985, [R20-3347]. For example, infection of Vero E6 cells with the SARS-CoV-2 variant BavPat1/2020 was completely blocked in the presence of BI 767551 at concentrations as low as 0.05 µg/ml as indicated by the absence of detectable cytopathic effects. Moreover, BI 767551 demonstrated high activity against a panel of six SARS-CoV-2 pseudovirus variants with an average 50% inhibitory concentration (IC_{50}) of 0.007 µg/ml in a neutralization assay using ACE2-expressing human 293T cells.

1.2.2 Predicted and observed pharmacokinetic characteristics

A two-compartment pharmacokinetic model was applied to characterize monoclonal antibody (mAb) distribution and clearance, assuming that the systemic pharmacokinetic parameters in the model are the same as that of a typical mAb [R15-2538]. Antibody concentrations in lung interstitial and epithelial lining fluids after intravenous and after inhalative administration of

BI 767551 were modelled using a minimal physiologically-based PK model directly connected to the serum compartment. The bidirectional drug transfer rate between lung interstitial and epithelial lining fluids were derived by fitting this model to datasets from the literature [R20-3347; R20-3367].



[redacted]

For more detailed information, please refer to Investigator Brochure (IB)[c34274645-02].

1.2.3 Drug interactions

BI 767551 is a therapeutic protein and its clearance occurs mainly by protein catabolism. The clearance of therapeutic antibodies does not involve CYP enzyme-mediated metabolism or drug transporters but is mediated primarily by non-saturable elimination pathways such as fluid-phase endocytosis, phagocytosis, and catabolism. Therefore, the potential of small molecule drugs to affect the exposure of BI 767551 is considered to be limited. The virus neutralizing activity of BI 767551 is mediated by the interaction with free virions and preventing cellular infection. This mode of action is not anticipated to affect the PK profile of co-administered medications, since BI 767551 is not expected to directly modulate inflammatory cytokine expression, modulate the expression of CYP 450 enzymes or alter human physiological processes that regulate small molecule drug metabolism.

1.2.4 Residual Effect Period

The Residual Effect Period (REP) of BI 767551 is 90 days.

1.2.5 Data from non-clinical studies

To date, the following attributes of BI 767551 have been determined:

[redacted]

[redacted]

Toxicology

To support an inhalation route of administration, the potential for on-target and off-target toxicities and excipient toxicities was assessed through in vitro and in vivo studies and the existing scientific literature. [redacted] While there is limited data available on the safety of protein therapeutics when administered by inhalation, the existing data indicates that mAbs can be administered safely through this route [R20-3416]. [redacted]

On-target toxicities

As BI 767551 is directed toward a foreign target, on-target toxicities are expected to be limited to effects of interaction with SARS-CoV-2. Antibody-dependent enhancement (ADE) of disease is a concern that originates from the potential for negative consequences of principal a ntibody functions that could offset beneficial antibody effects and result in clinical deterioration. Fc-mediated uptake of antibody-bound viral particles resulting in increased infection and disease is a phenomenon observed for dengue virus, particularly at non- or low level eutralizing [R20-3984]. In addition, disposition of immune complexes might activate components of the complement system. Taken together, these processes could potentially result in increased productive infection or the triggering of uncontrolled hyper-inflammatory responses.

[redacted]

In addition, we are not aware of any pre-clinical or clinical reports suggestive of ADE in SARS-CoV-2 infection (animal models, convalescent plasma trials, monoclonal antibody trials). Therefore, the risk of ADE appears to be low.

Off-target toxicities

[redacted]

[redacted]

Excipient Assessment

[redacted]

For details on the results from these pre-clinical studies, please refer to the Investigator's Brochure [c34274645-02].

1.2.6 Data from clinical studies

Clinical experience

[redacted]

[redacted]

Safety summary

Clinical data for BI 767551 is limited at this time, and the safety profile of BI 767551 has not been established. As described below, a limited number of healthy volunteers and SARS-CoV-2-infected individuals have been administered BI 767551.

[redacted]

Details on all reported AEs as of April 01, 2021 are presented in the Investigator's Brochure (c34274645-02).

1.3 RATIONALE FOR PERFORMING THE TRIAL

This clinical trial is potentially a pivotal registration study for the i.v administration of the SARS-CoV-2- neutralizing human monoclonal antibody BI 767551 for the treatment of non-hospitalized patients with COVID-19. It is conducted to clinically evaluate the efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.

The preliminary results from the Phase II part will evaluate the concept of pharmacological activity of BI 767551 in non-hospitalized patients with mild to moderate COVID-19 symptoms. This part of the trial is designed to establish MoA for this compound. From this Phase II part, the lowest efficacious and safe dose and regimen from Phase II will be taken into the Phase III part to assess clinical outcomes.

The Phase III part will evaluate the efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.

The safety and establishment of the concept of pharmacological activity may warrant the investigation in alternate disease severities and settings for infection.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Treatment with BI 767551 has the potential to provide benefit to patients with mild to moderate COVID-19 by reducing the risk of progressing to hospitalization or death, by preventing viral uptake and accelerating viral clearance.

The inhaled route of administration may provide accelerated virus neutralization in the respiratory tract being the first to be exposed by the virus.

First in man studies are currently being carried out in both healthy volunteers and SARS-CoV-2 infected individuals and as data from that study becomes available, the data will be incorporated into the program and where necessary, this protocol will be adapted via amendment(s).

1.4.2 Risks

In order to protect the patient's safety during conduct of this trial, an independent DMC has been established for the review of clinical trial safety data.

Table 1.4.2:1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product / BI 767551		
Hypersensitivity reaction	As BI 767551 is a human monoclonal antibody, the anticipated adverse effect is a hypersensitivity reaction induced via intravenous and/or inhaled route of administrations. Typical compound-related signs and symptoms of hypersensitivity reactions of mild to severe grading could include pruritus, urticaria, fever, rigor/chills, diaphoresis, bronchospasm, cardiovascular collapse, anaphylaxis, and cytokine release syndrome.	In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with the severity of the reaction and local standard of care to interrupt and treat the condition. Emergency medicines and ability to handle such reactions must be available at the site. Systemic hypersensitivity reaction is defined as an adverse event of special interest (AESI). It is subject to close monitoring.
Irritation of Airways	Administration of inhaled BI 767551 and excipients may result in irritation of the airways and pulmonary tissues that could manifest as cough, wheezing, bronchial narrowing, or bronchospam resulting in respiratory distress.	Inhalers and/or nebulizers for the application of bronchodilators will be available at the site of the trial drug administration.
Off-target toxicity	As BI 767551 was identified from a human memory B cell in a SARS-CoV-2-convalescent individual and based on the results of off-target profiling, the risk of off-target-mediated toxicity of BI 767551 can be considered as low. Please refer to current IB (c34274645-02).	Trial patients will be carefully monitored for any unspecific toxicities.

Table 1.4.2:1 Overview of trial related risks (continued)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Viral Resistance	There is a potential risk of treatment failure due to the development of viral variants that are resistant to BI 767551 *(viral resistance)*. It is possible that resistance-associated variants to BI 767551 could have cross-resistance to other monoclonal antibodies targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known. Resistant strains of virus can also arise independent of antibody use.	Viral RNA genome samples will be collected for each patient in this trial. Trial patients will be carefully monitored as part of the reviews by the DMC who will have access to unblinded data. Any lack of responsiveness may finally be assessed based on the genomic analysis of samples and the circulating variants at that time.
Antibody-dependent enhancement	[redacted] Fc receptor-mediated effects may enhance disease or infection by increased viral replication or immunological reaction (e.g., in pulmonary tissues). ADE effect has not been reported in Phase II clinical trial of a SARS-CoV-2-neutralizing monoclonal antibody (LY-CoV555, [redacted]) administered to recently infected outpatients (R20-4045).	Patients will be carefully monitored for potential worsening of symptoms, including respiratory distress.

Table 1.4.2:1 Overview of trial related risks (continued)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Blunting of vaccine response	Administration of BI 767551 may result in blunting of SARS-CoV-2 vaccine responses should these vaccines become available.	Monitoring of the immune response to vaccination or delayed or repeated vaccination may be required. Patients with previous SARS-CoV-2 vaccination are excluded.
Drug-induced liver injury (DILI)	Rare but severe event, that must be monitored in all clinical studies, independent of intervention and indication, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Trial procedures		
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of lightheadedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) compression; (b) close clinical monitoring for AEs; (c) selection of experienced sites and site staff; (d) Safety recommendations provided in laboratory manual
NP and OP swabs	Upper respiratory tract samples will be obtained by naso- and oropharyngeal swabs that may cause discomfort, tissue irritation or damage, or local bleeding.	Deeper swab biosamples will be obtained by trained trial staff. Anterior nasal swabs have more limited risk.

1.4.3 Discussion

BI 767551 is currently under evaluation in Phase I in healthy volunteers and ambulatory COVID-19 patients. It is not yet known whether its administration results in beneficial clinical effects. In SARS-CoV-2-infected subjects, administration of BI 767551 may reduce the risk of progressing to severe disease and contribute to accelerated viral clearance.

Several other SARS-CoV-2-neutralizing antibodies are under clinical development. Recently, two new therapies (*Bamlanivimab* by [redacted]; *Casirivimab in combination with Imdevimab* by [redacted]) have gained FDA-authorization for emergency use for the indication of mild-to-moderate COVID-19 in adults and pediatric patients (12 years and older) with a positive COVID-19 test, who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Antibody-dependent enhancement cannot be ruled out completely, but the risk is considered low that BI 767551 increases the risk of progression of COVID-19 based on preclinical studies. Rather, by targeting the receptor-binding domain of the SARS-CoV-2 spike (S) protein with high affinity and by not blocking the ACE-2 receptor, BI 767551 neutralizes SARS-CoV-2, preventing infection and increasing clearance thereby reducing the risk of severe disease.

Hypersensitivity reactions are anticipated adverse effects. In addition, although no human antigen target is described for BI 767551, all trial subjects will be carefully monitored for any unspecific effects. As described in this section, this and other theoretical risks associated with BI 767551 will be monitored along with a mitigation plan.

The data will be evaluated between the first (Phase II) and second (Phase III) parts to ensure that the antibody can perform as expected regarding increase in viral clearance. Only then will the study proceed to the larger Phase III portion. In addition, an Independent DMC will monitor subject's safety and BI 767551 efficacy during the the trial. In case BI 767551 does not demonstrate a potential for efficacy (interim futility analysis), the study may also be recommended to be stopped by the DMC.

Taking into account current knowledge of nonclinical data and relevant anticipated effects, BI 767551 has currently a positive Benefit-Risk profile for the treatment of patients with mild to moderate COVID-19 symptoms.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This trial has two sequentially enrolling parts with different objectives.

The overall objective of this trial is to evaluate the concept of pharmacological activity of BI 767551 in non-hospitalized patients with mild to moderate COVID-19 symptoms and to identify a potentially efficacious and safe dose regimen from Phase II part to take into the Phase III part.

The Phase II part of the trial will aim to prove the concept of pharmacological activity of different dose levels and routes of administration of BI 767551 in comparison to placebo and to identify efficacious and safe dose regimens in non-hospitalized patients with mild to moderate COVID-19 symptoms. The primary objective is to numerically compare the BI 767551 dose levels and routes of administration to placebo for the ratio of the time-weighted change from baseline in viral shedding over 8 days. The primary treatment comparison will be as treated, including all data prior to start of any other treatment with a similar mode of action that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA).

Secondary objectives of Phase II are to numerically compare the BI 767551 doses and routes of administration to placebo for virological outcomes.

The Phase II part of the trial will support the decision on whether to move to Phase III and which dose level and route of administration to take to the Phase III part of the study. The IV route of administration has been shown to be efficacious in development programs for other neutralizing antibodies however, the inhaled route of administration is a convenient, novel route of delivery and more directly addresses lung infection. If shown to be efficacious in Ph II, the protocol may be amended to select the inhaled route of administration to be carried forward into Ph III.

The Phase III part of the trial will aim to confirm efficacy, safety and tolerability of the dose regimen of BI 767551 selected from the Phase II part in comparison to placebo in non-hospitalized patients with mild to moderate COVID-19 symptoms. The primary objective is to demonstrate superiority of the BI 767551 dose regimen for the difference in the proportion of patients hospitalized or death from any cause over 29 days. The primary treatment comparison will be performed on all randomised patients, including all data prior to start of any other treatment with a similar mode of action that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA).

Secondary objectives of Phase III are to numerically compare the BI 767551 dose regimen to placebo for virological and other clinical outcomes.

2.1.2 Primary endpoint(s)

The primary endpoint in Phase II is the time-weighted change from baseline in viral shedding over 8 days in site collected nasopharyngeal (NP) swabs by RT-qPCR, defined as a change from baseline in log_{10} viral load. Refer to Section 7.2.3 for further details.

The primary endpoint in Phase III is hospitalization or death from any cause by Day 29.

2.1.3 Secondary endpoint(s)

2.1.3.1 Secondary endpoints in Phase II

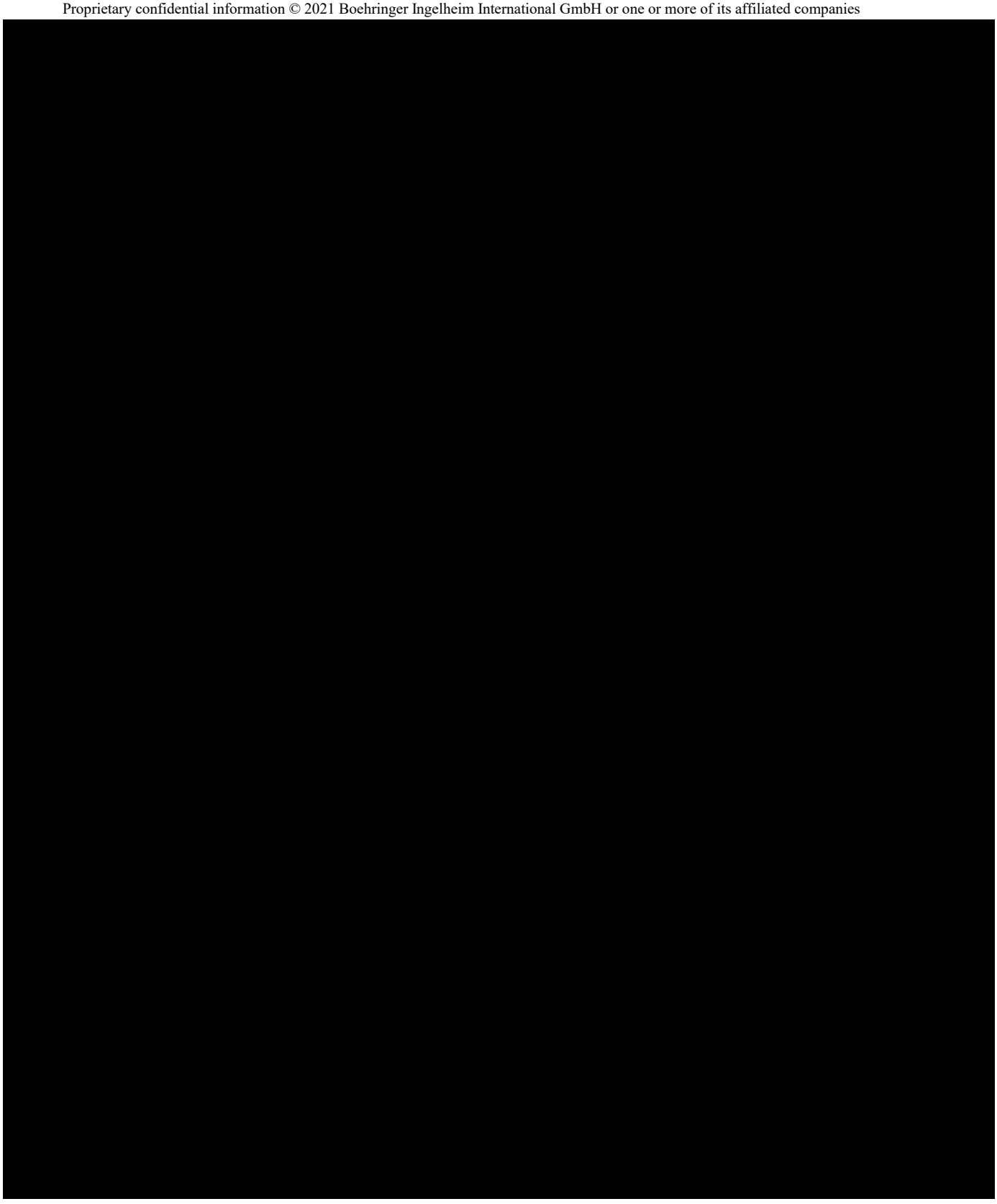
The secondary endpoints in Phase II are:

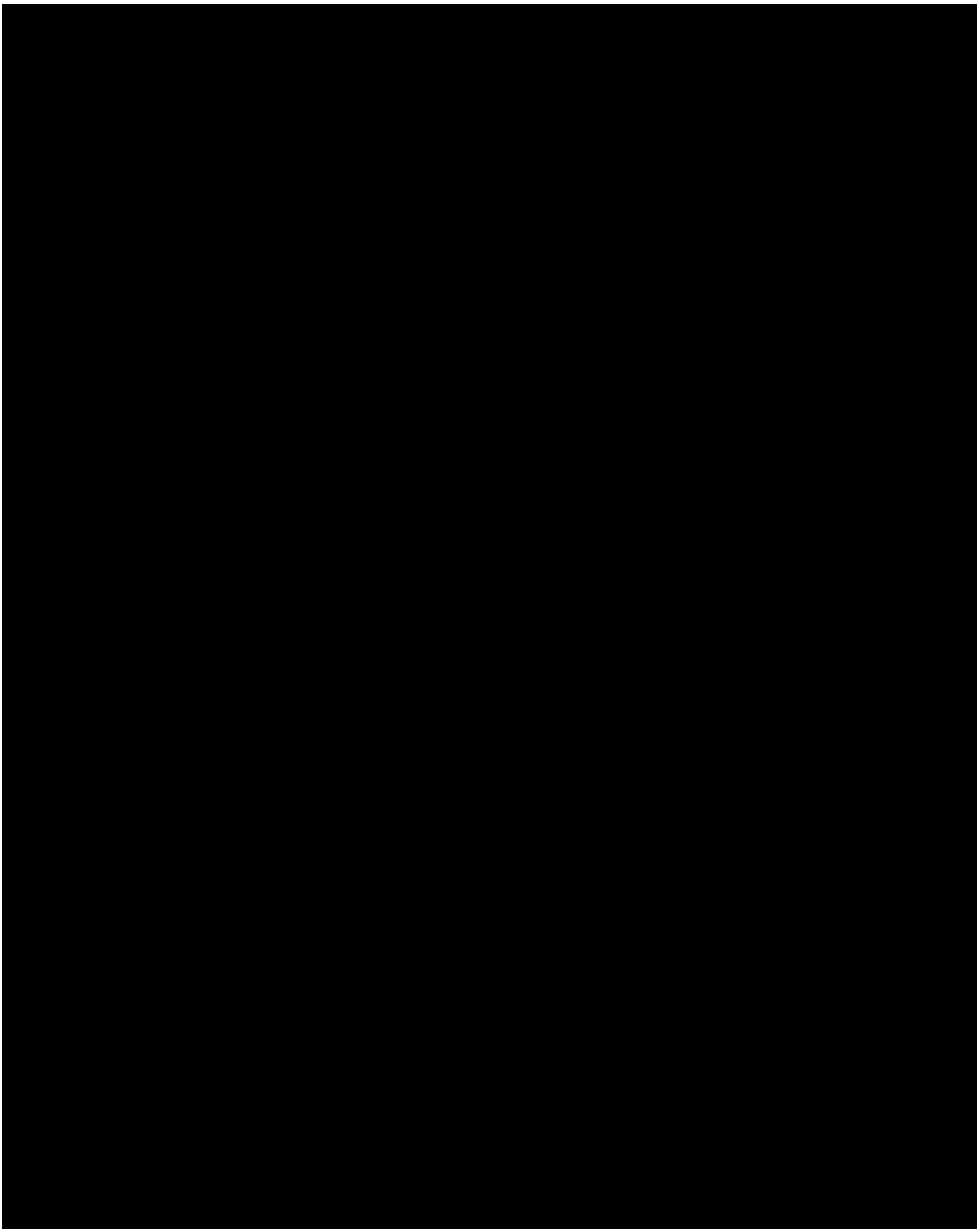
- Time-weighted change from baseline in viral shedding over 29 days in site collected NP swabs by RT-qPCR, defined as a change from baseline in log_{10} viral load.
- Loss of detection of SARS-CoV-2 RNA by site collected NP swab at Day 4, 8, 15, 22 and 29.

2.1.3.2 Secondary endpoints in Phase III

The secondary endpoints in the Phase III are:

- Time to death over 29 days
- Hospitalization by Day 29
- Hypoxia or hospitalization or death from any cause by Day 29
- Hypoxia by Day 29
- Time to clinical improvement over 29 days, defined as the time to either an improvement of two points on the 11-point WHO Clinical Progression Scale or a score of 0 on the Clinical Progression Scale, whichever comes first (see Section 5.1.2).
- Time to loss of detection of SARS-CoV-2 RNA by site collected NP swabs over 29 days





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a Phase II/III seamless, randomised, double-blind, placebo controlled, parallel group, design study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.

The study comprises two parts in an operationally seamless design. The exploratory Phase II part will assess viral load measures of SARS-CoV-2 RNA by NP swab to evaluate the neutralizing mode of action (MoA) of BI 767551 and provide data to select the dose level or dose regimen also considering safety and tolerability to take into the Phase III portion should there be adequate neutralizing ability. Phase II includes both inhaled and i.v. routes to explore neutralizing potential, safety and PK to provide a comparison against Placebo of doses and routes ahead of decision of dose and route for the Phase III portion. For more details please see Section 4.1.2.

The confirmatory Phase III part of the study will investigate clinical outcomes for events of hospitalization or death throughout a 29 day period and further assessment of safety and tolerability for one dose regimen vs placebo. The patients will be followed for a 90-day observation period to assess any long-term outcomes from patients.

In Phase III, randomisation will be stratified by “high” versus “low” risk of progression to COVID-19. This is to ensure equal distribution of patients in these two groups to each treatment group. There is no minimum number of “high” risk patients for this study. For the definition of “high” and “low” risk please refer to Section 7.4.

Patients will be enrolled (screened) in the trial once the appropriate informed consent has been obtained. At the start of the trial, patients who successfully complete screening and still meet the inclusion/exclusion will be randomised in Phase II in a 2:2:2:1 ratio to one of the four arms:

- Single placebo i.v. infusion with placebo inhalation
- Single low dose 10 mg/kg of BI 767551 i.v. infusion with placebo inhalation
- Single high dose 40 mg/kg of BI 767551 i.v. infusion with placebo inhalation
- Single placebo i.v. infusion with inhalation 250 mg of BI 767551

Following CTP amendment 1, it is planned to include patients in an equal allocation ratio to each treatment arm. Therefore, patients will be randomised in a 1:1:1:2 ratio to receive a single dose of either Placebo i.v. + Placebo inhaled, BI 767551 i.v. 10 mg/kg dose + Placebo inhaled, BI 767551 i.v. 40 mg/kg + Placebo inhaled or Placebo i.v. + BI 767551 250 mg inhaled, respectively, once approximately 112 patients have been randomised using the initial randomisation ratio. When approximately 112 patients have been randomised, the randomisation scheme will be implemented in sites or countries with approval for CTP amendment 1. At the

time of implementation of the revised scheme, sites or countries may be placed on hold for recruitment until approval of CTP amendment 1 is granted.
Patients will receive one single dose of active treatment or placebo on day of randomisation (Day 1).

In Phase III, eligible patients will be randomised in a 1:1 ratio to receive active treatment as a fixed dose (either 700 mg i.v. or 2800 mg i.v. or 250 mg inhaled), or placebo.

Patients in both Phase II and Phase III parts will be followed for a 90-day observation period. The study schematic is shown in Figure 3.1:1.

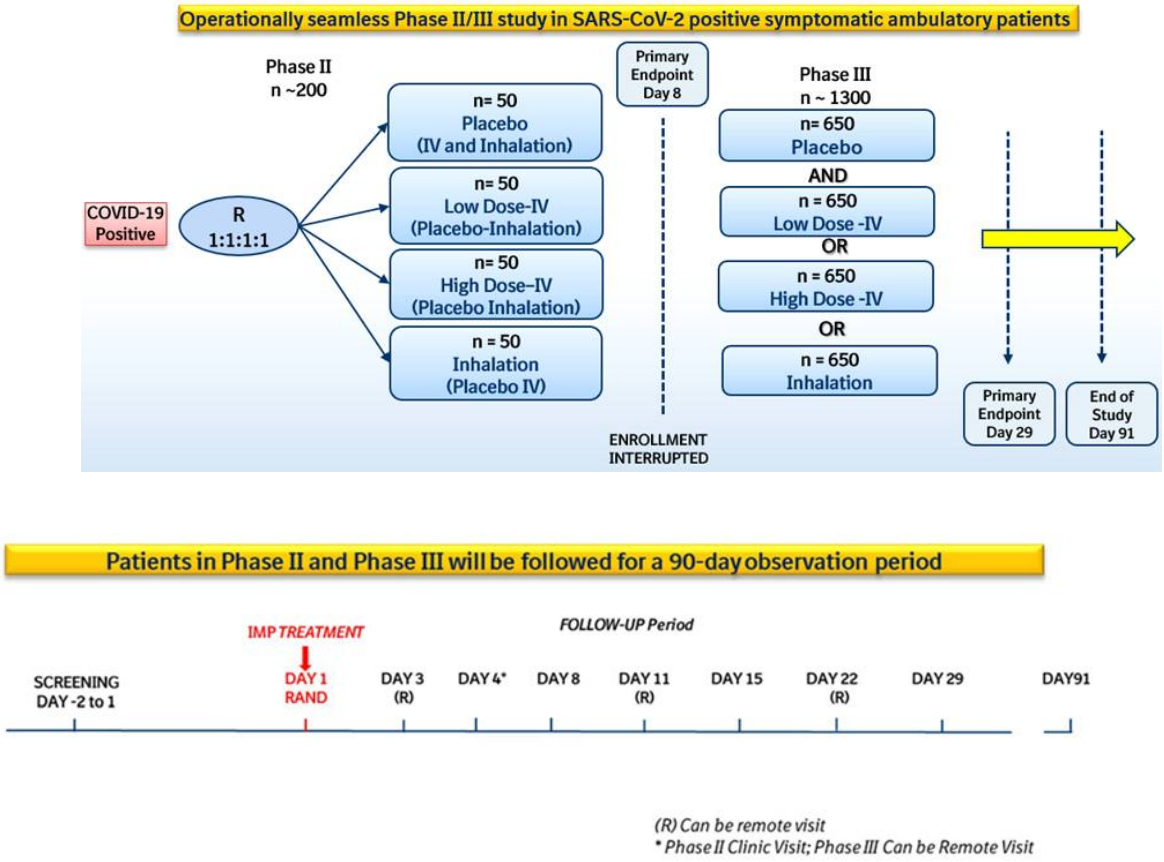


Figure 3.1:1 Study Schematic

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

This seamless, trial design, with separate exploratory Phase II and a confirmatory Phase III, will include pre-defined decision criteria for continuing BI 767551 dose and selecting the dose regimen from Phase II into Phase III (see Section 3.1), with the intent of ensuring that a positive

proof of concept of pharmacological activity will quickly be followed by the confirmation of clinical efficacy and safety of BI 767551.

A parallel group, randomised, seamless, double-blind, placebo controlled, design trial was considered most appropriate to assess the efficacy and safety of BI 767551 in symptomatic, non-hospitalized adults with mild to moderate COVID-19 symptoms.

Phase II will aim to prove the concept of pharmacological activity and dose/exposure-response relationship, and thus to select the dose regimen for Phase III of this trial. Phase III will investigate the most efficacious, tolerable and safe dose regimen from the Phase II regimens, unless an unexpected safety or efficacy finding requires dose modification beyond the pre-specified transition scenarios in Section 3.1.

A control placebo group is included in this study to reduce bias with regard to the treatment dependent effects and to preserve the integrity of the assessments of safety and efficacy. The control arm reduces the subjective bias in completion of symptom diaries by participants.

A DMC, which is independent of the sponsor 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. The DMC will also assess efficacy at two planned interim analyses (See Section 7.2.8). Futher details are provided in the DMC charter.

3.3 SELECTION OF TRIAL POPULATION

Approximately 200 patients are planned to be randomised in Phase II at approximately 30-40 study sites; each site is expected to randomise approximately 3 patients. In Phase III there are approximately 1300 patients planned to be randomised at approximately 60 sites and approximately 23 patients per site are planned to be randomised.

The majority of sites in Phase II are located in 7 countries and may expand to other countries to focus on regions where the incidence of COVID-19 is high. Approximately 20 countries are planned for Phase III. Given the expected regional fluctuation in SARS-CoV-2 infection rates, it may become necessary to open new countries and sites and to potentially suspend existing sites, or countries.

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 be directed to stop screening additional patients for this trial. This applies to both parts of the study. Patients already in screening at this time will be allowed to continue to randomisation if eligible.

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

If retrospectively it is found that a patient has been randomised in error (i.e., did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

Patients will be selected for the trial according to pre-defined eligibility criteria and written informed consent has to be obtained prior to initiation of any trial related procedures.

Randomisation of patients shall happen no later than 3 days after informed consent and within 5 days of symptom onset.

3.3.1 Main diagnosis for trial entry

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

Eligibility criteria for Phase II and Phase III are the same. Patients participating in Phase II are not eligible for Phase III. The trial will include non-hospitalized patients with mild to moderate COVID-19.

The trial will also include patients with mild to moderate COVID-19 symptoms that are at high risk for progression of disease due to underlying cardiovascular or respiratory disease, diabetes, chronic kidney disease, or other comorbidities, and immunocompromised persons (e.g., HIV-infected patients, organ transplant recipients, or patients receiving cancer chemotherapy) as long as they do not meet other exclusion criteria. See Section 7.4 for the definition of high risk patients.

3.3.2 Inclusion criteria

1. ≥ 18 years old, males and females.
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
3. Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (NP or nasal swab or saliva) collected no more than 72 hours prior to start of treatment.
4. Patients experienced mild to moderate COVID-19-related symptoms or measured fever for no more than 5 days prior to start of treatment where symptoms are defined by fever, feeling feverish, fatigue, cough, shortness of breath at rest or during activity, sore throat, body pain or muscle pain/ aches, chills, headache, nasal obstruction or congestion, loss of smell or taste, nausea, diarrhea, vomiting, or dysgeusia.

5. One or more of the following signs/symptoms present on day of start of treatment: fever, feeling feverish, fatigue, cough, shortness of breath at rest or during activity, sore throat, body pain or muscle pain/ aches, chills, headache, nasal obstruction or congestion, loss of smell or taste, nausea, diarrhea, vomiting, or dysgeusia.
6. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to 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. A list of contraception methods meeting these criteria is provided in Section 4.2.2.3.

3.3.3 Exclusion criteria

1. Body weight of less than 40 kg.
2. Severe or critical COVID-19 including at least one of:
    - Oxygen saturation (SpO2) ≤ 93 % on room air or on their usual level of oxygen supplementation in case of chronic oxygen use
    - Ratio of arterial oxygen partial pressure (PaO2 in millimeters of mercury) to fractional inspired oxygen (FiO2) < 300 (in case arterial blood sample was taken)
    - Respiratory rate ≥ 30/min or heart rate ≥ 125/min. Measure should be obtained at rest by study staff within 24 hours of start of treatment.
    - History of hospitalization for COVID-19
    - Current or imminent need for hospitalization or immediate medical attention in the clinical opinion of the site investigator. Does not include patients hospitalized for isolation only.
3. Receipt of intraveneous immunoglobulin within 12 weeks prior to Visit 2 (see Section 4.2.2.1).
4. Receipt of COVID-19 convalescent plasma treatment at any time prior to Visit 2 (see Section 4.2.2.1).
5. Receipt of any SARS-CoV-2 monoclonal antibody treatment at any time prior to Visit 2 (see Section 4.2.2.1).
6. Receipt of SARS-CoV-2 vaccine at any time prior to Visit 2.
7. Receipt of an investigational product for COVID-19 within 5 half-lives prior to Visit 2.
8. Receipt of systemic steroids (e.g. prednisone, dexamethasone) within 4 weeks prior to Visit 2 unless used for chronic condition (see Section 4.2.2.1).
9. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.

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 post menopausal state is defined as post menopausal for at least one year.

10. Any co-morbidity requiring surgery within 7 days prior to study entry, or that is considered life threatening in the opinion of investigator within 30 days prior to study entry.
11. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.
12. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
13. Currently enrolled in any other type of medical research judged not to be compatible with this study.
14. Known allergy/sensitivity or any hypersensitivity to any of the components used in the formulation of the interventions.
15. Previous enrolment in this trial. Patients participating in Phase II are not eligible for Phase III. Re-screening is allowed once, for repeat of RT-qPCR or antigen SARS-CoV-2 test, if required. The test method used for initial screening (RT-qPCR or antigen) should be used for re-screening. See Section 6.2.1.
16. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Discontinuation 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.

Every effort should be made to keep the patients in the trial: if possible, to complete all procedures in clinic and/or remotely as indicated in the Flow Chart, or at least to collect important information on vital status and whether the patient has been hospitalized at the planned completion date. In case of early discontinuation, site staff should make every effort to retrieve all trial materials (i.e study diary) from patient.

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 Section 5.2.6.2).

As there is only one time drug administration, patients may be less motivated to adhere to the study visit schedule. Investigator and site staff should work to detect early signs of lost interest and strongly encourage the patients to continue to complete regularly scheduled study visits until the trial ends. Should that not be acceptable to the patient, the patient should complete the Prematurely Discontinued before Day 29 or the Prematurely Discontinued after Day 29 visit

(whichever is appropropriate). Vital status and whether the patient has been hospitalized should be collected at the planned completion date.

If a patient experiences a worsening of COVID-19 during the course of the trial, he/she can receive treatment with other therapies at investigator discretion and responsibility and will be followed up as initially planned (refer to Section 4.2.1). If a treated patient receives a prohibited treatment during the trial, he/she will continue the trial as initially planned and the prohibited treatment should be recorded as concomitant medication.

3.3.4.1 Discontinuation of Trial Treatment

In case the infusion or inhalation of study drug is permanenty discontinued before the whole amount of prepared solution has been administered to the patient, drug administration will not be re-initiated. Every effort should be made to keep the patient in the trial and perform all study procedures. If not possible, the patient will undergo the procedures at the Prematurely Discontinued before Day 29 or the Prematurely Discontinued after Day 29 visit (whichever is appropriate) and follow-up as outlined in the Flow Chart and Section 6.2.3. A phone contact at the end of the planned observation period should occur to collect the most relevant information: vital status (please see Section 5.2.6.1.1), outcome events, adverse events, or last contact date in case of lost to follow-up. The reason for interrupting trial treatment must be documented in the patient files and CRF.

If new efficacy / safety information becomes available, BI 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.

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.

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 treatment and 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

The study will include BI 767551 and placebo. The identity of the medicinal products is divided by phase of the study.

In Phase II the medication is dose by weight i.v or fixed dose inhalation (nebulized) with the following treatment arms:

- Placebo i.v. + Placebo inhaled
- BI 767551 i.v. 10 mg/kg + Placebo inhaled
- BI 767551 i.v. 40 mg/kg + Placebo inhaled
- Placebo i.v. + BI 767551 250 mg inhaled

In Phase III, the medication will be administered via either i.v as a fixed dose or inhalation with the following potential treatment arms:

- BI 767551 i.v. 700 mg or 2800 mg or 250 mg inhaled
- Placebo

4.1.1 Identity of the Investigational Medicinal Products

4.1.1.1 Test Products for Phase II

Sterile normal saline (NaCL 0.9%) procured from a commercial source and approved for clinical application will be used as placebo for the intravenous infusion.

Table 4.1.1.1:1 BI 767551

Substance:	BI 767551
Pharmaceutical formulation:	Concentrate for solution for infusion/nebulizer solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	1000 mg/vial (50 mg/ml), 20 ml
Posology:	i.v. infusion or inhalation (as required per instructions) Single i.v. infusion, 10 mg/kg or 40 mg/kg Single i.v. inhalation, 250 mg
Mode of administration:	i.v. infusion Inhalation

Table 4.1.1.1:2 Solvent for dilution

Substance:	Solvent for dilution of BI 767551 (used as placebo for inhalation)
Pharmaceutical formulation:	Solvent for dilution of BI 767551 concentrate for solution for infusion/nebulizer solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a, 20 ml in glass vial
Posology:	To be used for i.v.infusion (calculated by body weight) or inhalation (as required per instructions)
Mode of administration:	i.v. infusion inhalation

4.1.1.2 Test Products for Phase III

Table 4.1.1.2:1 BI 767551 (For infusion)

Substance:	BI 767551
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	1000 mg/vial (50 mg/ml), 20 mL in glass vial
Posology:	i.v. infusion (as required per instructions) Single i.v. infusion 700 mg or 2800 mg
Mode of administration:	i.v. infusion

Table 4.1.1.2:2 BI 767551 (for inhalation)

Substance:	BI 767551
Pharmaceutical formulation:	Concentrate for nebulizer solution

Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	250 mg/vial (50 mg/ml), 5 mL in glass vial
Posology:	Single inhalation 250 mg
Mode of administration:	Inhalation

Table 4.1.1.2:3 Placebo for BI 767551 (for infusion)

Substance:	Placebo for BI 767551
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a, 20 ml in glass vial
Posology:	Single i.v. infusion equal to the volume of treatment for 700 mg or 2800 mg
Mode of administration:	i.v. infusion

Table 4.1.1.2:4 Placebo for BI 767551 (for inhalation)

Substance:	Placebo for BI 767551
Pharmaceutical formulation:	Concentrate for nebulizer solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a, 5 ml in glass vial
Posology:	Single inhalation equal volume for 250 mg
Mode of administration:	Inhalation

Table 4.1.1.2:5 Solvent for dilution

Substance:	Solvent for dilution of BI 767551 or for dilution of Placebo, if needed
Pharmaceutical formulation:	Solvent for dilution of BI 767551 concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a, 20 ml in glass vial
Posology:	To be used as diluent for i.v. infusion for BI 767551 or placebo up to final volume defined in instructions
Mode of administration:	i.v. infusion

4.1.2 Selection of doses in the trial and dose modifications

A viral dynamic model, based on the influenza A model developed by Baccam et al. was used in combination with a pharmacokinetic model to predict the human efficacious dose [R20-3336] (refer to n00282535 and Section 1.2.2 for further details).

In the 1487-0001 study, patients will receive treatment no more than 5 days after symptom onset. For this later treatment start, which is considered a more realistic scenario in clinical practice, the viral dynamics model indicates that the maximum obtainable response in the model is smaller than with treatment onset at symptom onset. In addition, the maximum obtainable response is less sensitive to dose (i.e. no relevant difference between e.g. 40 mg/kg and 10 g/kg). Therefore,

a lower i.v. dose (10 mg/kg) may show comparable efficacy as the higher (40 mg/kg) i.v. dose in clinical practice and is therefore included in Phase II.

For inhalational administration, a single dose of 250 mg is predicted to be efficacious. Assuming 6-30% deposition in the lower airway, [redacted]. Given the novelty and uncertainty in pharmacokinetics for inhaled delivery of antibody therapeutics and their use in the treatment of respiratory viruses, the efficacious dose was selected as the maximum feasible dose 250 mg.

To account for emerging variants, IC_{50} values were incorporated into the mechanistic viral dynamic PK/PD model and scanned across a range from 1.5 to 15000 ng/mL, assuming a hill slope of 1. [redacted]

Dose for inhalation:

Following inhalative administration, maximum exposure in ELF is reached immediately at the end of the inhalation, predicted peak concentrations in ELF are about [redacted] potentially leading to faster onset of action and more rapid virus neutralization.

Simulated BI 767551 ELF concentrations for a single inhaled dose of BI 767551 were compared to live virus 100% neutralizing concentrations (NC_{100}). After a single inhaled dose of 250 mg (assuming ≥ 6% deposition in the lower airways), BI 767551 ELF concentrations were predicted

to be greater than [redacted] [c35245352].

A single dose of 250 mg (assuming 6% lung deposition as a conservative scenario), is predicted to provide ELF exposure above the NC_{100} of the wildtype virus for [redacted]

Doses for intravenous administration:

For a single IV dose of 10 mg/kg (Ph II) or 700 mg (Ph III) BI 767551, respectively, ELF concentrations are predicted to be greater than [redacted]

Fixed dosing

In the ongoing Phase I studies, i.v. doses are administered based on body weight, in accordance with common practice for early trials with therapeutic antibodies. In this trial, it is planned to use fixed dosing, as this offers advantages in clinical routine (ease of dose preparation, less chances for dosing errors and no drug product wastage) which are considered to be of particular relevance in a pandemic situation with high patient emergence.

Modelling and simulations were applied to confirm that a fixed dosing regimen for intravenous administration is not associated with reduced efficacy or safety concerns compared to weight-based dosing regimen. The before-mentioned PK model was used to predict mAb distribution for a simulated study population with a body weight-range from 40-150 kg. Simulations show that the distribution of individual exposure values following a single fixed dose of 700 mg essentially overlaps with the distribution of individual exposure values after a single weight-based dose of 10 mg/kg in a study population with a body weight range from 40 kg to 150 kg. In addition, simulations suggest that the C_{min} following a fixed dose to a patient at the upper end of the simulated weight range is comparable or even slightly higher than the C_{min} following a weight-based dose to a patient at the lower end of the simulated weight range. Thus, fixed dosing regimen is not expected to exceed, nor to undercut the exposure range obtained with the corresponding weight-based dosing regimen and hence is considered to be efficacious and safe.

Although no upper weight range is specified in the inclusion criteria, a lower range of 40 kg is included to avoid potential higher exposure in lower weight individuals.

For patients above 175 kg, a maximum dose of 7000 mg will be administered in the Phase II part of the study.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 2:2:2:1 ratio at Visit 2 (and in a 1:1:1:2 ratio after CTP amendment 1 has been approved, please refer to Section 7.4 for further details) in Phase II to either Placebo i.v. + Placebo inhaled, BI 767551 i.v. 10 mg/kg dose + Placebo inhaled, BI 767551 i.v. 40 mg/kg + Placebo inhaled or Placebo i.v. + BI 767551 250 mg inhaled, respectively, and in a 1:1 ratio to BI 767551 i.v. or placebo in Phase III via Interactive Response Technology (IRT). The appropriate medication numbers will be assigned and documented by the unblinded pharmacist (Phase II part only). For Phase III, the pharmacist will be blinded to the treatment assignment.

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

BI 767551 is a human monoclonal antibody of the IgG1 kappa isotype (see Section 1.2). It is produced by Boehringer Ingelheim and provided to the study pharmacies as a stock solution at a concentration of 50 mg/ml in single-use vials containing a volume of 20 ml. Stock vials will be stored at 5±3°C. The Solvent for dilution of BI 767551 will also be provided in single-use vials containing a volume of 20 ml.

At Day 1, patients will be randomised to one of four treatment arms in Phase II or to one of the two treatment arms in Phase III by the IRT.

The pharmacist or his/her qualified delegate (unblinded for Phase II) will prepare the trial medication according to the medication handling instructions (as specified in the ISF).

For Phase II, the unblinded pharmacist or his/her qualified delegate will prepare the medication as instructed to ensure that the treatment blinding is maintained throughout administration.

Inhalation

BI 767551 or placebo will be administered as a single inhalation through a mouthpiece (Aerogen® Ultra) using a mesh nebuliser (Aerogen® Solo) to generate an aerosol. The inhalation procedure will start approximately 25 minutes following start of infusion and will require approximately 15-20 minutes. Please see Appendix 10.1 for Instructions for use of the Aerogen® Solo nebuliser.

Infusion

BI 767551 or placebo for intravenous infusion will be administered as a single infusion using a peripherally inserted catheter, preferably into an upper extremity vein, over a period of 60 min

(+/- 10 minutes) using a 0.2 µm nylon in-line filter and polyurethane-based infusion system. Polypropylene-coated infusion bags containing the appropriate quantitify of diluted or undiluted BI 767551 or placebo will be provided by the local study pharmacy after preparation according to the handling instructions. At the end of the infusion, the infusion system will be flushed using at least 25 ml of sterile normal saline at the infusion flow rate. For Phase II, the dose of BI 767551 or the amount of placebo will be body weight adjusted (weight to be entered in IRT). For Phase III the dose of BI 767551 or the amount of placebo will be fixed dose.

No specific rescue therapy for BI 767551 is available. In case of an acute infusion reaction, the infusion will be interrupted and not be re-initiated. For infusion reactions requiring medical intervention, rescue medication including, but not limited to, acetaminophen/paracetamol, antihistamines, glucocorticoids, and IV fluids must be available on-site. In case of bronchial hyperresponsiveness (e.g., bronchospasm), bronchodilators and antiinflammatroy medication may be provided by inhalation or intravenously as deemed clinically appropriate.

Phase II

The solvent for dilution of BI 767551 will be used a placebo for the inhaled application.

Sterile normal saline (NaCl 0.9%) procured from a commercial source and approved for clinical application will be used as placebo for the intravenous infusion.

Prior to the reconstitution, preparation and the administration, the vials should be checked by the unblinded pharmacist or his/her qualified delegate for any changes (e.g. color).

Phase II and Phase III

Handling and preparation of the medicinal product should be performed according to routine site procedures using aseptic techniques. Prior to the reconstitution, preparation and the administration, the vials should be checked for the absence of particles.

The local Clinical Monitor or CRA should be contacted for questions or concerns regarding appearance of the solution.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The access to the randomisation code will be kept restricted until its release for analysis.

For Phase II, patients, investigators, central reviewers, and everyone involved in trial conduct with exception of the pharmacist, or analysis or with any other interest in this double-blind trial will remain double-blind with regard to the randomised treatment assignments until a snapshot is taken after the last patient randomised completes Day 8 for the interim analysis. This snapshot

will be used to determine the dose of BI 767551 to be used in the Phase III part. At the timepoint of the interim analysis for Phase II, the sponsor will be unblinded to the treatment allocation of patients in Phase II, but patients and investigators will remain double-blind until after the final database lock.

This study design includes an unblinded pharmacist who prepares the medication for the patient during the Phase II part. This unblinded function is needed due to a visible difference in packaging and the colouration of the BI 767551 versus placebo. The pharmacy/dispensing team will be unblinded to treatment group and will receive appropriate training in advance of starting the trial, to ensure they maintain compliance within the pharmacy department. Only unblinded pharmacists will be involved in IMP preparation for Phase II and will not be involved in the assessment of patients.

For Phase III patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind part of the trial will remain blinded with regard to the randomised treatment assignments until after the database lock after Last Patient Completed. The access to the randomisation code for the Phase III part will be kept restricted until its release for analysis.

The randomisation codes will be provided to bioanalytics prior to last patient completed in Phase II and Phase III to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded to the sponsor.

The independent DMC will have access to the unblinded treatment codes in order to allow them to periodically assess the trial data to ensure the overall safety and integrity of the trial, as well as to conduct the pre-specified interim analyses during the Phase III part as detailed in Section 7.2.8. For further details refer to Section 8.7 as well as the DMC charter.

Further details regarding the timepoint of unblinding the database for analysis are documented in the TSAP.

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 BI's Pharmacovigilance group 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 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. 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 or deligate 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 (if applicable).

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 by 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

provided 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 or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient 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

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (see Section 3.3), are permissible. In case of adverse event in need of treatment, symptomatic therapy according to investigator judgement will be permitted.

Infusion reaction
In case of an acute infusion reaction, the infusion will be interrupted and not be re-initiated. For infusion reactions requiring medical intervention, rescue medication including, but not limited to, acetaminophen/paracetamol, antihistamines, glucocorticoids, and IV fluids must be available on site.

Inhalation reaction
In case of bronchial hyperresponsiveness (e.g., bronchospasm), bronchodilators and/or anti-inflammatory medications may be provided by inhalation or intravenously as deemed clinically appropriate.

Rescue treatment
During the trial, if COVID-19 worsens, the patient can be treated with medications at the discretion of the investigator (refer to Restricted medication Table 4.2.2.1:1, footnote 2) as per local guidelines. Any additional investigational products related to COVID-19 could be given for COVID-19 disease worsening, after Day 2 at the discretion of the investigator but may require additional safety monitoring by the site.

All efforts should be made to inform the patient of the importance of completing the protocol specified visits (See Flow Chart) up to Visit 9. Patients refusing to complete the scheduled visits after the day of treatment should at least provide safety information by phone at the respective visits.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications listed in Table 4.2.2.1:1 must not have been taken before Visit 2 (V2) for the time periods as specified, and are not permitted throughout the study participation to Visit 9 (V9), Day 29.:

Table 4.2.2.1:1 Restricted medications

Medication or class of medications	Restriction before randomisation (V2)	Restriction from randomisation (V2) until V9 (Day 29)
Systemic steroids[1,2]	4 weeks prior to V2	Not allowed
Ivermectin[1,2]	Starting from V2	Not allowed
Remdesivir[2]	Starting from screening visit to V2	Not allowed
HIV protease inhibitors[1]	Starting from screening visit to V2	Not allowed
Intravenous immunoglobulin[2]	12 weeks prior to V2	Not allowed
COVID-19 convalescent plasma treatment[2]	Any time prior to V2	Not allowed
Other SARS-CoV-2 monoclonal antibody[2,3]	Any time prior to V2	Not allowed
SARS-CoV-2 vaccine[3]	Any time prior to V2	Not allowed
Investigational products (including those for COVID-19)[2]	5 half-lives prior to V2	Not allowed
Hydroxychloroquine, Chloroquine, Methotrexate[1,2]	Starting from screening visit to V2	Not allowed
Systemic immunomodulating or immunosuppressive treatments[1,2]	4 weeks prior to V2	Not allowed

[1]Unless used for treatment of chronic or urgent, acute condition other than COVID-19. No restrictions on corticosteroids with only a topical effect (e.g. inhaled, dermal, otic or opthalic corticosteroids).
[2]In case of COVID-19 disease worsening, please refer to Section 4.2.1 for the details on use of treatment.
[3]Not recommended to be given until after Day 91 unless used with discretion as rescue therapy.

4.2.2.2 Restrictions on diet and life-style

Not Applicable

4.2.2.3 Contraception requirements

Women of childbearing potential (for the definition of WOCBP, please refer to Section 3.3.2) and men able to father a child 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 the trial, and for a period of at least 90 days after the study drug administration. A list of contraception methods meeting these criteria is also provided in the patient information.

For female Patients:
Acceptable methods of birth control for this trial are:

- Hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or post-menopausal for at least one year
- 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)
  - Note that progestogen-only hormonal contraception where inihibition is ovulation is not the primary mode of action is not considered as highly effective
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (if partner is sole sexual partner and has received medical assessment of surgical success)
- Abstinence. This is defined as being in line with the preferred and usual lifestyle of the patient. 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.

For male Patients:
Acceptable methods of birth control for this trial are:

- Barrier contraception (i.e., condom)
- Vasectomised sexual partner with documented absence of sperm
- Abstinence. This is defined as being in line with the preferred and usual lifestyle of the patient.

In addition, men with pregnant partners should use barrier contraception (i.e., condom) during the pregnancy of the partner.

4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol, under supervision of the investigating physician or a designee at the site. At the time of study medication administered, the date, time and route(s) will be entered into the eCRFs.

The only reasons for deviations from the treatment schedule in the protocol would be due to the rare events of dosing mistakes or damaged treatment kits.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Efficacy in the exploratory Phase II part will be assessed via viral load measures of SARS-CoV-2 RNA in NP swabs and OP swabs. The neutralizing MoA of BI 767551 is expected to reduce viral load in the treatment groups to a larger degree compared to placebo.

The confirmatory Phase III part will investigate clinical outcomes for events of hospitalization or death throughout a 28 day period.

5.1.1 SARS-COV-2 RNA Assessment

SARS-CoV-2 RNA levels will be determined from frozen (-80°C) transport medium using a clinically validated quantitative reverse-transcriptase PCR assay (RT-qPCR) at the visits specified in the Flowchart. Results will be provided as Ct (Cycle threshold) values as well as quantitatively (copies/mL) based on a reference standard.

At the screening visit, a single NP, nasal swab or saliva is sufficient to document the absence or presence of SARS-CoV-2 infection by RT-qPCR or antigen test. This will be performed at the trial site's local laboratory and/or Point-of-Care testing. Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test from any respiratory tract specimen (NP, nasal swab or saliva) is also acceptable.

Starting on day of randomisation (Day 1), NP swabs and OP swabs will be collected at clinic visits and remotely (at patient's home). On in-person clinic visits and in-person remote visits, swabs will be collected by a home health care nurse or site staff. Anterior nasal swabs will be self-collected (or collected by home healthcare nurse or site staff) on days outlined in the Flowchart.

Baseline viral load measures taken and analyzed by the central lab will be used for the analysis.

5.1.2 Improvements on the WHO Clinical Progression Scale

The following 11-point WHO Clinical Progression Scale will be used for the assessment of Clinical improvement (Figure 5.1.2:1):

Figure 5.1.2:1 WHO Clinical Progression Scale [R20-2002]

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: **WHO clinical progression scale**
ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed based on adverse events, serious adverse events (SAEs), laboratory parameters, physical examination, and vital signs. Observational period is 90 days. Only descriptive analyses are planned.

5.2.1 Physical examination

A complete physical examination will be performed at Screening (Visit 1). It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Subsequent physical examinations after screening should be targeted to symptoms.

Height and body weight measurements as well as smoking status review will be performed at the time points specified in the Flowchart. The results must be included in the source documents available at the site.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling. This includes systolic and diastolic blood pressure, body temperature, respiratory rate, pulse rate (electronically or by palpation count for 1 minute) and resting peripheral oxygen saturation. Measurements must be taken while patient is in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

At screening to confirm eligibility only respiratory rate, pulse rate (electronically or by palpation count for 1 minute) and resting peripheral oxygen saturation should be taken. Confirmation of PaO_2/FiO_2 ratio <300 only required in case arterial blood sample was previously taken.

At dosing visit (Day 1), vital signs will be assessed pre-dose, at the end of the infusion and 2h (+/- 5 min) after the infusion.

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

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 Flowchart. Patients do not have to be fasted for the blood sampling for the safety laboratory. The maximum volume of blood needed per patient for all laboratory assessments is approximately 300 mL during the course of the trial.

For all scheduled visits, all analysis will be performed by a central laboratory. Local laboratories may be used for safety laboratory assessments in case of urgent need.

Instructions regarding sample collection, sample handling/ processing and sample shipping for all visits after screening are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator.

It is the responsibility of the investigator to evaluate the laboratory reports. 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 central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3:1 Safety laboratory tests

Functional lab group	**Test name**
Anti-SARS-CoV-2[1]	RT-qPCR Anterior nasal swab RT-qPCR Nasopharyngeal RT-qPCR Oropharyngeal
Haematology	Blood typing (only at Baseline) Complete blood count: Red blood cell count (RBC) Haematocrit (Hct) Haemoglobin (Hb) White Blood cell count including differential/Leukocytes Platelet Count/ Thrombocytes
Coagulation and Inflammation	D-Dimer Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International Normalised Ration (INR) C-Reactive Protein (CRP) Ferritin

Table 5.2.3:1 Safety laboratory tests (continued)

Functional lab group	Test name
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gammaglutamyl transferase (GGT) Creatine kinase (CK) Troponin, only if CK is elevated Lactate dehydrogenase Lipase Type B natriuretic peptide (BNP), or NT-proBNP
Electolytes	Potassium Sodium Calcium Chloride Glucose
Substrates	Creatinine Total Bilirubin, Total protein Albumin Uric Acid Urea eGFR
SARS-CoV-2 Antibody Serology[1]	IgG, IgA, IgE[3]
Urine pregnancy test[2]	Human Serum Chorionic Gonadotropin in urine
Serum Pregnancy test[2]	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Leukocytes Esterase Urine pH Specific Gravity Urobilinogen Urine Bilirubin Urine Blood
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sediment Crys., Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes

1 Not for safety parameter but collected for central lab

2 Only for female patients of childbearing potential. Urine and serum pregnancy testing will be performed as indicated in the Flow Chart. In case of remote visits, clinical site may provide subjects with at-home urine pregnancy test kits (may be sponsor-provided)
3 To be performed if a validated assay is available.

5.2.4 Electrocardiogram

Not applicable.

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, 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.

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

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 hospitalization or prolongation of existing hospitalization
- 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 hospitalization 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 eDC 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 5.2.6.1.2.
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 Section 5.2.6.1.2, 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 5.2.6.1.2.

The following are considered as AESIs:

Inhalation related bronchospasm

Inhalation of the investigational medicinal product may result in airway irritation and/or hypersensitivity that can result in bronchospasm manifesting wheezing, prolonged expiration and respiratory distress.

Hypersensitivity/allergic reaction

Any suspicion of severe infusion reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.4; R11-4890)

Infusion of biological products including monoclonal antibodies may be associated with the development of infusion related reactions that can occur during and/or within hours of the infusion. Symptoms of infusion related reactions may be related to immediate hypersensivity (allergic reaction, anaphylaxsis) or cytokine-release syndrome. Symptoms of cytokine release syndrome may include, but are not limited to, fever, tachypnea, headache, tachycardia, hypotension, all types of rashes including flushing, and/or hypoxia.

Potential Severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up 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 sample, or in samples drawn within 30 days of each other, or
- 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 adverse events should be classified and recorded in the CRF according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (also known as the DAIDS AE Grading Table; R21-0379)

For specific events that are not included in the DAIDS AE Grading Table, the generic scale (Table 5.2.6.1.5:1) is to be used:

Table 5.2.6.1.5:1 Generic AE Grading Scale [R21-0379]

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activites; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
Grade 5	Events resulting in death.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compund, 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 trial 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 trial 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.
- There is an 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 individual patient's end of trial (= the End of Study (EoS) visit): all AEs (serious and non-serious) and all 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 drug related SAEs and trial drug 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 5.2.6.1.2), but not on the CRF.

Vital Status Data Collection

Patients who discontinue the trial 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, discontinuation of trial treatment. From then on until the individual patient's end of the trial the investigator must report any occurrence of cancer, report all deaths / fatal AEs regardless of relationship, and trial drug related SAEs and trial drug related AESIs the investigator becomes aware of as well as information on any AEs leading to hospitalization, whether related to trial drug or not.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 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.

[redacted]

Details on sample collection for BI 767551 characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

[redacted]

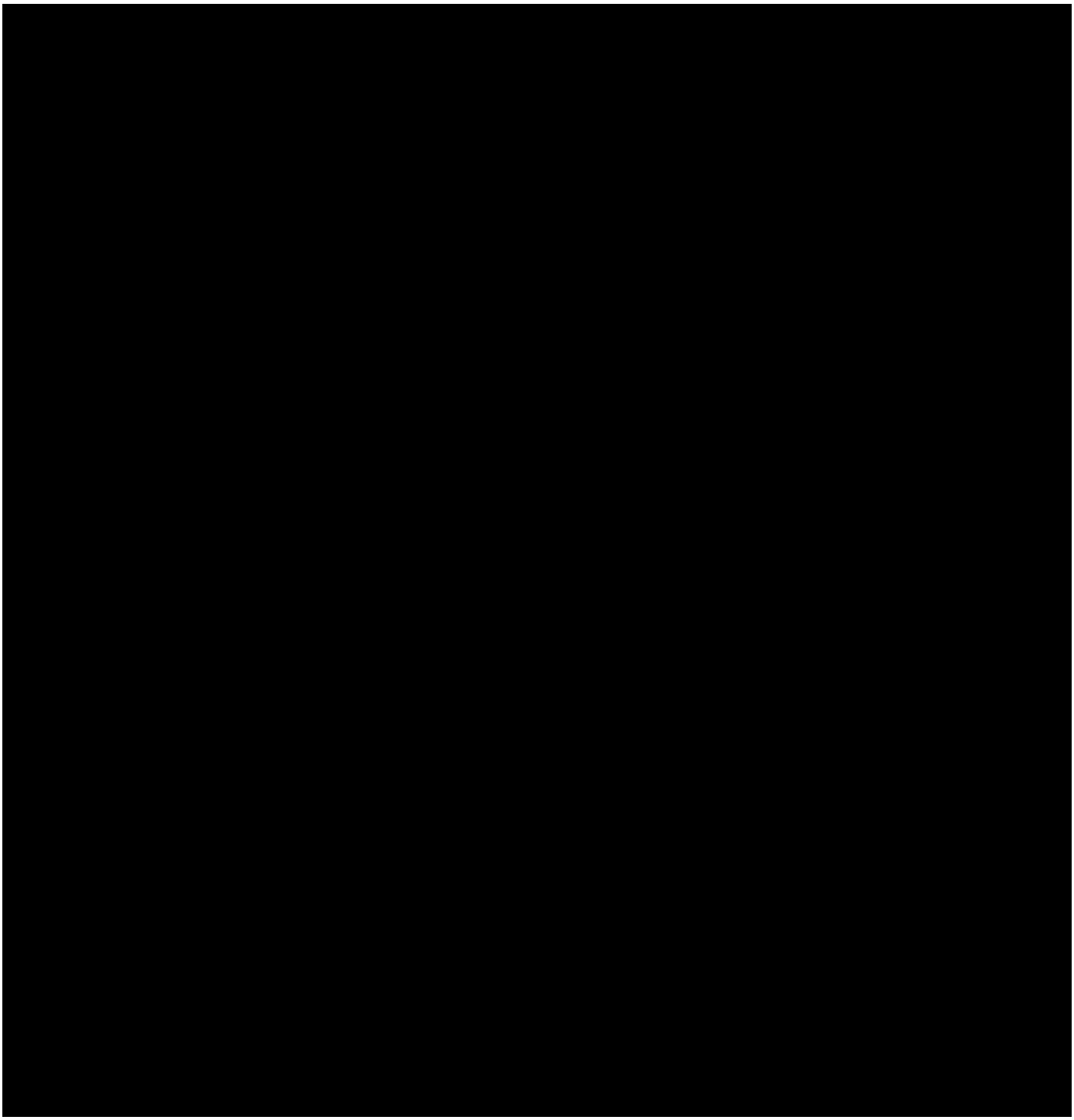
Refer to Section 5.6.2 for other assessments.

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS



[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint measurements will be consistent with the recognized standard for symptomatic ambulatory patients with COVID-19.

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. [redacted]

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

The trial consists of three periods, a screening period, single dose treatment and a follow-up period.

In Phase II, randomised patients will receive a single dose of BI 767551 or placebo as infusion or inhalation. In Phase III, randomized patients will receive a single dose of BI 767551 or placebo as infusion or inhalation.

All required procedures are described in the Flowchart and in Sections 6.2.

After single treatment patients will be followed-up on Day 3,4,8,11,15,22, 29 and Day 91 / EOS visit.

6.1 VISIT SCHEDULE

No study procedures may be initiated prior to the patient or patient's legally acceptable representative signing the informed consent.

All subjects are to adhere to the visit schedule as specified in the Flowchart. Each visit date (with its window) is to be counted from Day 1 (Visit 2 date = visit with first IMP administration). If any visit has to be rescheduled, subsequent visits should be calculated again from Day 1.

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 flowchart and the respective protocol sections. Additional details on procedures at selected visits are provided below.

At all applicable visits vital signs should be collected prior to blood sampling.

NP swabs will be obtained by inserting a swab in one nostril along the nasal septum to the nasopharynx until resistance is felt, reaching a depth that is proximately the length from the outer nostril opening to the ear. Once resistance is felt, the swab will be left in place for a few seconds to allow for absorption of secretions and is slowly removed while rotating. OP swabs will be obtained by swabbing the posterior pharynx and tonsillar areas. Care should be taken to avoid accidental swabbing of the gums, tongue, or teeth. SARS-CoV-2 RNA levels will be determined from frozen (-80°C) transport medium using a clinically validated quantitative reverse-transcripase real-time PCR assay (RT-qPCR) assay. Results will be provided as Ct (Cycle threshold) values as well as quantitatively (copies/ml) based on a reference standard. These assays will be performed at central laboratory.

On days without an in-person visit, the anterior swabs will be self-collected by the patient on their own same time every day, when completing the study diary and temperature measurement. Patients will turn in their self-collected (remote) swabs at their next in-person visit.

6.2.1 Screening and run-in period(s)

Screening Period
Once the patient has consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the enrollment log and be registered in the IRT. Each patient will be assigned a unique patient number, via the IRT system and enrollment will be recorded in eCRF. For the schedule of assessments and procedures during the screening period refer to the Flowchart.

During the screening visit, demographics information will be collected. This includes:

- age on the day of informed consent (in years)
- Sex (male, female in order to describe the subject`s sex at birth),
- For women: of childbearing potential yes / no in order to characterize the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed and to support the calculation of the kidney function via the CKD EPI formula unless not acceptable according to local regulations.

Study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the trial until completion of all study requirements will be emphasized. No trial procedures should be done unless the patient has consented to taking part in the trial.

SARS-CoV-2 infection documentation is recorded on the eCRF. Positive RT-qPCR or antigen test will be obtained prior to randomisation. Documentation of laboratory-confirmed SARS-CoV-2 infection as determined by molecular test from any respiratory tract specimen (NP, nasal swab or saliva) is also acceptable.

Patients will be asked about their first symptoms related to COVID-19 and their current symptoms. The time of symptom onset should be recorded.

Urine pregnancy testing should be done prior to administration of study drug for all women of childbearing potential. Study drug should only be administered in case of a negative test result.

Medical History:
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 or his legal representative, documented in their medical records, would be acceptable. Medical history includes estimated date and time of first SARS-CoV-2 infection symptoms as well as symptom details.

Information on clinically significant previous and concomitant illnesses, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical history at screening.

Patients who do not meet eligibility critera should be documented as a screen failure. The patient must be registered as a screen failure in IRT system.

Re-screening

Re-screening of a previously screen failed patient will be permited once. Patients who have or RT-qPCR or antigen SARS-CoV-2 test within the screening window with a value outside the range specified by the inclusion criteria may have the test repeated once to determine eligibility. The RT-qPCR or antigen SARS-CoV-2 re-test performed must be the same test method used for initial screening and the result must be available within the screening window, prior to Visit 2 (Day 1). All remaining eligibility criteria must also be met. In case of re-screening patient will obtain new patient number per IRT.

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.

Baseline Conditions

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

In addition, as noted in Section 5.2.6.1. if any worsening of the underlying disease or of other pre-existing conditions or changes in vital signs, physical examination and laboratory test results, as judged clinically relevant by the investigator already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

6.2.2 Treatment Period(s)

The patient is randomised (Day 1; Visit 2) not later than 3 days after information consent upon confirmation of the eligibility criteria via IRT. Study medication dispensing and administration can occur on the same day (Day 1).

For the schedule of assessments and procedures during the treatment period refer to the Flowchart.

For Dosing and Treatment schedule please refer to Section 4.1.

The below procedures should be completed in the following order prior to trial drug administration. Those listed as optional do not need to be repeated when Visit 1 and Visit 2 are performed on the same day.

- Review of eligibility criteria (optional)
- SARS-Cov-2 symptoms review (optional)
- 11-point WHO Clinical progression scale (optional)
- Medical History (optional)
- Physical examination (optional)
- Vital signs
- Safety blood and urine samples collection
- Serum pregnancy test (see below for details on pregnancy testing)
- Blood samples for inflammatory and coagulation markers
- [redacted]
- NP [redacted] swabs will be collected by site staff (If Visit 2 occurs on the same day as Visit 1 and the sample collected for screening was NP or nasal, the Visit 2 NP sample should preferably be taken from the other nostril). Care must be taken to ensure one (1) sample is taken at screening for eligibility and the second sample is taken as part of V2 procedures.
- [redacted]
- Dispensing of study diary
- IRT call (Phase II only: weight needed in IRT for weight-based dosing)

The patient will be monitored for possible infusion reactions and inhalation related reactions (bronchospasm) at the site for approximately 2 hours following study drug administration.

Vital signs will be assessed pre-dose, at end of infusion, and at approximately 2 hours after study drug administration. See Section 5.2.2.

Symptom targeted physical examination will be performed on day of treatment (if V1 and V2 are performed on separate days). See Section 5.2.1

Blood sampling shall be done prior to study drug administration. Patients do not have to be fasted for the blood sampling for the safety laboratory.

[redacted]

Pregnancy test for women of childbearing potential only. Negative urine pregnancy test must be confirmed prior to study drug administration. Serum test required at Visit 2. In case remote visits

are planned during the follow-up period, clinical site may provide subjects with at-home urine pregnancy test kits (may be sponsor-provided).

NP [redacted] swabs will be taken by study staff for SARS-CoV-2 testing prior to IMP administration.

[redacted]

On day of treatment, participants will complete the study diary with site staff prior to IMP administration. Participant's answers will be recorded into the eCRFs. Participants will be asked to complete the diary at approximately the same time every day.

Participants will be given a thermometer and pulse oximeter to record their temperature and oxygen saturation each day in the diary.

Sites will capture information for a secondary contact that the site can contact if the participant cannot be reached (e.g. spouse, friend, neighbour). Contact information for secondary contacts will not be recorded in the eCRF

Concomitant medication review
Data concerning concomitant medications will be collected throughout the trial, as specified in the Flowchart.

Adverse event review is to be done at every visit, see Section 5.2.6 for more details.

6.2.3 Follow-up period and trial completion

Patients will be followed after treatment period up to Day 91. Follow-up period consists of 8 visits: Days 3,4,8,11,15,22,29 and Day 91 /EOS visit.

For the schedule of assessments and procedures during the follow-up period refer to the Flow chart. Sites will review with patient if there are any updates to the information provided for their secondary contact. Contact information will not be recorded in the eCRF

Participants will complete a study diary by recording their temperature, oxygen saturation and completing all questions every day up to protocol Day 29 (within the visit window). On days with a clinic or remote visit, patients will be reminded to complete all entries every day (preferably the same time every day) and to bring their diary with them to the next clinic visit. Clinic visit diary entry may also be completed at the clinic. In case of remote visits, every effort should be made to retrieve the study diary answers (or a copy of the answers), otherwise retrieve

the study diary from the participant at the next clinic visit. Guidance for reviewing and data entry of the participant's answers will be provided in the ISF.

NP [redacted] swabs will be collected during in-patient visits as per Flowchart by site staff.

[redacted]

Symptom targeted physical examination will be performed up to Day 91. Weight will be collected at Days 29 and 91.

Vital signs measurements shall include blood pressure measurement, body temperature, respiratory rate, pulse rate and resting peripheral oxygen saturation. Measurements shall be performed before blood sampling at each clinic visit until Day 29.

Blood samples for haematology and chemistry will be collected at timepoints indicated in the Flowchart. For women of childbearing potential urine pregnancy tests will be performed at timepoints indicated in the Flowchart. In case urine pregnancy test positivity, serum pregnancy test shall be performed as well.

Blood samples (plasma and serum) for inflammatory and coagulation markers will be collected at time points indicated in the Flowchart.

[redacted]

Concomitant therapy information is to be collected at each visit, during on site visit or per telephone or e-mail during remote visits until Day 91 and at last visit in case patient discontinues the trial prematurely before completion Day 29.

AEs/SAEs collection shall be performed until Day 91 and at last visit in case patient discontinues the trial prematurely before completion Day 29.

If needed in the opinion of the investigator, after the EoS (End of Trial) visit additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

Vital status information is to be collected for each patient that completes the EOS visit. In case patient discontinues the trial prematurely before their scheduled EOS visit, vital status information and information whether the patient has been hospitalized shall be collected at planned completion date of each individual patient. Any locally approved means of vital status information collection is accepted.

Early treatment discontinuation

In case the infusion or inhalation of study drug is permanenty discontinued before the whole amount of prepared solution has been administered to the patient, drug administration will not be re-initiated. Patients should be encouraged to follow all study procedures until their individual EOS visit. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation (see Section 3.3.4.1) and follow up as outlined in the Flowchart (and Section 6.2.3).

Trial completion:

Trial completion is defined as a patient having reached the EOS visit. EOS visit will be at Week 12, Day 91.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Phase II of the study is exploratory in nature. Phase III has a group-sequential design with two planned interim analyses. Further details about the interim analyses can be found in Section 7.2.8. The methods to control the global overall significance level for the primary endpoint are described in Section 7.1. Sample size calculations and information on the O'Brien and Fleming local nominal alpha levels for the different interim analyses and the final analysis and the probabilities of stopping the trial at an interim analysis or at the final analysis are summarized in Table 7.5.2:1.

7.1 NULL AND ALTERNATIVE HYPOTHESES

In Phase II, no confirmatory testing is performed and hence no null and alternative hypotheses are defined. All p-values are to be understood as exploratory. A justification of the sample size is provided in Section 7.5.1.

In Phase III, the superiority of BI 767551 compared to placebo will be tested for the proportion of patients hospitalized or who died from any cause by Day 29.

The null hypothesis is:
H0: The probability to get hospitalized or to die by Day 29 in the BI 767551 arm is equal to the probability to get hospitalized or to die by Day 29 in the placebo arm.

The alternative hypothesis is:
H1: The probability to get hospitalized or to die by Day 29 in the BI 767551 arm is smaller than the probability to get hospitalized or to died by Day 29 in the placebo arm.

The control of the global overall significance level of 2.5% (one-sided) is assured for the primary endpoint as follows: Adjustments accounting for the planned interim analyses are done using the Lan-DeMets spending function approach with an O'Brien and Fleming boundary. For the primary endpoint, statistical significance will be declared (either at one of the interim analyses or in the final analysis) if the analysis is significant at the local nominal one-sided alpha level. These O'Brien and Fleming local nominal one-sided alpha levels are given in Table 7.5.2:1 for each interim and the final analysis for the planned information fraction. The one-sided p-value is required for the primary endpoint due to the use of a group sequential design.

7.2 PLANNED ANALYSES

7.2.1 General considerations

In Phase II, efficacy analyses will be based on all randomised patients that have been treated.

In Phase III, efficacy analyses will follow the intention-to-treat principle and will include all randomised patients whether the patient is treated with the study medication or not. For the confirmatory analysis of the primary endpoint of Phase III of the study, only the data of the patients randomised in Phase III will be included.

Safety analyses will include all treated patients who are documented to have taken any dose of the study medication and will be reported separately for Phase II and Phase III patients, as well as integrated across both parts where possible.

In Phase II, all analyses will be based on the treatment group as treated. In Phase III, all analyses will be based on the treatment group as randomised by IRT.

Although there is no per protocol data set in the study, reasons for important protocol deviations will be specified in the TSAP. Patients with important protocol deviations will be identified at Review Planning Meetings and listed in the CTR.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:

- Start of a product with a similar mode of action as trial medication that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA)
- Start of a restricted medication as defined in Table 4.2.2.1:1, except any product with a similar mode of action as trial medication that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA)
- Death

The strategies for handling intercurrent events in this trial are as follows:

Primary strategy: This is the effect of randomising a patient to a treatment, but excluding the effects of any other products with a similar mode of action as trial medication that have proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA). Start of a restricted medication as defined in Table 4.2.2.1:1, except any product with a similar mode of action as trial medication that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA) will be handled using the treatment policy approach as defined in ICH E9(R1). Death will be handled using the composite approach as defined in ICH E9(R1). The use of any other products with a similar mode of action as trial medication that have proven efficacy will be handled using the while-on-treatment approach as defined in ICH E9(R1), with the treatment period defined as the period from first administration of randomised medication to the end of the residual effect period or to the start of the intercurrent event, whichever occurs first.

Secondary strategy: This strategy is similar to the primary strategy, except for the intercurrent event “use of any other products with a similar mode of action as trial medication that have

proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA)", which will be handled using the composite approach as defined in ICH E9(R1).

Table 7.2.2:1 provides an overview of the handling of intercurrent events within the different strategies.

Table 7.2.2:1 Handling of intercurrent events as per ICH E9(R1) within the different strategies

Intercurrent Event	**Strategy for handling of intercurrent events**	
	Primary strategy	**Secondary strategy**
Start of a product with a similar mode of action as trial medication that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA).	While-on-treatment	Composite
Start of a restricted medication as defined in Table 4.2.2.1:1, except any product with a similar mode of action as trial medication that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA)	Treatment policy	Treatment policy
Death	Composite	Composite

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.
The handling of intercurrent events that are not listed will be decided during blinded review and will be documented in the TSAP.

7.2.3 Primary objective analyses

Primary endpoint analyses in Phase II

The primary endpoint of Phase II is defined in Section 2.1.2.

Viral load data will be log-transformed prior to analysis. Time-weighted average change in $\log_{10}$ viral load from baseline is defined as:

$$\frac{\sum_{i=a}^{b-1}\{0.5 * (Y_i + Y_{i+1}) * (t_{i+1} - t_i)\}}{(t_b - t_a)}$$

- Where
  - a = baseline assessment at Day 1
  - b = last assessment at or prior to the threshold day (Day 8 for the primary endpoint)
  - Y_i = change from baseline in $\log_{10}$ viral load at visit i (and where Y_a=0)
  - t = time at the specified time point (the actual study day)

An analysis of covariance (ANCOVA) model with $\log_{10}$ baseline viral load and baseline serology status as covariates will be used. Adjusted means and 95% confidence intervals (CIs) will be provided by treatment group. The ratio of the mean time-weighted change from baseline in $\log_{10}$ viral load will be used to quantify the treatment effect, comparing each active treatment arm to placebo as the reference. Intercurrent events will be handled using the Primary strategy as defined in Section 7.2.2.

Primary endpoint analyses in Phase III

The primary endpoint of Phase III is defined in Section 2.1.2.

The cumulative proportion of patients hospitalized or dying by Day 29 will be estimated for each randomised group using Kaplan-Meier (KM) methods to take account of losses to follow-up. It will be estimated overall and within each stratum. The analysis will be stratified by "high" versus "low" risk of progression to severe COVID-19 and baseline serology status.

For patients with known event of hospitalization or death:

Time to hospitalization or death [days] = earlier date of hospitalization or death – date of randomisation + 1.

For patients with no known event of hospitalization or death or where censoring rules apply:

Time to hospitalization or death [days] = date of censoring – date of randomisation + 1.

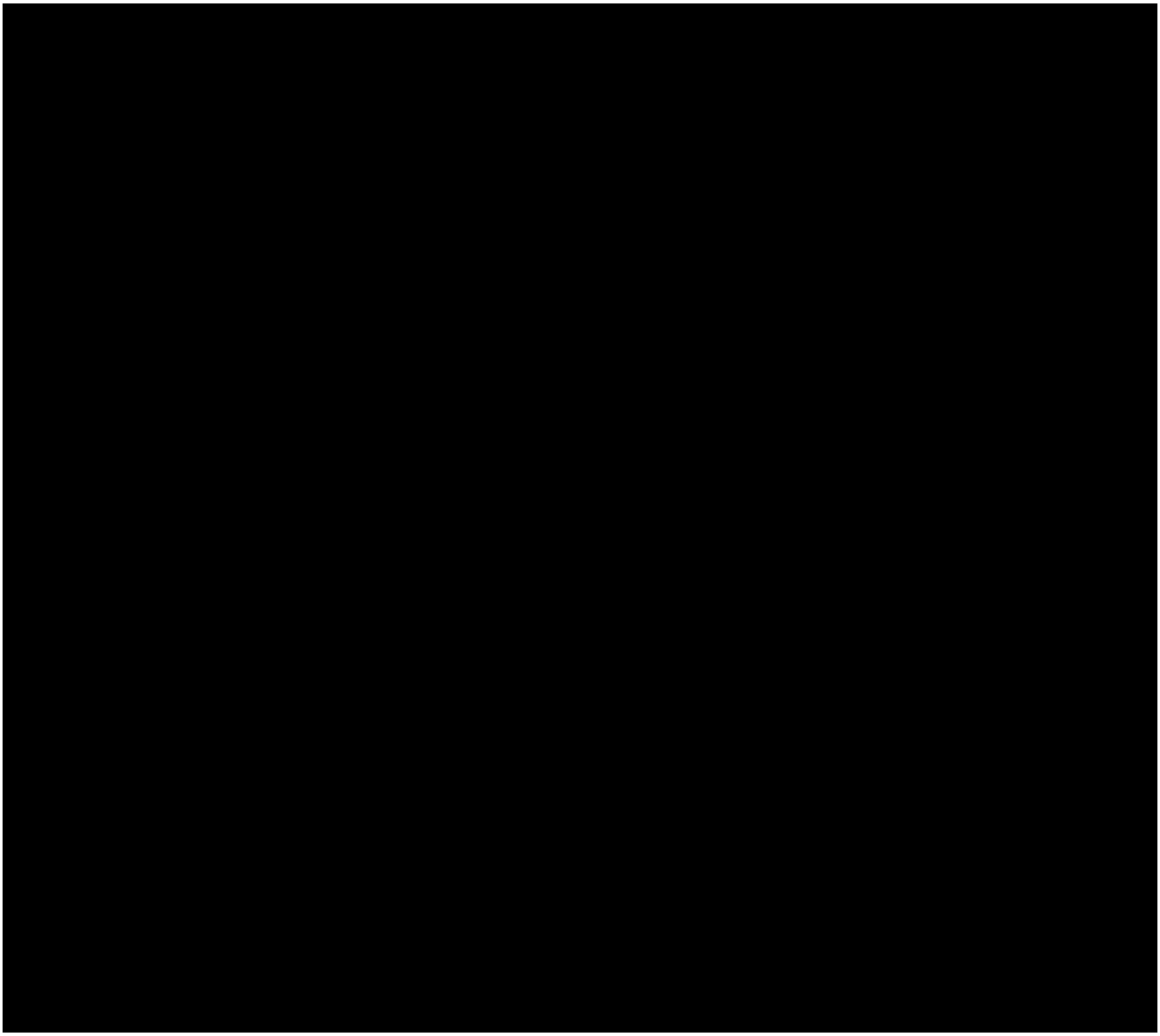
Missing data are handled by using survival analysis techniques. Intercurrent events will be handled using the Primary strategy as defined in Section 7.2.2. For further details on censoring rules of the primary analysis, refer to Table 7.3.1:1.

At each interim analysis and the final analysis, the two-sided asymptotic 95% repeated confidence interval for the difference in the KM hospitalization or death probability estimate by Day 29 will be found within each stratum. Repeated confidence intervals will be derived as described in (R20-3707).

Since the observations in the two treatment groups are independent, the variance of the Kaplan-Meier probability difference is equal to the sum of the Kaplan Meier probabilities' variances found by Greenwood's method.

The difference in the Kaplan-Meier estimates by Day 29 overall will be calculated as the weighted average of the estimated Kaplan-Meier probability differences within each stratum. The weights will be defined as the "Mantel-Haenszel" weights, using the derivation as described in Greenland and Robins (R09-1299). The variance for the overall risk difference will be calculated accordingly. The two-sided asymptotic 95% repeated confidence interval for the Kaplan-Meier probability differences will be shown overall and within each stratum.

One sided p-values will be obtained from a z-test and will be compared with the O'Brien and Fleming local nominal alpha levels.



[redacted]

7.2.4 Secondary objective analyses

No key secondary endpoints have been defined for this study.

Secondary endpoints are defined in Section 2.1.3.

Time-weighted change from baseline endpoints will be analysed as described in Section 7.2.3 for the Phase II primary endpoint.

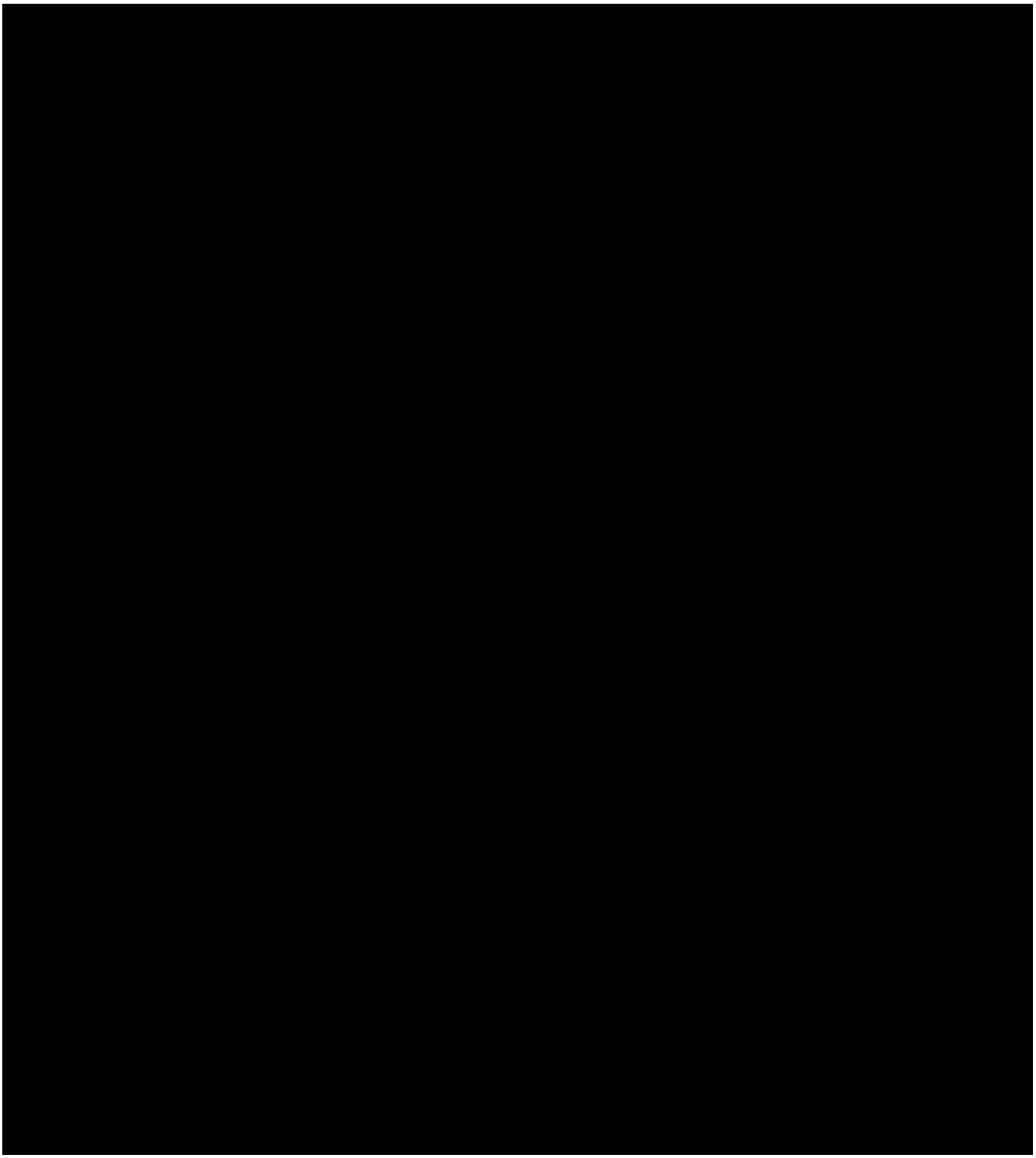
Endpoints relating to the occurrence of a certain event by Day 29 (such as Hospitalization by Day 29, Hypoxia or hospitalization or death from any cause by Day 29, Hypoxia by Day 29) will be analysed as described in Section 7.2.3 for the Phase III primary endpoint.

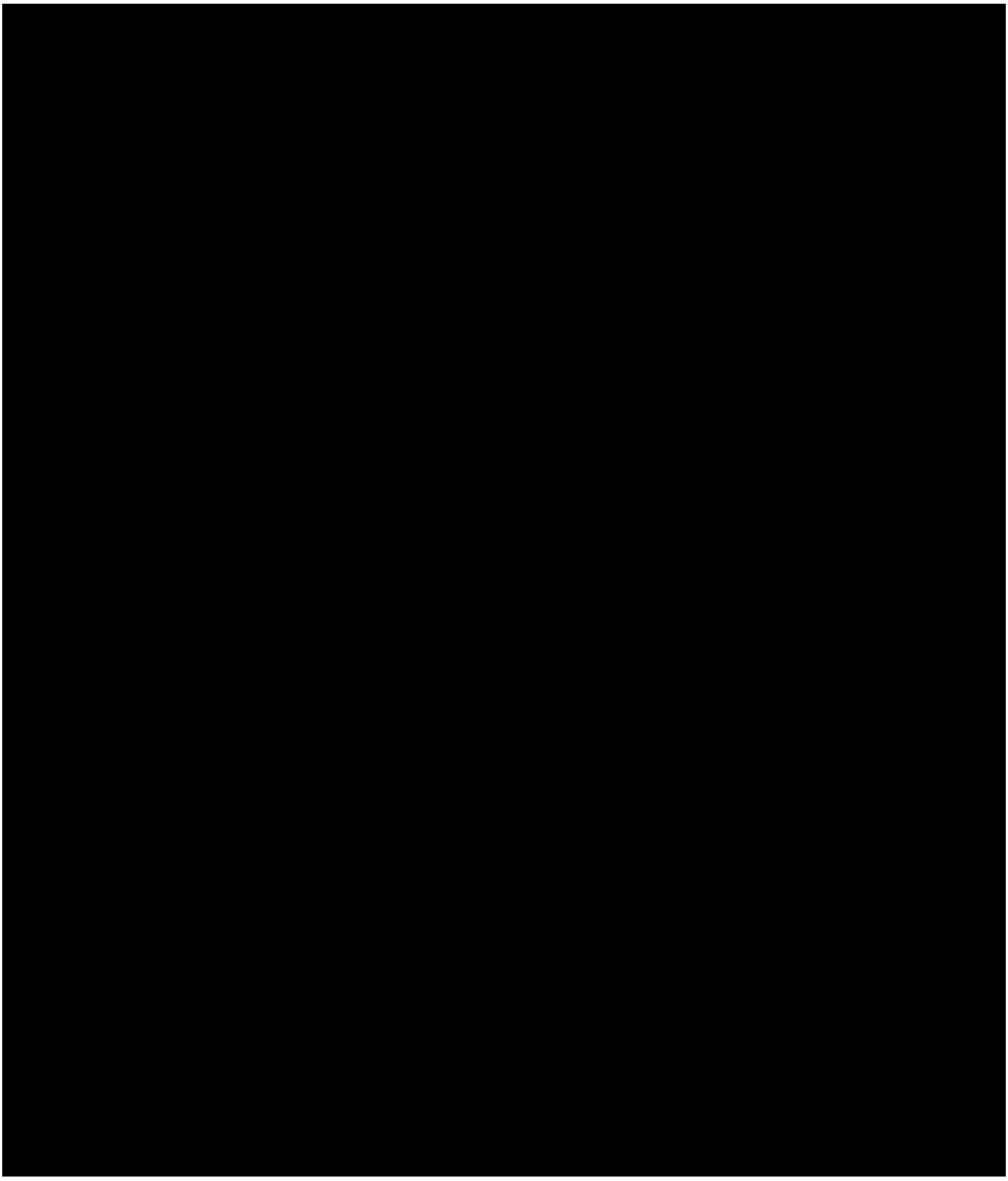
For binary endpoints, comparisons between treatment groups will be performed using a logistic regression model adjusting for the binary covariate baseline serology status. For binary endpoints that are not based on viral load data, “high” versus “low” risk of progression to severe COVID-19 will also be included in the model as a covariate. A likelihood-ratio test will be performed to evaluate the differences between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing each active treatment arm to placebo as the reference.

For time-to-event endpoints, a Cox proportional-hazards model will be used to derive the hazard ratio and 95 % confidence interval (CI) of the active treatment regimens versus placebo. The model will include baseline serology status as covariate. For endpoints that are not based on viral load data, “high” versus “low” risk of progression to severe COVID-19 will also be included in the model as a covariate. Breslow’s method for handling ties will be used. A log-rank test will be used to evaluate the effect of each active treatment arm compared to Placebo. Kaplan-Meier plots by treatment group will also be presented. The cumulative proportion of patients presenting an event will be estimated for each treatment group using Kaplan-Meier methods. For those endpoints where a sufficient number of events can be observed to calculate the median time-to-event, the median and the corresponding 95% CI using Greenwood variance that is incorporated into the Brookmeyer and Crowley method (R09-6372) with a loglog transformation will be provided for each treatment group.

Any p-values presented for the secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made. Two-sided p-values will be provided.

The strategy for handling of intercurrent events will be specified in the TSAP for secondary endpoints.





[redacted]

7.2.6 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. All adverse events with an onset between start of treatment and end of the REP, a period of 90 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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 (as graded according to DAIDS Table 5.2.6.1.5:1 [R21-0379]), 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.

7.2.7 Other Analyses

This section is not applicable.

7.2.8 Interim Analyses

In Phase II, an unblinded interim analysis will take place after all patients have completed one week of follow-up. This interim analysis will be performed by the sponsor. The purpose of this exploratory interim analysis is to perform an evaluation of the pharmacological activity by looking at viral load data over time from all patients of this Phase II part. If the drug does not have the expected effect on viral load, no effect on clinical endpoints can be expected. In this case, the trial will be stopped after the exploratory Phase II part. Otherwise, the confirmatory Phase III part of the trial will be started. One active treatment arm will be kept in Phase III depending on data collected and evaluated in the Phase II part. Data from patients included in the Phase II part of the trial will not be used for any confirmatory analyses.

In Phase III, two interim analyses are planned: a first interim analysis is planned after approximately 33% of patients have been followed up for 28 days. The second interim analysis is planned after approximately 67% of patients have been followed up for 28 days. Depending on the primary endpoint results based on the data available at the time of the interim analyses, the decision will be taken to either continue the trial or to stop the trial, either for efficacy or for futility.

If the trial claims for early efficacy at the first interim analysis the recruitment will continue until a total of 650 patients are included in the Phase III part of the trial. At the point of claiming for early efficacy at the first interim analysis the placebo arm will stop recruitment. Both interim analyses in the Phase III will be performed by a DMC and only the DMC will get access to unblinded data.

The DMC will also review data on a regular basis during Phase II and Phase III.

7.3 HANDLING OF MISSING DATA

7.3.1 Efficacy endpoints

For the analysis of the primary endpoint of Phase II and of other continuous endpoints, missing data will not be imputed. For continuous endpoints analysed using a MMRM, the mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption".

For the analysis of the primary endpoint of the Phase III and of other time-to-event endpoints or endpoints assessing the occurrence of an event by a pre-defined timepoint, missing or incomplete data will not be imputed but will be handled using standard survival analysis techniques (i.e. censoring). For the primary analysis of the primary endpoint the censoring rules are outlined in Table 7.3.1:1.

Table 7.3.1: 1 Censoring Rules for the primary analysis of the primary endpoint of Phase III

Rule #	Situation	Outcome (event or censored)	Date of event or censoring
1	Patient has been hospitalized or has died within the first 29 days and date of hospitalization or death is known	Event	Date of event
2	Patient has been hospitalized or has died within the first 29 days and date of hospitalization or death is unknown	Event	Imputed date of event: 1 day after the date of last contact when the patient is known to be alive and not hospitalized
3	Patient is alive and has not been hospitalized within the first 29 days	Censored	Day 29
4	Patient is alive and has not been hospitalized within the first 29 days but has started within the first 29 days another drug with a similar mode of action as study treatment that has proven efficacy (either preliminary via EUA by FDA or via full approval by the FDA or EMA).	Censored	Start date of drug with similar mode of action
5	Unknown	Censored	Date of last contact when the patient is known to be alive and not hospitalized

[redacted] Censoring rules for secondary or further endpoints will also be provided in the TSAP.

For the analysis of the categorical endpoints, missing data will be imputed using the worst

case. Further details will be provided in the TSAP.
For further endpoints, handling of missing data will be described in the TSAP.

7.3.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

[redacted]

7.4 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment.

At the start of Phase II, patients will be randomised in a 2:2:2:1 ratio to either Placebo i.v. + Placebo inhaled, BI 767551 i.v. low dose + Placebo inhaled, BI 767551 i.v. high dose + Placebo inhaled, or Placebo i.v. + BI 767551 inhaled, respectively. Following CTP amendment 1, it is planned to include patients in an equal allocation ratio to each treatment arm (1:1:1:1 ratio). Therefore, patients will be randomised in a 1:1:1:2 ratio to receive a single dose of either Placebo i.v. + Placebo inhaled, BI 767551 i.v. 10 mg/kg dose + Placebo inhaled, BI 767551 i.v. 40 mg/kg + Placebo inhaled, or Placebo i.v. + BI 767551 250 mg inhaled, respectively, once approximately 112 patients have been randomised using the initial randomisation ratio. When approximately 112 patients have been randomised, the randomisation scheme will be implemented in sites or countries with approval for CTP amendment 1. At the time of implementation of the revised scheme, sites or countries may be placed on hold for recruitment until approval of CTP amendment 1 is granted.

No stratification will be used.

In Phase III, approximately equal numbers of patients will be randomised to each treatment group. Randomisation will be stratified by “high” versus “low” risk of progression to severe COVID-19. High risk is defined as patients who meet at least one of the following criteria:

- Have a BMI ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years and <65 years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease/other chronic respiratory disease.

There is no minimum number of "high" risk patients required for this study.

BI will arrange for the randomisation and the 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 CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

7.5.1 Determination of sample size for Phase II

To determine the sample size for the Phase II part of the trial, we simulated log10 scale viral load data over time per patient similar to the results published for other neutralizing antibodies (R20-3600, R20-3601). The average reference slope is 1.25 (similar to R10933+R10987 8.0g IV in 10^6 in (R20-3600) and similar to LY-COV555+LY-CoV016 in (R20-3601)). An additional average slope of 0.85 for the treatment arm is assumed similar to the results published for other neutralizing antibodies (R20-3600, R20-3601).
Table 7.5.1:1 shows the likelihood of an AUC ratio above different thresholds calculated on 1000 simulation runs with varying number of patients per treatment arm.

Table 7.5.1:1 Percentage of simulation runs with AUC ratio for one treatment group above thresholds ("true positives"/power).

	AUC ratio				
Number of patients per treatment arm	>1.5	>1.45	>1.4	>1.35	>1.3
40	66%	74%	81%	87%	92%
50	69%	78%	85%	90%	94%
60	72%	81%	88%	93%	96%

Table 7.5.1:1 shows that a sample size of 50 patients per treatment arm gives a probability of 85% that the AUC ratios are above 1.4. We consider this to be sufficiently large probability (>80%) to show a relevant difference in time weighted viral load between the treatment arms (measured by the AUC ratio). Furthermore, an evaluation of false positive signals showed that the probability for an AUC ratio >1.4 is 2% if there is no difference in the slope between the treatment arms.

Table 7.5.1:2 shows the likelihood of an AUC ratio above different thresholds for at least one out of three treatment groups (two i.v. and one inhaled) calculated on 1000 simulation runs with varying number of patients per treatment arm.

Table 7.5.1: 2 Percentage of simulation runs with AUC ratio for at least one out of three treatment groups above thresholds ("true positives"/power).

	AUC ratio				
Number of patients per treatment arm	>1.5	>1.45	>1.4	>1.35	>1.3
40	76%	83%	88%	94%	97%
50	79%	87%	91%	95%	98%
60	82%	90%	94%	97%	99%

Table 7.5.1:2 shows that a sample size of 50 patients per treatment arm gives a probability of 91% that the AUC ratios are above 1.4. This is a sufficiently large probability to show a relevant difference in time weighted viral load between the treatment arms (measured by the AUC ratio). Furthermore, an evaluation of false positive signals showed that the probability for an AUC ratio >1.4 is only 4% if there is no difference in the slope between the treatment arms.

7.5.2 Determination of sample size for Phase III

In Phase III, with a sample size of 641 per treatment group, the study has 80% power to detect a relative reduction of 50% in the proportion of patients hospitalized or dying over 29 days between the study groups (BI 767551 vs. placebo), using the following assumptions:

- There are limited data available on the treatment effect and variability for the primary endpoint. Based on recent publications, the proportion of patients who get hospitalized or die over 29 days in the placebo arm is assumed to be 7.5%.
- Two interim analyses and one final analysis, with stopping guideline for efficacy of BI 767551 versus placebo determined using the Lan-DeMets spending function approach with an O'Brien and Fleming boundary.

[redacted]

Table 7.5.2:1 summarizes the details of such a design.

Table 7.5.2:1 Design details and sample size calculation for a group sequential design in Phase III

Assuming that only a low number of patients might be lost to follow up, it is planned to randomise approximatively 1300 patients in Phase III.

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 or delegate 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 CTR.

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 investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

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 or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, 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.

The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

Due to COVID-19 restrictions study conduct, including site monitoring and access to source documents, may need to be adjusted accordingly. See Appendix 10.3 for further details.

For the eCRF, 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, including dispensing of trial medication
- 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

During the conduct of the study, it may not be possible for the investigator / institution to allow site trial-related monitoring, audits, IRB/IEC review or regular inspections due to COVID-19. However, once site visits are allowed again, the site will need to provide a direct access to the eCRF 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 eCRFs 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

Not Applicable

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 Study is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the 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.
Last Patient Last Visit for Primary Endpoint (LPLVPE) **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. (please refer to Section 2.1.2 Primary Endpoints)
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.

Principal Investigators participating in the trial include those with a specialty in infectious disease, critical care, or pulmonary disease.

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 results from the unblinded interim analysis for the Phase II will be shared with the DMC for review of safety and efficacy data and to provide recommendation how to move forward with the trial.The DMC will recommend to the sponsor whether to continue or stop the trial due to safety or ethical concerns. Two interim analyses will be performed by the DMC during Phase III. Thse

analyses encompass futility and efficacy. Only the DMC will have access to unblinded data during this portion of the study. Measures will be put in place to ensure blinding of the project and trial team and all other trial participants during the conduct of each Phase (see Section 4.1.5 for further details). The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

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.

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 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.

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operative Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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.

A central laboratory service, a central images service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 INSTRUCTIONS FOR THE USE OF THE AEROGEN SOLO NEBULISER

BI 767551 nebuliser solution (50gm/mL) is intended to be nebulized undiluted or diluted with co-supplied Solvent for dilution of BI 767551. The materials for administration of the study medication are: Aerogen® Solo nebuliser, Aerogen® Pro-X Controller, Aerogen® Ultra and Mouthpiece

The Aerogen® Solo nebuliser and Aerogen® Ultra are for single patient use only, not to be used on more than one patient to prevent cross infection. The Aerogen® Pro-X Controller is for re-use.

Refer to the Aerogen Solo System Instruction Manual document in the ISF for information on how to install the system and conduct the inhalation procedure. The following steps are outlined in the Instruction Manual and should be performed:

1. Assemble the Aerogen® Solo system

   **Always perform a functional test of the Aerogen® Solo before use as described in the Functional Test section of the manual

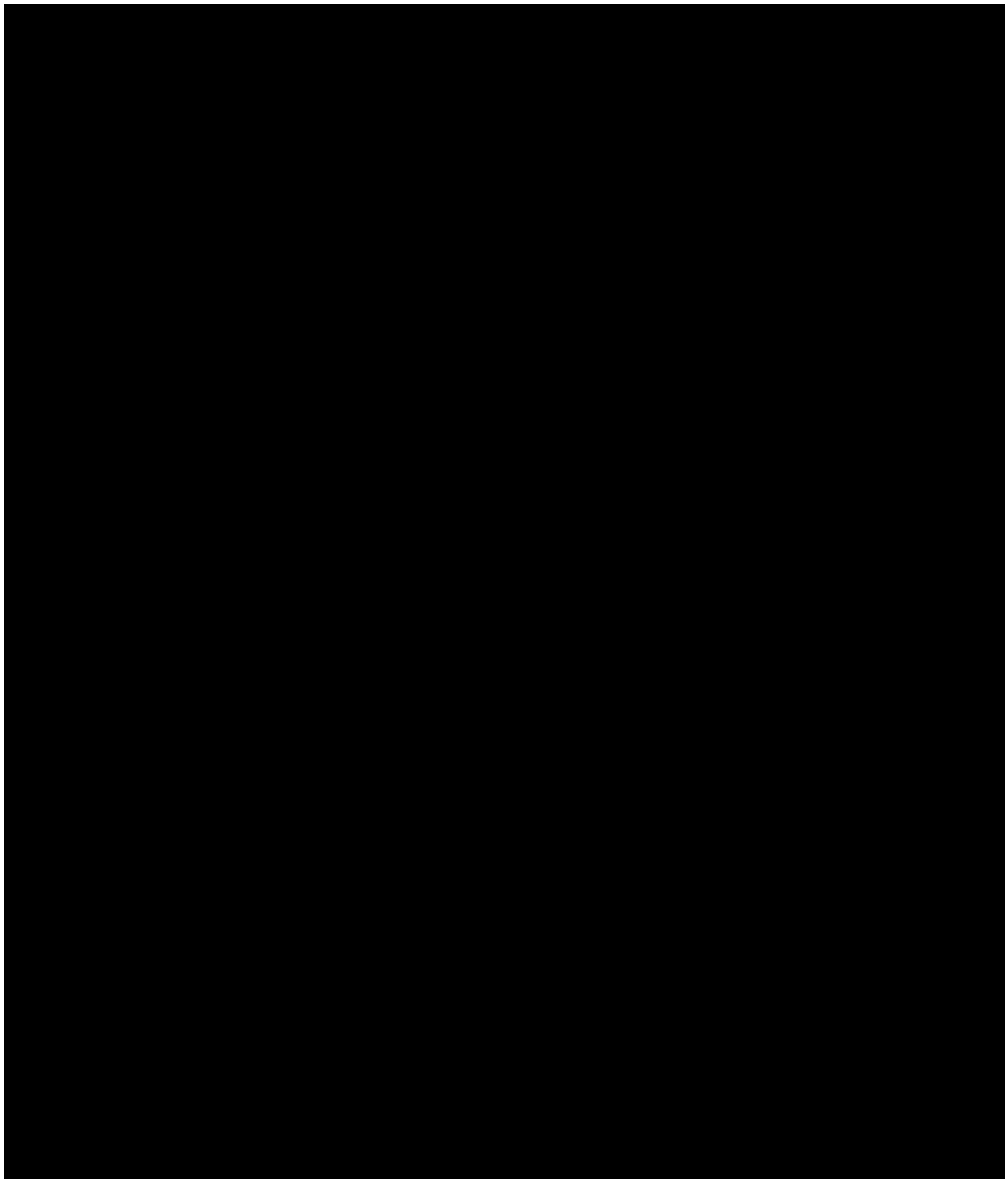
2. Follow the instructions for Installation for use Off-Ventilator for Use with a Mouthpiece

3. Once the nebuliser is assembled for use, transfer content of the syringes[1] to the nebuliser product chamber.

The inhalation procedure will take approximately 15-20 minutes.

Following completion of the inhalation, the used Aerogen® Solo nebuliser and Aerogen® Ultra will be discarded as per local standard procedures. The Aerogen® Pro-X Controller should be cleaned after each use following the instructions outlined in the Instruction Manual.

[1]Refer to the BI 767551 nebulization Medication Handling Instructions in the ISF for complete instructions on storage, handling preparation and administration of the nebuliser solution.



10.3 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

Due to restrictions during the COVID-19 pandemic, study conduct may need to be adjusted.

In exceptional cases, when it is impossible to conduct the visits at the trial site, visits may be performed at the patient's home or remotely (via telephone and/or internet based means of communication). The visits may also be performed as a combination of home and remote visits. Based on the benefit-risk assessment (see Section 1.4), the visit procedures may be adjusted for the purpose of particular visits, whereby critical safety measures will remain in place. All home/remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country need to be respected for all modifications.

Under these circumstances, the following modifications can be considered:

Remote visit

If a patient is not able to come to the site for an outpatient visit, a remote visit (by phone) should be performed instead and all assessments that can be done by phone should be performed.

Assessments that can be performed during a remote visit are:
Collection of adverse events, concomitant therapy, vital signs, physical exam, 11-point WHO Clinical Progression Scale data collection, collection of NP swabs, and review of study diary. If home visits by trial staff members are possible, further assessments can be done.

Safety lab, other laboratory tests

Blood analysis for safety laboratory can be done in a local laboratory outside the hospital. The results of the laboratory tests are to be reported and transferred to the investigator, who has to ensure medical review and proper documentation in the eCRF.

Monitoring

Due to the nature of this trial and the risks associated with COVID-19, site monitoring visits as physical on-site interaction may not take place, the focus will be on centralized oversight/monitoring.
Site initiation visit (SIV), Site monitoring visits (SMV) and Site close out visits (COV) will occur remotely unless the Trial Team requires a visit to be on site due to an identified risk where the required mitigation may need to be performed on-site.

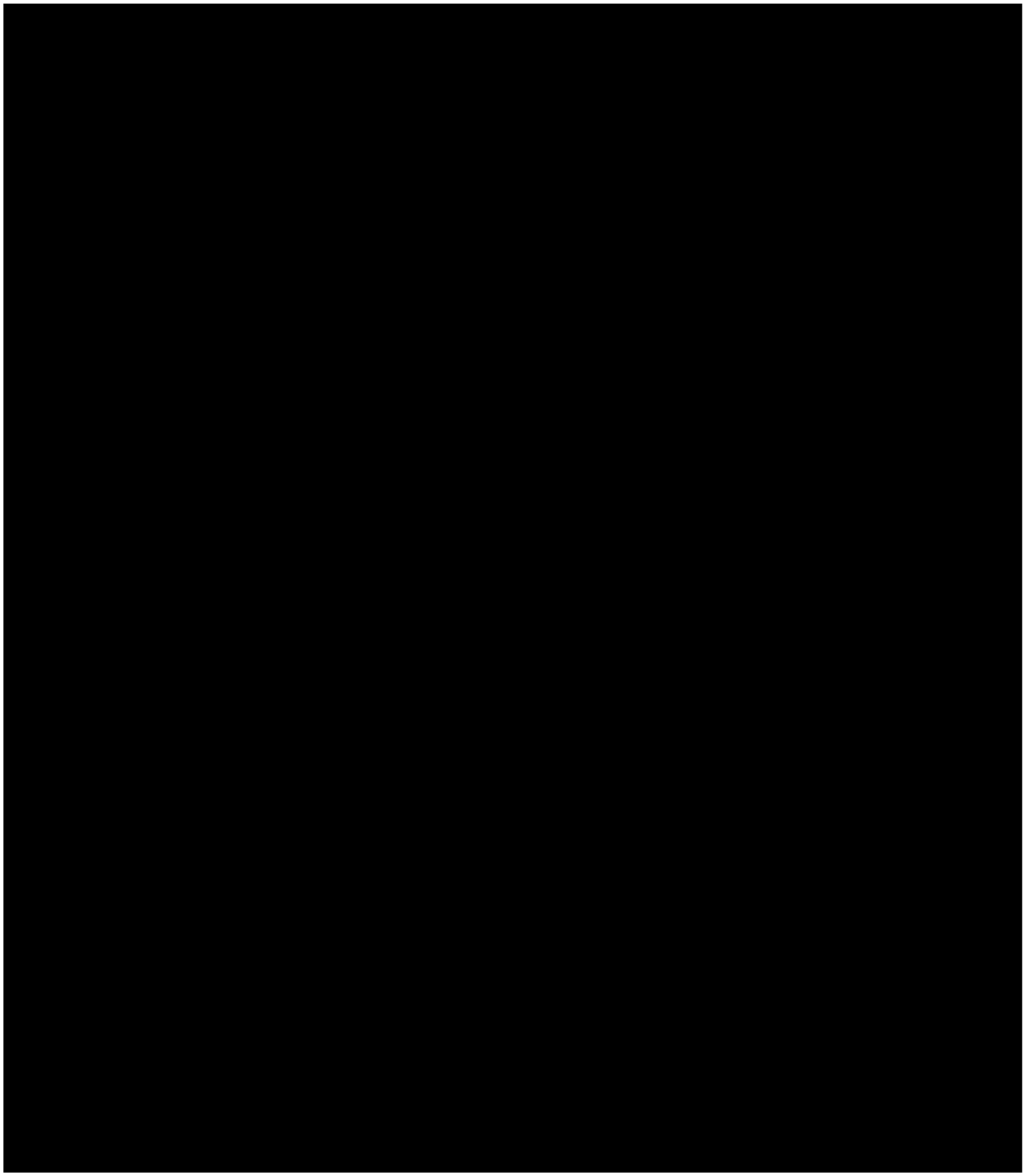
10.4 DIAGNOSIS OF ANAPHYLAXIS

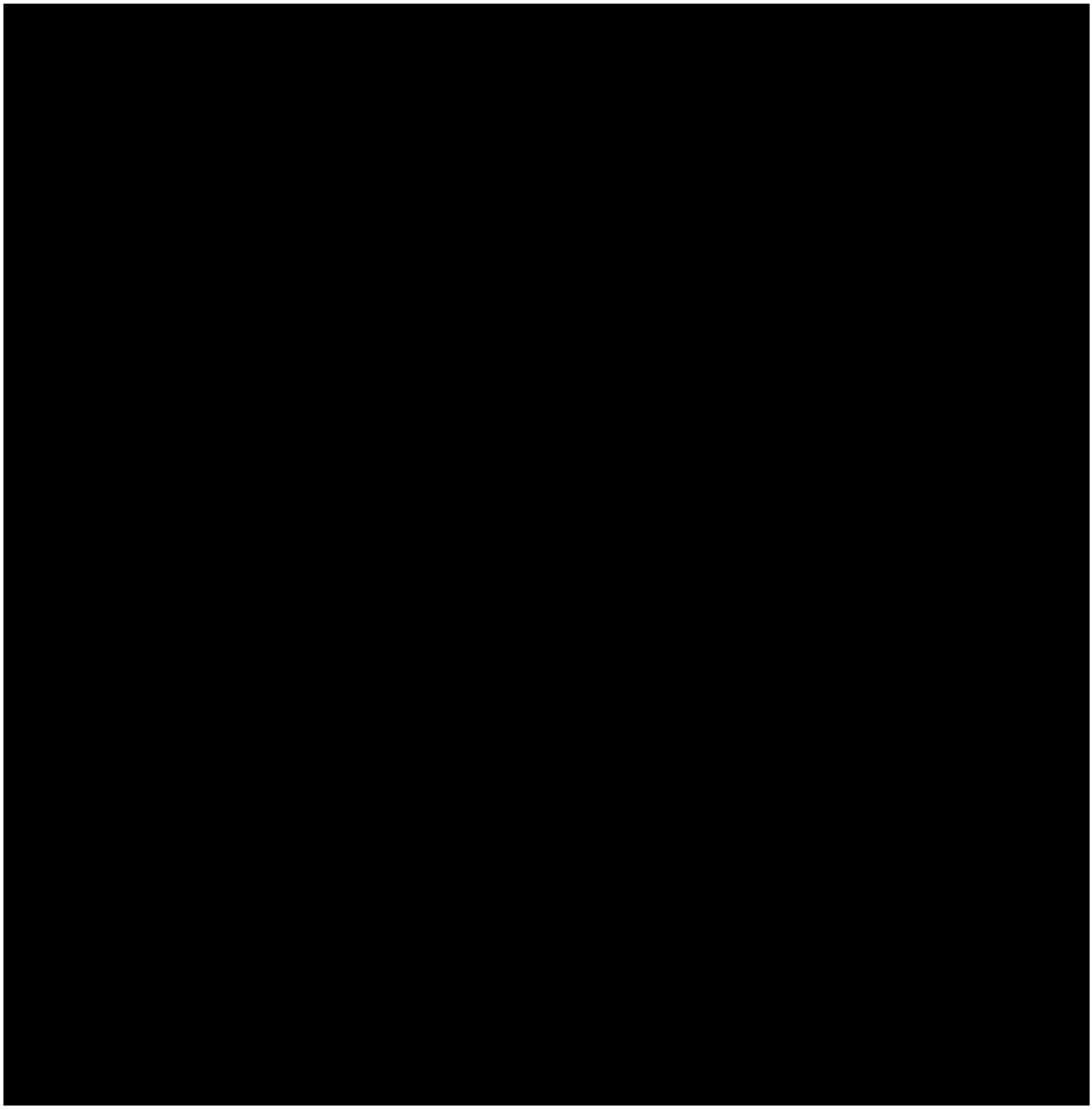
Clinical Criteria for diagnosing anaphylaxis [R11-4890]

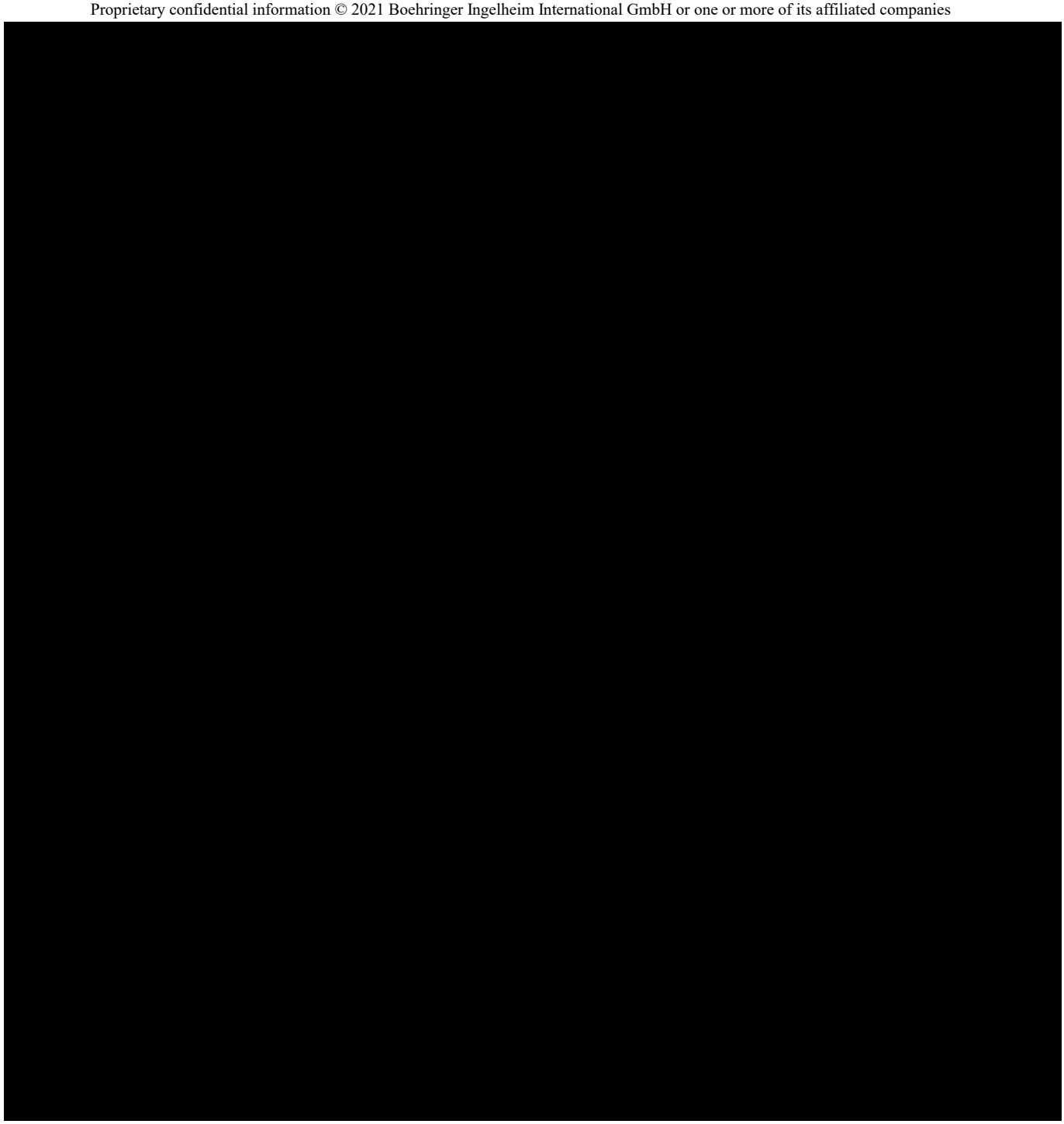
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.5 BI 767551 AND THE EMERGING VARIANTS OF CONCERN







11. DESCRIPTION OF GLOBALB AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of Amendment		20 April 2021
EudractCT number		2020-005588-29
BI Trial number		1487-0001
BI Investigational Product		BI 767551 (formerly EX 14870 or DZIF-10c)
Title of Protocol		A Phase II/III seamless, randomised, double-blind, placebo controlled, parallel-group, group-sequential study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis Trial Rationale
Description of Change		Revised wording for Phase III part to remove reference to i.v. dose
Rationale for change		Includes the possibility to add the inhalation arm in Phase III
Section to be changed		Clinical Trial Protocol Synopsis Trial Design
Description of Change		Phase II: revised wording to increase number

		of patients randomised in the inhalation arm Phase III: Trial Design included inhalation arm
Rationale for change		Phase II: Include more patients in the inhaled arm Phase III: Includes the possibility to add the inhalation arm in Phase III.
Section to be changed		Clinical Trial Protocol Synopsis Total number of patients randomised
Description of Change		Increased number of patients to be randomized in Phase II from 140 to 200
Rationale for change		To include more patients in the inhaled arm.
Section to be changed		Clinical Trial Protocol Synopsis Number of patients per treatment group
Description of Change		Phase II: Increased number of patients in each treatment arm for Phase II from 40:40:40:20 to 50:50:50:50 Phase III: Added inhaled arm
Rationale for change		Phase II: To include more patients in the inhaled arm as well as the placebo and i.v. arms so that an equal number of patients per arm is reached at the end of recruitment in phase II. Phase III: Includes the possibility to add the inhalation arm in Phase III

Section to be changed		Clinical Trial Protocol Synopsis Dose Phase III
Description of Change		Added Single 250 mg inhalation (nebulized) under Phase III
Rationale for change		Includes the possibility to add the inhalation arm in Phase III
Section to be changed		Clinical Trial Protocol Synopsis Mode of administration
Description of Change		Added inhalation under Phase III
Rationale for change		Includes the possibility to add the inhalation arm in Phase III
Section to be changed		Flow Chart: Collect/update secondary contacts
Description of Change		Foot note #20 added: Details can be entered in site source not CRF
Rationale for change		It is sufficient to have this information in the source data only
Section to be changed		Flow Chart: Physical Examination

Description of Change		Added foot note #21 for Visit 5 and 7
Rationale for change		Performed only if these visits are clinic visits
Section to be changed		Flow Chart: "Retrieval of study diary"
Description of Change		Changed to "Review by e.g. phone and retrieval of study diary"
Rationale for change		In case of home visit the patients will send dairy only after the visit to the site
Sections to be changed		Flow chart: Prematurely discontinued (Before/After Day 29) and EOS
Description of Change		Added all missing assessments so that these visits are identical
Rationale for change		EOS and Premature discontinued have identical procedures
Sections to be changed		Flow chart: Randomisation IRT call
Description of Change		Changed name of procedure from Randomisation (IRT call) to IRT call Added 'X' at screening visit
Rationale for change		Procedure is required at screening visit as well as randomisation visit

Sections to be changed		[redacted]
Description of Change		Visit EOS Day 91 collection range changed from +7 to +14
Rationale for change		To adapt to flow chart visit window for EOS
Sections to be changed		Abbreviations and Definitions
Description of Change		Added the following: [redacted] PFU Plaque forming units [redacted] VOC Variant of Concern
Rationale for change		To provide abbreviations added in the protocol
Sections to be changed		Sections 1.2.2 Predicted and observed pharmacokinetic characteristics; 1.2.5 Data from non-clinical studies; 1.2.6 Data from clinical studies.
Description of Change		Actual nonclinical and clinical Phase I data added
Rationale for change		Alignment with updated Investigator Brochure
Sections to be changed		Section 1.2.6 Data from clinical studies
Description of Change		Update to safety data

Rationale for change		Alignment with updated Investigator Brochure
Sections to be changed		Section 1.3 Rationale for performing the Trial
Description of Change		Update/Clarify rationale for phase II Removed reference to NIAID study
Rationale for change		To provide a more accurate rationale for conducting the Phase II trial, as a result of increasing the number of patients randomised in the inhalation group in Phase II. [redacted]
Sections to be changed		Section 1.4.1 Benefits
Description of Change		[redacted]
Rationale for change		[redacted]
Sections to be changed		Section 2.1.1 Main Objectives
Description of Change		Include rationale of the investigation of inhaled route
Rationale for change		Includes the possibility to add the inhalation arm in Phase III
Sections to be changed		Section 3.1 Overall Trial Design

Description of Change		-patients per arm increased from 40/40/40/20 (total 140) to 50/50/50/50 (200) randomisation ratio changed from 2:2:2:1 to 1:1:1:2 Revised to include possibility to carry the inhalation arm into Phase III. Changes included details on revised study design Updated study schematic to reflect change to randomisation ratio and possibility of continuing the inhaled arm into Phase III
Rationale for change		Phase II to include both inhaled and i.v. routes to explore neutralizing potential, safety [redacted] to provide a comparison versus Placebo of doses and routes ahead of decision of dose and route for the Phase III. Randomisation ratio in phase II modified to include more patients in the Placebo i.v. + BI 767551 250 mg inhaled arm so that an equal number of patients per arm is reached at the end of recruitment in phase II.
Sections to be changed		Section 3.2 Discussion of trial design, including the choice of control groups
Description of Change		Updated information for Phase III as follows: - removed iv - replaced dose level with dose regimen
Rationale for change		To allow the possibility of carrying the inhalation arm into Phase III
Sections to be changed		Section 3.3 Selection of Trial Population

Description of Change		Changed number of patients planned to be randomised from 140 to 200
Rationale for change		To include more patients in the inhaled arm
Sections to be changed		Section 3.3.2 Inclusion criteria #6 updated footnote 1
Description of Change		A post-menopausal state is defined as post-menopausal for at least 1 year
Rationale for change		Alignment with updated Investigator's Brochure
Sections to be changed		Section 4 Treatments
Description of Change		Update of administration of investigational medication either i.v or inhalation as well as the update of test product details for Phase III. For inhalation arm the planned concentration was added. Further, rationale and details on selection of doses and dose modification for Phase III. Data updated in accordance to the most current IB
Rationale for change		To have the possibility to add the inhalation arm in Phase III
Sections to be changed		Section 4.1.8 Drug Accountability
Description of Change		Delete the following text: "Patients should be instructed to return unused investigational drug".

Rationale for change		Not applicable to this trial.
Sections to be changed		Section 4.2.2.3 Contraception requirements
Description of Change		Acceptable methods of birth control: updated first bullet to state post-menpausal for at least 1 year
Rationale for change		Alignment with updated Investigator's Brochure
Sections to be changed		Section 5.2.3 Safety Laboratory Parameters
Description of Change		Increased maximum volume of blood needed per patient for all laboratory assessments from 250 mL to 300 mL
Rationale for change		To reflect the increased blood volume due to additional blood sample collections at Visit 5 and Prematurely discontinued (Before Day 29) and Prematurely discontinued (After Day 29)
Sections to be changed		Section 6 Investigational Plan
Description of Change		Addition of inhalation route for Phase III
Rationale for change		Update based on modified study design to possibly include inhalation group in Phase III
Sections to be changed		Section 6.2 Details of Trial Procedures at Selected Visits

Description of Change		[redacted]
Rationale for change		To allow more flexibility in case samples cannot always be collected in the evening
Sections to be changed		Section 6.2.1 Screening and run in period
Description of Change		Deleted: Gender identity (male, female, other in order to describe how the subject self identifies regardless of their genotypic or phenotypic sex)
Rationale for change		Information not being collected in CRF
Sections to be changed		Section 7.2, Table 7.2.2:1
Description of Change		Table header changed to “Primary Strategy” and “Secondary Strategy”
Rationale for change		Handling of incurrent events wording was simplified to Primary and Secondary strategy
Sections to be changed		Section 7.4 Randomization
Description of Change		Phase II R 2:2:2:1 changed to R 1:1:1:2
Rationale for change		To include more patients in the Placebo i.v. + BI 767551 250 mg inhaled arm so that an equal number of patients per arm is reached at the end of recruitment in Phase II.

Sections to be changed		Section 7.5.1 Determination of Sample size for Phase II
Description of Change		Adapt sample size according to the updated study design
Rationale for change		Phase II to include both inhaled and i.v. routes to explore neutralizing potential, safety [redacted] to provide a comparison of doses and routes versus Placebo ahead of decision of dose and route for the Phase III
Sections to be changed		Section 9.2 Unpublished References
Description of Change		Addition of references
Rationale for change		References added to support new or updated text in CTP
Sections to be changed		[redacted]
Description of Change		Addition of Appendix 10.5
Rationale for change		[redacted]

APPROVAL / SIGNATURE PAGE

Document Number: c33563257 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-02

Title: A Phase II/III seamless, randomised, double-blind, placebo-controlled, parallel-group, group-sequential study to evaluate efficacy, safety and tolerability of BI 767551 for the treatment of symptomatic, non-hospitalized adults with mild to moderate COVID-19.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	20 Apr 2021 18:54 CEST
Approval-Therapeutic Area [redacted]		20 Apr 2021 18:59 CEST
Approval-Team Member Medicine		21 Apr 2021 02:14 CEST
Author-Trial Statistician		21 Apr 2021 06:27 CEST
Author-Trial Clinical Pharmacokineticist		21 Apr 2021 16:02 CEST
Verification-Paper Signature Completion		21 Apr 2021 17:42 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed