# CLINICAL STUDY PROTOCOL

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|---|---|
| **Protocol Title:** | **A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Patients With Mild to Moderate COVID-19** |
| **Protocol Identifier:** | BGB-DXP593-102 |
| **Phase:** | 2 |
| **Investigational Products:** | BGB-DXP593<br>Placebo |
| **Proposed Indication:** | COVID-19 |
| **Sponsor:** | BeiGene, Ltd.<br>c/o BeiGene USA, Inc.<br>2955 Campus Drive, Suite 200<br>San Mateo, California 94403<br>USA |
| **Sponsor Medical Monitor:** | [redacted] |
| **Original Protocol Version 0.0:** | 14 August 2020 |
| **Amendment 1.0** | 03 September 2020 |
| **Amendment 2.0** | 27 October 2020 |

# FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Patients With Mild to Moderate COVID-19

**BeiGene, Ltd., Approval:**

[redacted] 27-Oct-2020

Date

Sponsor Medical Monitor

# INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Patients With Mild to Moderate COVID-19

Protocol Identifier: BGB-DXP593-102

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

**Instructions for Investigator:** Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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# SYNOPSIS

**Name of Sponsor/Company:** BeiGene, Ltd.

**Investigational Products:** BGB-DXP593; Placebo

**Title of Study:** A Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of SARS-CoV-2 neutralizing antibody BGB-DXP593 in patients with mild to moderate COVID-19

**Protocol Identifier:** BGB-DXP593-102

**Phase of Development:** 2

**Number of Patients:** Approximately 172

**Study Centers:** Approximately 20 to 30 centers internationally

**Study Objectives:**

**Primary:**

- To evaluate the efficacy of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19

**Secondary:**

- To evaluate the safety of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19
- To characterize the pharmacokinetic (PK) profile of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19
- To evaluate the potential immunogenicity of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19

**Exploratory:**

- [redacted]

**Study Endpoints:**

**Primary:**

- Change from baseline to Day 8 in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) viral shedding as measured by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal swab samples

**Secondary:**

- Time-weighted average change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples
- Proportion of patients requiring hospitalization due to worsened COVID-19
- Time to resolution of all COVID-19-related symptoms
- All-cause mortality rate at Day 29

- Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- PK parameters: maximum observed concentration ($C_{max}$), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_t$), AUC from time zero to Day 29 ($AUC_{0-29}$), AUC from time zero to infinity ($AUC_{inf}$), time to maximum observed concentration ($t_{max}$), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution ($V_z$) as appropriate
- Immunogenic responses to BGB-DXP593 evaluated through the detection of antidrug antibodies (ADAs)

**Exploratory:**

[redacted]

**Study Design**

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of BGB-DXP593 in patients with mild to moderate COVID-19.

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, patients will be randomized in a 1:1:1:1 ratio to receive placebo, BGB-DXP593 5 mg/kg, BGB-DXP593 15 mg/kg, or BGB-DXP593 30 mg/kg. Patient randomization will be stratified by country and disease severity (mild versus moderate COVID-19). The patients will receive a single intravenous infusion of placebo or BGB-DXP593 over 30 to 90 minutes. The patients will then be followed to Day 113 (± 7 days) to assess the efficacy, safety, PK, and immunogenicity. Nasopharyngeal swabs will be collected according to the Schedule of Assessments to evaluate the change in viral load using RT-qPCR testing of SARS-CoV-2.

An Independent Data Monitoring Committee (IDMC) will periodically monitor safety and efficacy data. The first safety review is planned after at least 12 patients have received study treatment and have been followed up for 7 days.

The study design schema is in Section 3, Figure 2.

**Study Assessments:**

Patients will be monitored for safety, efficacy, PK, and immunogenicity during the study.

Assessments of safety will include adverse events, SAEs, clinical laboratory tests, physical examinations, vital signs, and electrocardiograms (ECGs). Adverse events will be graded for severity per the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

PK, ADA and biomarker sampling will be collected at specific intervals from Day 1 to Day 113.

RT-qPCR analysis will be used to assess the SARS-CoV-2 viral load in different samples at various timepoints, including nasopharyngeal swabs, saliva, and blood.

World Health Organization (WHO) 8-point ordinal scale will be used for clinical status assessment.

**Key Eligibility Criteria:**

To participate in this study, patients must have laboratory-confirmed SARS-CoV-2 infection (positive reverse transcription-polymerase chain reaction [RT-PCR] test or other testing methods authorized by local regulatory authorities) in any samples following local practice ≤ 72 hours prior to screening; have experienced COVID-19 symptoms for ≤ 7 days prior to treatment assignment (such as fever, cough, shortness of breath, sore throat, diarrhea, vomiting, and dysgeusia); and agree to the collection of nasopharyngeal swabs, saliva, and venous blood. Patients should not have oxygen saturation ($SpO_2$) ≤ 93% on room air or ratio of arterial oxygen partial pressure ($PaO_2$ in millimeters of mercury) to fractional inspired oxygen ($FiO_2$) < 300, respiratory rate ≥ 30/min, or heart rate ≥ 125/min. Patients should have no history of a positive SARS-CoV-2 serology test; no prior investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing; and no prior treatment with a SARS-CoV-2 specific monoclonal antibody or convalescent COVID-19 plasma; and should not have participated in a previous SARS-CoV-2 vaccine study.

**Investigational Product, Dose, and Mode of Administration:**

BGB-DXP593 will be administered intravenously at a dose of 5 mg/kg, 15 mg/kg or 30 mg/kg for 30 to 90 minutes; placebo will be administered intravenously for 30 to 90 minutes.

**Statistical Methods:**

**Analysis Sets**

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to the treatment assigned at randomization. This will be the primary analysis set for efficacy analyses.

The Safety Analysis Set includes all patients who have received the study drug (BGB-DXP593 or placebo). Patients will be analyzed according to their actual treatment received. The Safety Analysis Set will be used for all safety analyses.

The PK Analysis Set includes all patients who have received the study drug (BGB-DXP593) per the protocol and for whom any postdose PK data are available.

The ADA Analysis Set includes all the patients who have received the study drug and in whom both baseline ADA and at least 1 postbaseline ADA results are available.

**Primary Efficacy Analysis**

The statistical hypotheses to be tested for the primary endpoint are as follows:

$H_0$: there is a flat dose response curve comparing change from baseline to Day 8 in SARS-CoV-2 viral shedding in the placebo and the BGB-DXP593 dose groups

$H_1$: there is a non-flat dose response curve indicating a benefit of BGB-DXP593 over placebo

The primary analysis uses methodology for dose finding, employing both multiple comparison procedures and modelling techniques (MCPMod). The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one-sided α of 5%).

**Safety Analyses**

Safety will be assessed by monitoring and recording all adverse events, laboratory values, vital signs, and physical examinations. Descriptive statistics will be used to analyze all safety data by actual treatment arm in the Safety Analysis Set.

**Pharmacokinetic Analyses**

Noncompartmental or model-based analysis will be carried out for BGB-DXP593 serum concentrations. Parameters, such as $C_{max}$, $t_{max}$, $t_{1/2}$, $AUC_t$, $AUC_{inf}$, $AUC_{0-29}$, CL, and $V_z$ (as appropriate

for data collected), may be derived and summarized with descriptive statistics (sample size, mean, standard deviation, coefficient of variance, median, minimum, maximum, geometric mean, geometric coefficient of variance). Individual serum concentration-versus-time data will be tabulated and plotted by dose level. Additional PK analyses may be conducted as appropriate.

**Immunogenicity Analyses**

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK and safety may be evaluated if data allow.

**Sample Size Calculation**

Forty-one patients are needed with primary endpoint data per arm to provide at least 82% power to detect non-flat dose-response relationship at one-sided significance level $\alpha = 5\%$. MCPMod approach is used. In order to ensure 41 patients per arm with primary endpoint data, at least 43 patients per arm need to be randomized.

The calculation has been performed using R software, version 3.6.1.

# LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ACE2 | angiotensin-converting enzyme 2 |
| ADA | antidrug antibody |
| AE | adverse event |
| AUC | area under the concentration-time curve |
| $AUC_{inf}$ | AUC from time zero to infinity |
| $AUC_t$ | AUC from time zero to the time of the last quantifiable concentration |
| $AUC_{0-29}$ | AUC from time zero to Day 29 |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | maximum observed concentration |
| COVID-19 | coronavirus disease 2019 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture (system) |
| GCP | Good Clinical Practice |
| $IC_{50}$ | concentration for inhibition of 50% maximal activity |
| $IC_{99}$ | concentration for inhibition of 99% maximal activity |
| ICF | informed consent form |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| mAb | monoclonal antibody |
| MCPMod | multiple comparison procedures and modelling approaches |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| PK | pharmacokinetic(s) |
| RBD | receptor binding domain |
| RT-PCR | reverse transcription-polymerase chain reaction |
| RT-qPCR | reverse transcription-quantitative polymerase chain reaction |
| SAE | serious adverse event |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| TEAE | treatment-emergent adverse event |

| Abbreviation | Definition |
|---|---|
| $t_{max}$ | time to maximum observed concentration |
| $t_{1/2}$ | terminal half-life |
| $V_z$ | volume of distribution |

# 1. INTRODUCTION AND RATIONALES

## 1.1. Introduction

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infection caused by a new strain of coronavirus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). As of July 2020, over 14 million confirmed cases of COVID-19 worldwide have been reported to World Health Organization (WHO). COVID-19 is threatening the global public health, and the ongoing spread of COVID-19 has resulted in a worldwide pandemic demanding effective interventions against SARS-CoV-2 infections.

Currently, several treatment strategies are used clinically or are under development, such as viral-targeting therapeutics and host-targeting agents (such as anti-interleukin-6 antibodies, glucocorticoids) for the treatment of COVID-19. Unfortunately, there is no vaccine or prescribing drug regimen which has demonstrated significant efficacy in the treatment of COVID-19 patients in clinical studies so far (Jean et al 2020).

Convalescent plasma therapy has been used to treat COVID-19 by providing passive immune responses to viral infection. However, the outcomes of passive plasma therapy are unpredictable due to the variability of sera from different patients (Zhou and Zhao 2020). Convalescent plasma therapy is also associated with other risks, such as transfusion-related acute lung injury, transfusion-related overload, or transfusion transmitted infection (Sullivan and Roback 2020).

Neutralizing monoclonal antibodies (mAbs) generated from plasma of convalescent patients provide more specific and consistent immune response. The antibodies with high affinity to the virus can be selected. Although several SARS-CoV-2-specific neutralizing mAbs are under clinical investigation, no clinical studies have been completed to date. Therefore, neutralizing antibodies that effectively block virus entry into host cells are urgently needed (Cao et al 2020).

BGB-DXP593 (also named DXP593, BD-368-2, and WBP2281) is a highly potent neutralizing immunoglobulin G (IgG)1 monoclonal antibody specifically against SARS-CoV-2.

## 1.2. BGB-DXP593 as a SARS-CoV-2 Neutralizing Monoclonal Antibody

SARS-CoV-2 infects host cells through binding to human angiotensin-converting enzyme 2 (ACE2) expressed on host cells by the receptor-binding domain (RBD) of its Spike (S) protein (Walls et al 2020). BGB-DXP593 binds to the S protein RBD of SARS-CoV-2 with high specificity and affinity, efficiently blocking the binding of RBD to ACE2, thus preventing virus from entering host cells.

### 1.2.1. Nonclinical

#### 1.2.1.1. Pharmacology

BGB-DXP593 binds to the S protein RBD of SARS-CoV-2 with high specificity and affinity, as demonstrated by target-binding assays and surface plasmon resonance characterization (equilibrium dissociation constant [$K_D$] = 0.824 nM). BGB-DXP593 efficiently blocks the binding of RBD to its receptor ACE2 with a concentration for inhibition of 50% maximal activity ($IC_{50}$) of 0.81 nM in a competition enzyme-linked immunosorbent assay (ELISA).

The crystal structure of BGB-DXP593 antigen-binding fragment (Fab) in complex with RBD suggests that BGB-DXP593 would interfere with the interaction between RBD and ACE2. The structure shows that [redacted] of RBD have direct contact with BGB-DXP593. In addition, the structure also suggests that BGB-DXP593 would clash with both protomers in the ACE2 dimer.

In cell-based assays, BGB-DXP593 inhibits SARS-CoV-2 infections in both pseudovirus and authentic virus systems with an $IC_{50}$ of 8 pM (0.0012 µg/mL) and 0.1 nM (0.015 µg/mL), respectively, and a concentration for inhibition of 99% maximal activity ($IC_{99}$) of 0.6 nM (0.09 µg/mL) and 1.08 nM (0.162 µg/mL). BGB-DXP593 has wild-type human IgG1 fragment crystallizable region (Fc), which exhibit similar binding profile as regular IgG1 antibody in terms of binding to Fc γ receptors (FcγRs) and complement 1q (C1q), suggesting competent functions of antibody effector.

The neutralization efficacy of BGB-DXP593 against SARS-CoV-2 was assessed in two different models: human ACE2 (hACE2)-transgenic mice model and hamster (Mesocricetus auratus) model. The in vivo experiments exhibited that BGB-DXP593 could provide strong post-exposure prophylactic protection against SARS-CoV-2 in both models.

In hACE2 transgenic mice, 20 mg/kg BGB-DXP593 efficiently prevented SARS-CoV-2 virus from infecting lung tissues, achieving undetectable viral levels in the prophylactic treatment model, where BGB-DXP593 was injected 24 hours before the virus infection. Consistent with this observation, the body weights of the treated mice remained in stasis while that of the control mice dropped by over 5% at 5 days post infection. Similarly, BGB-DXP593 reduced the virus load by over 1000 fold in the post-exposure prophylaxis treatment model, where antibody was injected 2 hours after the infection. Additionally, the body weight of the treated mice remained unchanged over a course of 5 days, comparable to those in the prophylactic treatment model, suggesting that BGB-DXP593 maintained the fitness of the infected mice.

In the hamster post-exposure prophylaxis treatment model, BGB-DXP593 injection at a dose level of 2, 5, 10, or 20 mg/kg led to dose-dependent lung viral reduction at 7 days post infection, with the best response observed within the highest tested dose group (ie, 20 mg/kg). All dose groups showed improvement in body weight loss compared with the control group. BGB-DXP593 (20 mg/kg) also demonstrated a preventive effect in hamster model when injected 1 day or 3 days before infection, while the more contemporaneous injection (ie, 1 day before infection) achieved superior viral load reduction and body weight maintenance.

Please refer to the BGB-DXP593 Investigator's Brochure for additional details regarding nonclinical studies of BGB-DXP593.

#### 1.2.1.2. Toxicology

The toxicity and toxicokinetic profile of BGB-DXP593 was characterized in a 14-day repeat-dose toxicology study followed by a 28-day recovery in cynomolgus monkeys via intravenous infusion. A tissue cross reactivity was evaluated in the normal frozen tissues from both monkeys and humans. Cytokine release responses were evaluated using human peripheral blood mononuclear cells (PBMCs). All the data collection and analyses have been completed in these studies except for the recovery phase data and antidrug antibody (ADA) results in the 14-day repeat-dose study. Based on the available data, the missing information is not considered to have an impact on the results and data interpretation.

In the 14-day repeat-dose study in monkeys at the doses up to 300 mg/kg, no mortality or morbidity was noted throughout the study; no treatment-related findings or changes were noted, which included clinical observations, body weights, body temperature, ophthalmology, hematology, coagulation, serum chemistry, urinalysis, cytokines, gross lesions, organ weights and histopathology; no treatment-related changes in the cardiovascular, respiratory, or central nervous systems functions were noted. The systemic exposure evaluated by area under the concentration-time curve (AUC) from time zero to the 169.5 hours ($AUC_{0\text{-}169.5h}$) and maximum observed concentration ($C_{max}$) appeared to increase dose proportionally without apparent sex differences. No marked drug accumulation or changes were noted after weekly repeated doses. The NOAEL (No Observed Adverse Effect Level) is considered as 300 mg/kg in this study based on available data, which is approximately 60-fold of the proposed first-in-patient dose (5 mg/kg) and 10-fold of the proposed highest human dose (30 mg/kg) based on body weight.

No specific binding of BGB-DXP593 was detected in either normal monkey or human tissues in the tissue cross reactivity study by immunohistochemical method. No apparent BGB-DXP593 specific cytokine releases were detected in human PBMCs.

Please refer to the BGB-DXP593 Investigator's Brochure for more detailed information on the toxicology of BGB-DXP593.

### 1.2.2. Clinical Experience

A first-in-human study of BGB-DXP593 in healthy subjects (Study BGB-DXP593-101) is ongoing. No serious adverse event has been reported to date.

## 1.3. Study Rationale

COVID-19 is an acute respiratory syndrome caused by SARS-CoV-2 infection. BGB-DXP593 is a neutralizing mAb against the SARS-CoV-2 selected from convalescent COVID-19 patients. By binding to the RBD on the S protein of the virus, BGB-DXP593 can prevent the virus from entering the cells. Its pre- and post-exposure prophylaxis effects in hACE mice have been demonstrated (Cao et al 2020).

A few studies suggested that high viral load is associated with increased mortality (Fajnzylber et al 2020; Pujadas et al 2020; Wolfel et al 2020). Amongst the participants hospitalized with COVID-19, higher prevalence of detectable SARS-CoV-2 plasma viral load was associated with worse respiratory disease severity, lower absolute lymphocyte counts, and increased markers of inflammation, including C-reactive protein and interleukin-6 (Fajnzylber et al 2020). This study will explore if BGB-DXP593 can effectively reduce viral load in collected samples.

Patients who have experienced COVID-19 symptoms less than 7 days will be enrolled. By 7 days after onset of symptoms, anti-SARS-CoV-2 immunoglobulin M (IgM) or IgG can be detected in around 50% of patients (Wolfel et al 2020). Presence of anti-SARS-CoV-2 IgG in patients' blood is associated with reduced viral load. High viral loads were rare in individuals who had seroconverted (Bryan et al 2020).

This study will assess efficacy of BGB-DXP593 in lowering viral load at different dose levels. To date, there is no drug approved or recommended for mild to moderate COVID-19 (NIH COVID-19 treatment guidelines, 2020). Hence, using placebo as the control is appropriate.

To assess viral load at different time points, nasopharyngeal swabs, saliva and blood samples will be collected. Nasopharyngeal swabs are the clinically recommended sampling method for virologic tests. In addition, the viral load change in saliva samples will be assessed. The viral load in nasopharyngeal samples will be used for primary efficacy analysis. Collection of saliva is non-invasive. Studies suggested that viral loads in saliva are comparable to those in nasopharyngeal swabs during the first week of symptoms and decrease over time. Saliva can be positive up to 20 days post-symptom onset with viral loads correlating with symptom severity and degree of tissue damage. The viral load in saliva has good association with nasopharyngeal swabs (Khurshid et al 2020). A majority of patients do not have viremia. However, detection of viral RNA in blood is associated with poor outcomes.

### 1.3.1. Rationale for Selection of BGB-DXP593 Doses

A single dose of BGB-DXP593 of 5 mg/kg, 15 mg/kg and 30 mg/kg, as the dose levels being tested, are proposed based on an overall assessment of in vitro activity of BGB-DXP593 and toxicology data as describe below.

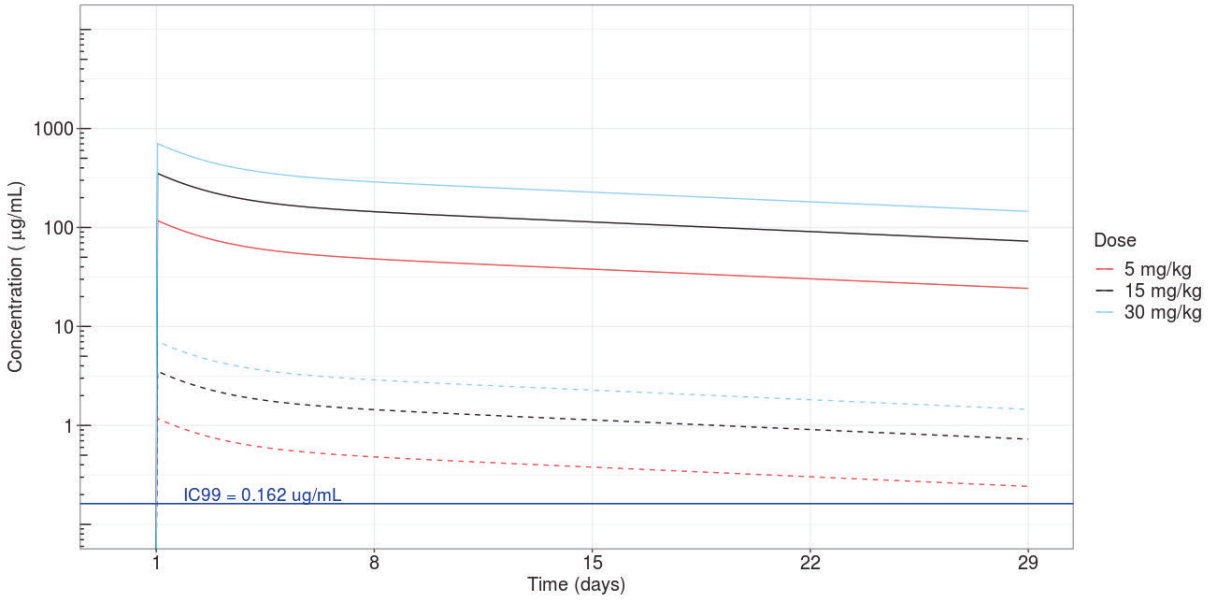
Based on the toxicology evaluation in cynomolgus monkeys, the NOAEL was determined to be 300 mg/kg. Applying a safety factor of 10, the MRSD (maximum recommended starting dose) is estimated as 30 mg/kg (body weight-based) which is the highest dose being tested in this study. In addition, based on the AUC from time zero to infinity ($AUC_{inf}$) and $C_{max}$ after the second dose at 300 mg/kg NOAEL in the toxicity study in monkeys, the projected safety margins at the proposed highest dose of 30 mg/kg are 5.0 and 11.1, respectively, which reflects favorably on the safety profile of BGB-DXP593 (Table 1).

The two lower doses of 5 mg/kg and 15 mg/kg are based on the results of the in vitro virus neutralization assays. In the in vitro virus neutralization assays, BGB-DXP593 potently inhibited SARS-CoV-2 infections in both pseudovirus and authentic virus systems with an $IC_{99}$ of 0.09 µg/mL and 0.162 µg/mL, respectively. Predicted serum and lung concentrations at various dose levels were compared to the $IC_{99}$ of 0.162 µg/mL from the authentic virus neutralization assay (higher value from the two assays). The biodistribution of monoclonal antibodies in lungs was taken into consideration. It has been reported in literature that lung biodistribution ranges from 0.5% to 15% (Hart et al 2001; Shah and Betts 2013; Hershberger et al 2019; Eigenmann et al 2017), therefore, a conservative value of 1% lung biodistribution was chosen for the simulations.

Predicted human serum concentration-time profiles showed that BGB-DXP593 doses at and above 5 mg/kg would maintain lung concentrations above the $IC_{99}$ of 0.162 µg/mL over 29 days (Figure 1). However, given that the impact of SARS-CoV-2 on lung biodistribution of monoclonal antibodies is not known, the two higher dose levels of 15 mg/kg and 30 mg/kg will also be tested.

Please refer to the BGB-DXP593 Investigator's Brochure for more detailed information.

**Figure 1: Simulated BGB-DXP593 Serum and Lung (Assuming 1% Biodistribution) Concentration-Time Profiles in Humans**




Abbreviation: $IC_{99}$, concentration of BGB-DXP593 required to achieve 99% inhibition of host cell infection in vitro in an authentic virus neutralization assay.
Solid lines: projected serum concentrations; dashed lines: projected lung concentrations assuming 1% biodistribution.

**Table 1: Projected Safety Margins at Proposed Doses in Humans**

| Safety margin | BGB-DXP593 Dose (mg/kg) | | |
|---|---|---|---|
| | 5 | 15 | 30 |
| AUC based | 30.3 | 10.1 | 5.0 |
| $C_{max}$ based | 66.4 | 22.1 | 11.1 |

Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed concentration

### 1.3.2. Rationale for Pharmacokinetic Sampling

The sampling schedule that follows the single dose of BGB-DXP593 is designed to capture data at a sufficient number of timepoints to provide a detailed profile of the concentration-time curve, including $C_{max}$, AUC from time zero to the time of the last quantifiable concentration ($AUC_t$), AUC from time zero to Day 29 ($AUC_{0-29}$), $AUC_{inf}$, time to maximum observed concentration ($t_{max}$), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution ($V_z$).

Rich PK sampling will be performed in the first-in-human study in healthy subjects (Study BGB-DXP593-101). PK sampling in this study is limited to essential site visits to reduce patient burden.

### 1.3.3. Rationale for Biomarker Strategy

Biomarker analyses will be performed to evaluate study treatment effects induced in patients as well as to explore potential predictive biomarkers of response to BGB-DXP593.

Seroconversion for patients with COVID-19 usually happens within the first week after symptom onset (Wolfel et al 2020). It has been shown that seroconversion occurred after 7 days in 50% of patients and almost all COVID-19 patients had neutralizing antibodies within 1 month after symptom onset, thus the existing anti-SARS-CoV-2 antibodies in patients may have an impact on the efficacy of BGB-DXP593, which is also an neutralizing antibody for SARS-CoV-2. Therefore, the baseline SARS-CoV-2 serology antibody levels may be related to the treatment effects of BGB-DXP593. Recent studies have suggested that the certain mutations on SARS-CoV-2 virus may impact the infectivity and severity of the virus, especially the mutations on the receptor binding domain of SARS-CoV-2, which may also impact the neutralizing activities of SARS-CoV-2 neutralizing antibodies (Baum et al 2020; Korber et al 2020; Li et al 2020). Thus, certain mutations on SARS-CoV-2 genome may also be related to the treatment effects of BGB-DXP593.

In addition, patients with COVID-19 have shown a strong upregulation of cytokine and interferon production, it is believed that dysregulated host immune response and production of inflammatory cytokines, known as the “cytokine storm”, correlates with disease severity and poor prognosis of SARS-CoV-2 infection (Tay et al 2020). Therefore, serum cytokine levels could be a marker for evaluating disease severity and the treatment effects of anti-SARS-CoV-2 neutralizing antibodies.

Considering the immune response induced by SARS-CoV-2 infection varies a lot among different patients, all patients may not be equally likely to benefit from treatment with anti-SARS-CoV-2 neutralizing antibodies. Predictive biomarker samples collected before dosing will be assessed in an effort to identify those patients with certain gene signatures who are most likely to respond to BGB-DXP593. Thus, gene signatures at baseline and after treatment in peripheral blood may serve as predictive biomarkers and may also help to explore the mechanism of response.

## 1.4. Benefit-Risk Assessment

On March 11, 2020, the Novel Coronavirus Disease, COVID-19, was declared a pandemic by the WHO. As of July 9, 2020, more than 12 million cases of COVID-19 have been reported globally, including more than 550,000 deaths. However, only remdesivir is approved for the treatment of severe COVID-19, and thus the unmet medical needs remain high.

Several studies showed that high viral load is associated with increased mortality. Seroconversion (detection of anti-SARS-CoV-2 IgM or IgG in blood) occurred in around 50% of patients 7 days after disease onset. Presence of anti-SARS-CoV-2 IgG is associated with viral load reduction (Bryan et al 2020; Fajnzylber et al 2020; Pujadas et al 2020; Wolfel et al 2020). With early administration of antiviral neutralizing antibodies, patients may benefit from early and rapid reduction of viral load and potential improved clinical outcomes.

BGB-DXP593 is a potent neutralizing antibody to SARS-CoV-2. It is human IgG type 1 selected from blood of convalescent patients. In preclinical studies, its pre- and post-exposure prophylactic effects to COVID-19 have been demonstrated. In a toxicological study in monkeys, no adverse events (AEs) were observed with repeated doses of BGB-DXP593 30-300 mg/kg.

As an exogeneous protein, use of BGB-DXP593 might be related with hypersensitivity reactions, though the immunogenicity is considered low due to its human origin. Potential antibody-dependent enhancement (ADE) has been observed in some viral infections, such as Dengue fever. Possibility of ADE with passive immunity cannot be excluded in COVID-19. However, clinical experiences with RSV, influenza and dengue provide strong evidence that the circumstances that are proposed to lead to ADE of disease—including low affinity or cross-reactive antibodies with limited or no neutralizing activity or suboptimal titres—are very rarely implicated as the cause of severe viral infection in the human host (Arvin et al 2020). BGB-DXP593 is a highly potent neutralizing antibody, and thus is unlikely to cause ADE. In addition, a large number of COVID-19 patients have received convalescent plasma therapy, where no hints of ADE have been identified (Joyner et al 2020).

There are no FDA-approved treatments or accepted standardized medical treatment options indicated for mild to moderate COVID-19. Patients may benefit from the treatment of BGB-DXP593 based on its mechanism of action and the proven efficacy in COVID-19 animal models. BGB-DXP593 has a favorable preclinical safety profile. Patients enrolled in this clinical study will be closely monitored by means of reporting AEs, recording vital signs, and conducting clinical laboratory safety tests of blood and urine. The favorable preclinical safety profile, potential wide range application in the COVID-19 population and high unmet medical need provides substantive evidence that BGB-DXP593 has a favorable risk-benefit profile.

## 1.5. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

### 2.1.1. Primary Objective

- To evaluate the efficacy of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19

### 2.1.2. Secondary Objectives

- To evaluate the safety of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19
- To characterize the pharmacokinetic (PK) profile of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19
- To evaluate the potential immunogenicity of BGB-DXP593 administered intravenously as a single dose in patients with mild to moderate COVID-19

### 2.1.3. Exploratory Objective

- [redacted]

## 2.2. Study Endpoints

### 2.2.1. Primary Endpoint

- Change from baseline to Day 8 in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) viral shedding as measured by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal swab samples

### 2.2.2. Secondary Endpoints

- Time-weighted average change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples
- Proportion of patients requiring hospitalization due to worsened COVID-19
- Time to resolution of all COVID-19-related symptoms
- All-cause mortality rate at Day 29
- Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

- PK parameters: maximum observed concentration ($C_{max}$), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_t$), AUC from time zero to Day 29 ($AUC_{0-29}$), AUC from time zero to infinity ($AUC_{inf}$), time to maximum observed concentration ($t_{max}$), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution ($V_z$) as appropriate
- Immunogenic responses to BGB-DXP593 evaluated through the detection of antidrug antibodies (ADAs)

### 2.2.3. Exploratory Endpoints

# 3. STUDY DESIGN

## 3.1. Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of BGB-DXP593 in patients with mild to moderate COVID-19.

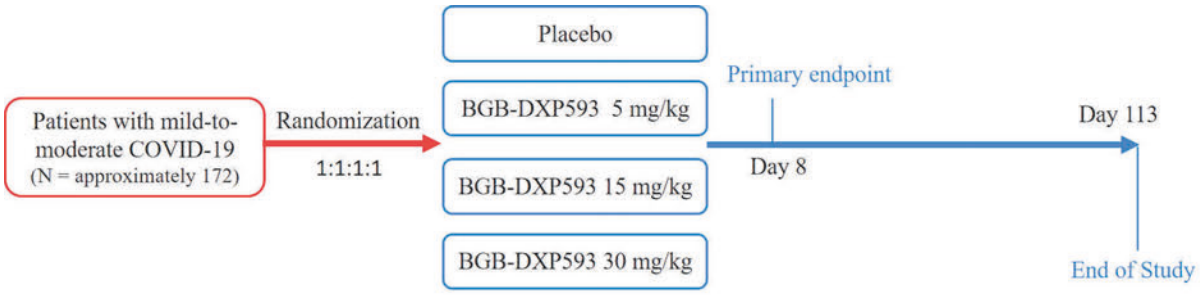
The study will be conducted across approximately 20 to 30 sites internationally.

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, patients will be randomized in a 1:1:1:1 ratio to receive placebo, BGB-DXP593 5 mg/kg, BGB-DXP593 15 mg/kg, or BGB-DXP593 30 mg/kg. Patient randomization will be stratified by country and disease severity (mild versus moderate COVID-19). The patients will receive a single intravenous infusion of placebo or BGB-DXP593 over 30 to 90 minutes. The patients will then be followed to Day 113 (± 7 days) to assess the efficacy, safety, PK, and immunogenicity. Nasopharyngeal swabs will be collected according to the Schedule of Assessments (Appendix 1) for RT-qPCR testing of SARS-CoV-2 to assess the change in viral load after study treatment. Approximately 172 patients will be randomized.

An Independent Data Monitoring Committee (IDMC) will periodically monitor safety and efficacy data. The first safety review is planned after at least 12 patients have been treated and followed up for 7 days.

The study schema is provided in Figure 2.

**Figure 2: Study Schema**




Note: Patients will be randomized based on stratification factors of country and disease severity (mild versus moderate COVID-19).

Patients will be monitored for safety, efficacy, PK, and immunogenicity during the study.

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, vital signs, and electrocardiograms (ECGs). AEs will be graded for severity according to the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

RT-qPCR analysis will be used to assess the SARS-CoV-2 viral load in different samples at various timepoints, including nasopharyngeal swabs, saliva, and blood. The viral load in nasopharyngeal swabs will be used for primary efficacy analysis.

WHO 8-point ordinal scale will be used for clinical status assessment.

PK and ADA sampling will be conducted at timepoints specified in Appendix 2.

Biomarker analysis will include, but are not limited to, SARS-CoV-2 mutations, serology, cytokines, and gene expression signatures.

Study procedures and assessments are further detailed in Section 7 and Section 8, respectively, and the Schedule of Assessments can be found in Appendix 1.

# 4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

## 4.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Participant must be at least 18 years of age at the time of signing the informed consent.
2. Laboratory-confirmed SARS-CoV-2 infection (positive reverse transcription-polymerase chain reaction [RT-PCR] test or other testing methods authorized by local regulatory authorities) in any samples following local practice ≤ 72 hours prior to screening
3. Have experienced COVID-19 symptoms for ≤ 7 days prior to treatment assignment, such as fever, cough, shortness of breath, sore throat, diarrhea, vomiting, and dysgeusia
4. Agree to the collection of nasopharyngeal swabs, saliva, and venous blood
5. Female patients of childbearing potential must be willing to use a highly effective method of birth control (see Appendix 4) from the time of study enrollment until 4 months after the study dosing
6. Male patients with female partners of childbearing potential must be willing to use a highly effective method of birth control (see Appendix 4) from the time of study enrollment until 4 months after the study dosing
7. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments

## 4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study:

**Medical Histories or Conditions**

1. Patient with severe COVID-19 having oxygen saturation ($SpO_2$) ≤ 93% on room air or ratio of arterial oxygen partial pressure ($PaO_2$ in millimeters of mercury) to fractional inspired oxygen ($FiO_2$) < 300, respiratory rate ≥ 30/min, or heart rate ≥ 125/min

   Note: For high altitude areas, $PaO_2/FiO_2$ ratio should be adjusted using formula: $PaO_2/[FiO_2 \times (\text{barometric pressure}/760)]$.
2. Patient requires mechanical ventilation or anticipated impending need for mechanical ventilation
3. Known allergies to any of the components used in the formulation of the interventions
4. Hemodynamic instability requiring use of pressors within 24 hours prior to treatment assignment

5. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
6. Any comorbidity requiring surgery within 7 days prior to screening, or that is considered life-threatening within 29 days prior to screening
7. Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study
8. History of a positive SARS-CoV-2 serology test (anti-SARS-CoV-2 IgA, IgM, or IgG)
9. History of a positive SARS-CoV-2 test (RT-PCR or other testing authorized by local regulatory authorities) prior to the one serving as eligibility for this study
10. Pregnant or breast feeding
11. Any concurrent immune-compromising conditions, including a) a known history of immunodeficiency disorders; b) malignant or nonmalignant disorders requiring use of immunosuppressive therapies
12. Any history of a severe allergic reaction prior to enrollment that has a reasonable risk of recurrence during the study

**Prior/Concomitant Therapy**

13. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
14. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
15. History of convalescent COVID-19 plasma treatment
16. Have received remdesivir
17. Have received any investigational treatment for COVID-19, including but not limited to antiviral agents, corticosteroids, interleukin-1 inhibitors, interleukin-6 inhibitors and intravenous immunoglobulin within 30 days before dosing

**Prior/Concurrent Clinical Study Experience**

18. Participation in a previous SARS-CoV-2 vaccine study
19. Participation, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
20. Concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

**Diagnostic Assessments**

21. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), and/or bilirubin > 2 x ULN
22. Liver insufficiency classified as Child-Pugh Grade C
23. Renal insufficiency: estimated glomerular filtration rate (eGFR) < 30 mL/min using Cockcroft and Gault formula
24. Patients who have been hospitalized due to COVID-19

    For COVID-19 patients that have been hospitalized regardless of disease severity due to local or country regulations, eligibility should be confirmed with the sponsor or designee.

# 5. STUDY TREATMENT

## 5.1. Formulation, Packaging, and Handling

### 5.1.1. BGB-DXP593

BGB-DXP593 is a neutralizing mAb formulated for intravenous injection in a single-use vial (United States Pharmacopeia [USP] type I), containing a total of 300 mg of antibody in 10 mL of buffered isotonic solution. BGB-DXP593 has been aseptically filled in single-use vials with a rubber stopper capped by an aluminum flip-off seal. One or multiple single-use vials are packaged into each carton box. The contents of the label from vials and carton boxes will be in accordance with all applicable local regulatory requirements.

The study drug will be dispatched to the study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The unblinded pharmacist is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. The study drug must be stored in a secure area, with access limited to the authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. BGB-DXP593 must be stored at temperatures between 2°C and 8°C and protected from light.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the BGB-DXP593 Investigator's Brochure for other details regarding BGB-DXP593.

### 5.1.2. Placebo

Placebo is a sterile concentrate solution for dilution for infusion. It shares the same formulation as BGB-DXP593 without the active pharmaceutical ingredient (BGB-DXP593 antibody). Each placebo vial is packaged into a single-carton box. The contents of the label for placebo vials will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal.

## 5.2. Dosage, Administration, and Compliance

BGB-DXP593 or placebo are administered intravenously with a single dose. On the day of dosing, study drug (BGB-DXP593 or placebo) should be reconstituted with 0.9% sodium chloride and will be administered by intravenous infusion for 30 to 90 minutes. Specific instructions for BGB-DXP593 preparation and administration are provided in the Pharmacy Manual. The dose of BGB-DXP593 for each patient will be based on the patient's actual body weight on the day of drug administration.

As a routine precaution, patients must be monitored for at least 2 hours after the infusion of study drug in an area with resuscitation equipment and emergency agents. The study drug must not be administered concurrently with any other drug.

Accurate records of the study drug received, dispensed, returned, and disposed of should be maintained in the site's Drug Inventory Log by an unblinded pharmacist. Refer to the Pharmacy Manual for details of study drug management, drug preparation, storage, and administration.

Guidelines for infusion-related reactions are provided in detail in Section 9.7.

## 5.3. Incorrect Administration

Any incorrect administration of the study drug should be noted in the patient's chart and on the appropriate electronic case report form (eCRF) without the study drug kit number. AEs associated with an incorrect administration of the study drug will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration must be reported within 24 hours of awareness via the SAE reporting process as described in Section 9.6.2. Supportive care measures should be administered as appropriate.

## 5.4. Dose Interruption or Modification

There will be no dose reduction of study drug in this study. A dose interruption is an interruption of an infusion.

Each patient will receive a single dose of the study drug via intravenous infusion. The infusion may be temporarily interrupted due to infusion-related reactions or other medical events.

If the AE is resolved or recovered to Grade 1 (whichever is more severe), the infusion should be resumed within 2 hours of the infusion interruption. If the patient is unable to resume the study drug within 2 hours of the infusion interruption, then the patient should be discontinued from the study treatment.

The treatment modification for infusion-related reactions is provided in Section 9.7.1.

## 5.5. Blinding

In this study, patients will be randomized to receive BGB-DXP593 or matched placebo in a double-blind fashion. The single dose of study drug will be prepared by an unblinded pharmacist. At the study sites, only the unblinded pharmacist for study drug preparation will know the treatment allocation of patients; other members who are directly involved in the clinical conduct of the study, including the staff for study drug administration, will not know. Both the intravenous infusion of BGB-DXP593 and placebo will be colorless. All the follow-up evaluations will be performed by blinded study site staff. It is imperative to maintain the blind to patient treatment assignment such that neither the investigator, nor the patient, nor medical or ancillary medical staff (except for the unblinded pharmacist who is responsible for the preparation of the study drug and has access to dispensation records), nor the blinded sponsor staff or its designees will know which study drug is being administered. Due to the ongoing need to assess safety, a limited number of sponsor staff will not be blinded to patient treatment assignment (see Section 11.1).

Every effort should be made to avoid unblinding the patient's treatment assignment unless necessary. Unblinding may be indicated and permissible only in specific situations as described below and if necessary, for the patient's welfare. Unblinding would occur through Interactive Response Technology (IRT) as per the instructions in the IRT site user manual. If unblinding has occurred, the sponsor must be notified immediately using the Unblinding Event Form. To ensure the continued blinding of study personnel, this form will not include the treatment assignment. Patients will remain on study for study follow-up.

The study will be unblinded after primary analysis database lock.

### 5.5.1. Emergency Unblinding

In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can occur. The investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to inform the medical monitor of their intent before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

The investigator performs the emergency unblinding for AEs through an IRT System.

### 5.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment assignment (ie, BGB-DXP593 or placebo), but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study or excluded from any analyses.

# 6. PRIOR AND CONCOMITANT THERAPY

## 6.1. Permitted Concomitant Medications/Procedures

Unless noted otherwise, most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for a patient's welfare are allowed. Standard of care therapy for mild to moderate COVID-19 is allowed according to local treatment guidelines.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 30 days before the study drug administration and during the study will be recorded in the eCRF including indication and dates of administration.

## 6.2. Prohibited Concomitant Medications/Procedures

Any approved or investigational drugs with established or potential activity against SARS-CoV-2 within 30 days of study drug administration are prohibited, including but not limited to, remdesivir, other antiviral agents, corticosteroids, interleukin-1 inhibitors, interleukin-6 inhibitors, and immunoglobulin. If clinically indicated, patients with worsened COVID-19 may be treated with standard of care therapy according to local treatment guidelines. For example, dexamethasone is allowed in hospitalized patients requiring oxygen support.

## 6.3. Potential Interactions Between the Study Drug and Concomitant Medications

The potential for drug-drug interaction between BGB-DXP593 and small-molecule drug products is very low, given that BGB-DXP593 is a monoclonal antibody. Because BGB-DXP593 is expected to be degraded into amino acids and recycled into other proteins, it is unlikely to have an effect on drug metabolizing enzymes or transporters.

# 7. STUDY PERIODS, VISITS, OR PROCEDURES

Study periods, visits and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 1).

## 7.1. Screening Period

Screening evaluations will be performed within 3 days before the study drug administration. A patient who agrees to participate in this study will sign the informed consent form (ICF) before undergoing any study-specific procedures. Refer to Section 8.1 for instructions regarding screening assessments. Rescreening is not allowed. If the site is able to complete all the screening procedures, randomization, and study treatment in 1 day, the screening assessments can be combined with the Day 1 assessments.

### 7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the IRT system to assign a unique patient number to a potential study participant. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

## 7.2. Enrollment

### 7.2.1. Confirmation of Eligibility

All screening results and relevant medical history must be available before eligibility can be determined. The investigator must confirm that all eligibility criteria are met. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

### 7.2.2. Enrollment/Randomization

Site personnel will randomize the patients to treatment arms (placebo, BGB-DXP593 5 mg/kg, BGB-DXP593 15 mg/kg, or BGB-DXP593 30 mg/kg) based on stratification factors of country and disease severity (mild versus moderate COVID-19), then the unblinded pharmacist will access the IRT system and dispense the study drug.

## 7.3. Treatment

Patients randomized will be treated with the study drug on Day 1 as described in Section 5.2. A single dose of the study drug will be administered intravenously to the patient. Vital signs of the patients will be monitored approximately every 15 minutes during the infusion and then hourly till 2 hours after the infusion. See Appendix 1 for detailed procedures on Day 1.

Refer to Section 7.5 for additional considerations regarding treatment continuation and withdrawal.

## 7.4. Follow-up Period

The follow-up period starts from the next day following the infusion of the study drug through Day 113 (± 7 days). Safety, efficacy, PK, immunogenicity, and biomarker assessments will be performed during the follow-up period as described in Appendix 1 and Appendix 2.

### 7.4.1. End-of-Study Visit

Patients who permanently discontinue from the study will be asked to return to the study center for the End-of-Study Visit, which is required to be conducted within 7 days after the premature study discontinuation. If the patient refuses to return for the End-of-Study Visit or are unable to do so, every effort should be made to contact the patient by telephone to determine their health status.

### 7.4.2. Safety Follow-up Visit After Premature Study Discontinuation

If patients discontinue the study within 30 days after study treatment, a Safety Follow-up Visit will be conducted at Day 31 (± 3 days) (30 days [± 3 days] after study treatment). If the premature discontinuation from study occurs within 7 days prior to Day 31 (± 3 days), the Safety Follow-up Visit can be combined with the End-of-Study Visit or Day 29 visit, as appropriate.

### 7.4.3. Lost to Follow-up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up.

## 7.5. Discontinuation From Study Treatment or From the Study

### 7.5.1. Patient Discontinuation From Study Treatment

Eligible patients will receive a complete dose of study drug. Patients have the right to discontinue study treatment infusion for any reason. In addition, the investigator has the right to discontinue a patient from study treatment. Patients who discontinue study treatment will remain on the study and continue to be followed for protocol-specified follow-up procedures (Appendix 1), if possible; this will include, but is not limited to, the safety assessments.

The primary reason for discontinuation from study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons including but not limited to the following:

- The investigator or sponsor determines it is in the best interest of the patient
- Significant or persistent adverse event(s)

### 7.5.2. Patient Discontinuation From the Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Completion of all study assessments

## 7.6. End of Study

The end of study is defined as the timepoint when the final data for a clinical study were collected, which is after the last patient has made the final visit to the study center. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an End-of-Study Visit as described in Section 7.4.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

# 8. STUDY ASSESSMENTS

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments will be performed and documented in the medical record for each patient.

The investigator and/or site personnel should use personal preventive equipment (PPE) appropriately when performing study assessments and procedures. PPE may be provided by the sponsor. The investigators should follow their hospital policy/local government policy of the country for the management of patient visits to the hospital.

Where applicable, the study dosing will occur only if the clinical assessment and local laboratory test values (that must be available before study dosing) have been reviewed and found to be acceptable per protocol guidelines.

## 8.1. Screening Assessments

Screening evaluations will be performed within 3 days before the study drug administration (Appendix 1). Patients who agree to participate will sign the ICF before undergoing any study-specific screening assessment. The screening period begins on the first day that a screening assessment is conducted. The investigator is to assess patient eligibility according to the latest screening assessment results. Rescreening is not allowed.

Results of laboratory tests (Section 8.2.3) performed before informed consent has been obtained and ≤ 3 days before the screening visit can be used for the purposes of screening.

For the description of assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 8.2) section.

### 8.1.1. Demographic Data, Medical History, and Prior Medications

Demographic data will include age or year of birth, gender, and race/ethnicity.

Medical history includes any history of clinically significant disease or surgery history; reproductive status (ie, of childbearing potential or no childbearing potential).

All medications (eg, prescription drugs, over-the-counter drugs, herbal medications) used by the patient within 30 days prior to the single study dose will be recorded.

### 8.1.2. Review of SARS-CoV-2 Test Result

At screening, the investigator should review the positive results of SARS-CoV-2 test (RT-PCR or other tests authorized by local regulatory authorities) to confirm eligibility.

## 8.2. Safety Assessments

### 8.2.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, respiratory rate, $SpO_2$, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated or supine position after resting for 10 minutes. The monitoring frequency is detailed in Appendix 1.

Height will be measured at screening only and weight will be measured before the single dose of study drug on Day 1. The data of height and weight will be recorded in the eCRF.

### 8.2.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE Version 5.0 and recorded in the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs in the eCRF. Refer to Section 9.3 regarding AE definitions and reporting and follow-up requirements.

### 8.2.3. Laboratory Safety Tests

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 3 per the timepoints shown in Appendix 1.

Samples for pregnancy testing will also be assessed. Urine pregnancy test using highly sensitive human chorionic gonadotropin will be performed in all women of childbearing potential per the timepoints specified in Appendix 1. A confirmation serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. Serum pregnancy tests may be substituted for urine pregnancy tests if the site is not able to perform urine testing.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

### 8.2.4. Electrocardiograms

A 12-lead ECG will be performed at each timepoint specified in Appendix 1. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in a semirecumbent or supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation) before each ECG collection.

### 8.2.5. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE Version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 9.6.

## 8.3. Efficacy Assessment

### 8.3.1. Viral Load

The nasopharyngeal swab, saliva, and blood samples will be collected at the timepoints shown in Appendix 1. The samples will be tested by the method of RT-qPCR in a central laboratory for the quantitative detection of nucleic acid from SARS-CoV-2.

To obtain nasopharyngeal swab samples, insert minitip swab with a flexible shaft (wire or plastic) through the nostril parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the patient, indicating contact with the nasopharynx. Swab should reach depth equal to distance from nostrils to outer opening of the ear. Gently rub and roll the swab. Leave swab in place for several seconds to absorb secretions. Slowly remove swab while rotating it. Specimens can be collected from both sides using the same swab, but it is not necessary to collect specimens from both sides if the minitip is saturated with fluid from the first collection. If a deviated septum or blockage create difficulty in obtaining the specimen from one nostril, use the same swab to obtain the specimen from the other nostril.

The process to collect saliva samples is defined in the laboratory manual.

### 8.3.2. WHO 8-Point Ordinal Scale

WHO 8-point ordinal scale will be used to assess clinical status of patients, at timepoints specified in Appendix 1.

| Descriptor | Score |
|---|---|
| No clinical or virological evidence of infection | 0 |
| No limitation of activities | 1 |
| Limitation of activities | 2 |
| Hospitalized, no oxygen therapy | 3 |
| Oxygen by mask or nasal prongs | 4 |
| Non-invasive ventilation or high-flow oxygen | 5 |
| Intubation and mechanical ventilation | 6 |
| Ventilation and additional organ support-pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO) | 7 |
| Death | 8 |

### 8.3.3. COVID-19-Related Symptoms and Disease Severity

Investigators will assess if patients have recovered from COVID-19 based on symptoms. The COVID-19-related symptoms include, but are not limited to fever, cough, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting. The assessments will be performed at the timepoints specified in Appendix 1.

Investigator will assess the disease severity at each visit:

**Mild COVID-19**

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

**Moderate COVID-19**

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen ($SpO_2$) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

**Severe COVID-19**

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$

  Note: For high altitude areas, $PaO_2/FiO_2$ ratio should be adjusted using formula: $PaO_2/[FiO_2 \times (\text{barometric pressure}/760)]$.
- No criteria for Critical Severity

**Critical COVID-19**

- Positive testing by standard RT-PCR assay or equivalent test
- Evidence of critical illness, defined by at least one of the following:

  – Respiratory failure defined based on resource utilization requiring at least one of the following:

- Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (ie, clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

– Shock (defined by systolic blood pressure < 90 mmHg, or diastolic blood pressure < 60 mmHg or requiring vasopressors)

– Multi-organ dysfunction/failure

## 8.4. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood will be collected to characterize the PK of BGB-DXP593 concentrations using validated immunoassays. Blood samples will be collected for characterization of ADAs. Validated screening and confirmatory assays will be employed to detect ADAs in the samples. Samples collected for analyses of blood concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Blood sampling for PK and ADA will be collected at the timepoints specified in Appendix 2.

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples. The actual time of each sample collected will be captured to the nearest minute in the eCRF and recorded in the database.

## 8.5. Biomarkers

Peripheral blood and/or saliva samples will be collected from patients at different timepoints specified in the Schedule of Assessments (Appendix 1) to explore the association of biomarkers with the efficacy of BGB-DXP593, including but not limited to, SARS-CoV-2 mutations, serology, cytokines and gene expression signatures.

Saliva samples will be collected at various timepoints for testing SARS-CoV-2 mutations to explore the association of potential mutations on the genomic region of the virus with the efficacy of BGB-DXP593.

Blood samples will be collected from patients on Day 1 before study drug administration for measurement of SARS-CoV-2 serology levels at baseline. Additional blood samples will also be collected at various timepoints before and after study drug administration for the measurement of potential biomarkers in peripheral blood including but not limited to cytokines and gene expression levels, for the exploration of the association of these biomarkers with the efficacy of BGB-DXP593.

Shipping, storage, and handling of blood or saliva samples for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1) for sample collection timepoints.

Blood samples will be individually processed and stored as described in the laboratory manual. Coded archival samples may be used for additional medical and/or scientific research that are outside of the current study purpose and objectives (but always in compliance with applicable

law). The research may relate to the diseases that are the subject of this study, validation of new techniques/assays, and/or associated potential medicines. This may include research to help developing ways to detect, monitor, or treat the target disease of this study.

## 8.6. Visit Windows

A visit window of ± 1 day is allowed for visits at Day 5, Day 8, and Day 15, ± 2 days is allowed for visits at Day 22 and Day 29, ± 3 days is allowed for visits at Day 57 and Day 85, and ± 7 days is allowed for visits at Day 113 (Appendix 1 and Appendix 2). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified.

## 8.7. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity, then diagnostic tests may be performed based on the investigator's assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

# 9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

## 9.1. Risks Associated With BGB-DXP593

No clinical data are available yet and no risk associated with BGB-DXP593 has been identified. No treatment-related toxicity was noted in monkeys at weekly repeated doses up to 300 mg/kg in the 14-day repeat dose study in monkeys.

## 9.2. General Plan to Manage Safety Concerns

### 9.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies with BGB-DXP593, as well as the nonclinical/clinical data from other SARS-CoV-2 neutralizing mAbs were considered. Patients with any history of a severe allergic reaction that has a reasonable risk of recurrence are excluded from the study (see Section 4.2 for the full list of exclusion criteria).

### 9.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE Version 5.0.

All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Section 9.6), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1.

Administration of the study drug will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

Blood samples will be drawn for determination of ADAs to BGB-DXP593 in patients who have received the study drug.

Investigators are instructed to report all AEs (includes pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 9.7.

## 9.3. Adverse Events

### 9.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to the study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected incorrect administration of either study drug or a concurrent medication

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

### 9.3.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE Version 5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.6.2.

### 9.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the BGB-DXP593 Investigator’s Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as “related” or “not related” based on all information available at the time of reporting. An AE is considered related if there is “a reasonable possibility” that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered “related” to study drug if any of the following criteria are met; otherwise, the event should be assessed as “not related”:
  - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
  - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient’s clinical condition or other concomitant AEs).

### 9.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes outlined in Section 9.6.2.

### 9.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to treatment interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 9.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it was more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for PK sampling or convenience

## 9.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the BGB-DXP593 Investigator's Brochure.

## 9.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

### 9.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug, only SAEs should be reported.

After initiation of the study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after study treatment or End-of-Study Visit, whichever is later. After the period, the investigator should report any SAEs that are considered to be related to the study drug.

For the follow-up period for AEs, see Section 9.3.4.

### 9.6.2. Reporting Serious Adverse Events

#### 9.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 2.

**Table 2: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee**

| | Timeframe for sending initial report | Documentation method | Timeframe for sending follow-up report | Documentation method | Reporting method |
|---|---|---|---|---|---|
| All SAEs | Within 24 hours of first knowledge of the SAE | SAE report | As expeditiously as possible | SAE report | Email or fax SAE report form |

Abbreviations: SAE, serious adverse event.

#### 9.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 9.6.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 9.3.3.

The sponsor will provide contact information for SAE receipt.

#### 9.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 9.5) will be submitted to all applicable regulatory authorities and investigators for BGB-DXP593 studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

### 9.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

### 9.6.4. Deaths

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an AE (eg, "death," "death of unknown cause," or "death unexplained").

### 9.6.5. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant within 30 days after the single dose of study drug, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

#### 9.6.6. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- BGB-DXP593 Investigator's Brochure

#### 9.6.7. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Individual signs and symptoms of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

### 9.7. Management of Infusion-Related Reactions and Severe Hypersensitivity

As a routine precaution, following completion of study drug(s) administration, patients must be monitored for at least 2 hours after the infusion of study drug in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

The management for infusion-related reactions, and severe hypersensitivity reactions, according to the NCI-CTCAE criteria are outlined in the following subsections.

#### 9.7.1. Managing Infusion-Related Reactions

The symptoms of infusion-related reactions include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

Patients should be closely monitored for infusion-related reactions. Immediate access to an ICU or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) are provided in Table 3.

**Table 3: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug**

| NCI-CTCAE grade | Treatment modification for Study Drug |
|---|---|
| **Grade 1 - mild**<br>Mild transient reaction; infusion interruption not indicated; intervention not indicated. | Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. |
| **Grade 2 - moderate**<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours. | Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity within 2 hours of the infusion interruption. The patient should be discontinued from study drug if the Grade 2 infusion-related reaction has not resolved or decreased over 2 hours of the infusion interruption. Any worsening is closely monitored. Proper medical management should be instituted as described below. |
| **Grade 3 – severe**<br>Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drug treatment. |
| **Grade 4 – life-threatening**<br>Life-threatening consequences; urgent intervention indicated. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drug treatment.<br>Hospitalization is recommended. |

Abbreviations: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

**NCI-CTCAE Grade 1 or 2 infusion reaction:** Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and, if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen.

**NCI-CTCAE Grade 3 or 4 infusion reaction:** Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

### 9.7.2. Severe Hypersensitivity Reactions

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction, the infusion must be stopped immediately and the patient discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm; and are often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then be placed on monitor immediately and an ICU should be alerted for possible transfer if needed.

# 10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Any deviations in the planned analysis as stated in the protocol will be delineated in the SAP. Any deviations from the SAP will be reported in the clinical study report. A data review will be conducted prior to database lock.

## 10.1. Statistical Analysis

### 10.1.1. Analysis Sets

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to the treatment assigned at randomization. This will be the primary analysis set for efficacy analyses.

The Safety Analysis Set includes all patients who have received the study drug (BGB-DXP593 or placebo). Patients will be analyzed according to their actual treatment received. The Safety Analysis Set will be used for all safety analyses.

The PK Analysis Set includes all patients who have received the study drug (BGB-DXP593) per the protocol and for whom any postdose PK data are available.

The ADA Analysis Set includes all the patients who have received the study drug and in whom both baseline ADA and at least 1 postbaseline ADA results are available.

### 10.1.2. Randomization Methods

Patients will be randomized using the IRT system with allocation ratio of 1:1:1:1 to placebo, BGB-DXP593 at 5 mg/kg, BGB-DXP593 at 15 mg/kg, and BGB-DXP593 at 30 mg/kg. Patient randomization will be stratified by country and disease severity (mild versus moderate COVID-19).

### 10.1.3. Patient Disposition

The number of patients randomized, treated, discontinued from study drug and/or the study will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF.

Important protocol deviations will be summarized and listed by category.

### 10.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the ITT Analysis Set and descriptive statistics. Continuous variables include but are not limited to age, weight, and height. Categorical variables include but are not limited to gender, geographical region, and race.

### 10.1.5. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the administration of study drug. Concomitant medications will be defined as medications that 1) started before the administration of study drug and were continuing at the time of the administration of study drug, or 2) started on or after the date of the administration of study drug up to 30 days after dosing.

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

## 10.2. Efficacy Analyses

### 10.2.1. Primary Endpoint Analyses

The statistical hypotheses to be tested for the primary endpoint are as follows:

$H_0$: there is a flat dose response curve comparing change from baseline to Day 8 in SARS-CoV-2 viral shedding in the placebo and the BGB-DXP593 dose groups

$H_1$: there is a non-flat dose response curve indicating a benefit of BGB-DXP593 over placebo

A Mixed Model Repeated Measures (MMRM) analysis will be used to analyze the primary endpoint of change from baseline to Day 8 in SARS-CoV-2 viral shedding. This model will include treatment, visit, and disease severity as discrete fixed effects; baseline viral shredding as a continuous fixed effect; and interaction between visit and treatment, interaction between visit and baseline, interaction between visit and disease severity, and patient as a random effect. The primary treatment comparisons will be the contrast between treatments at Day 8.

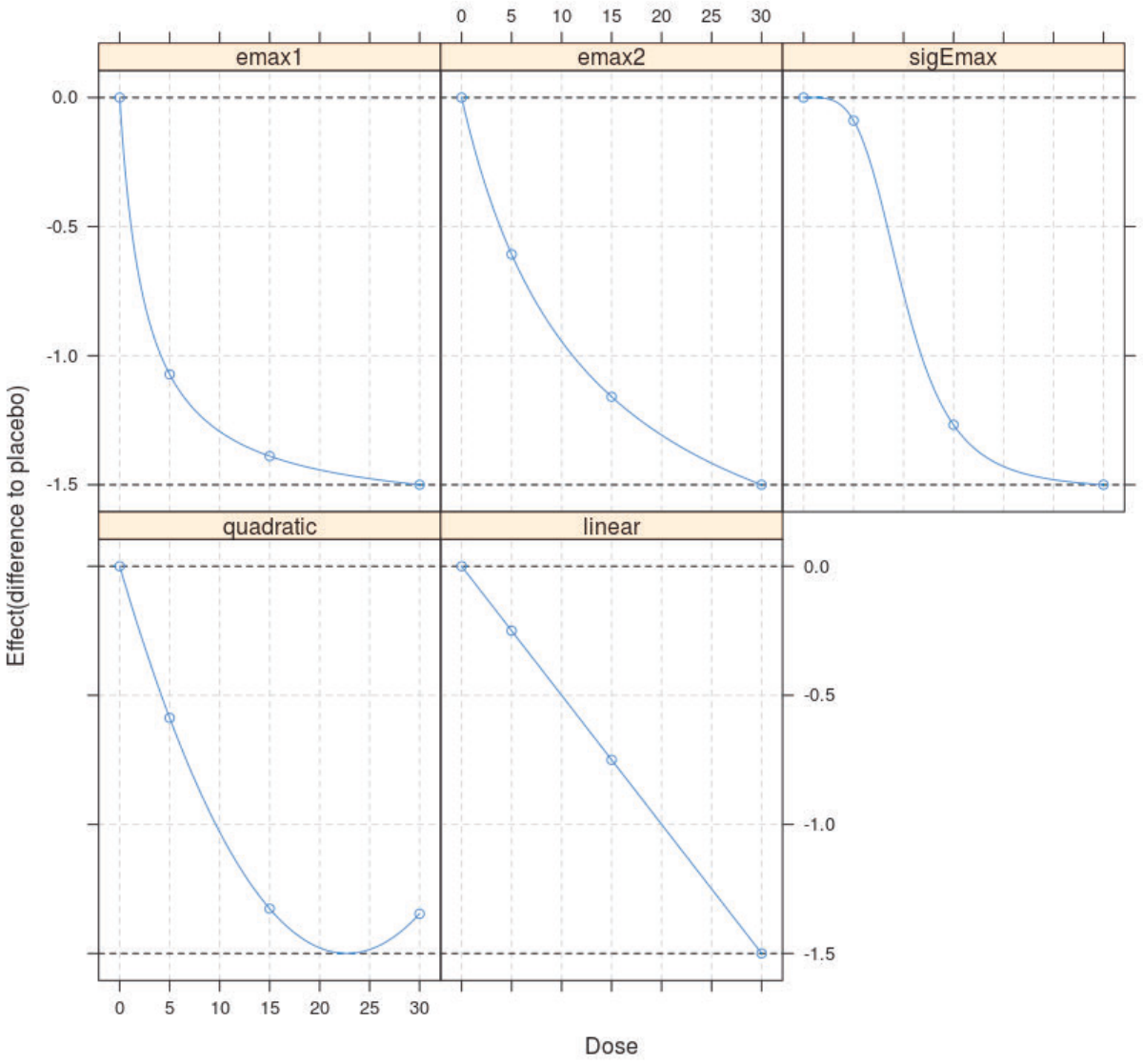
The analysis will be carried out and covariate-adjusted fixed effect estimates of average response for each treatment and the covariance matrix will be extracted from the fit and used for multiple comparison procedures and modelling approaches (MCPMod) analysis.

The primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques. The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one-sided $\alpha$ of 5%).

For the hypothesis testing and for the sample size calculation, the basic shape of each of the models to be tested must be predefined. The following models will be considered for this analysis: linear, Emax, SigEmax and quadratic.

The model assumptions and resulting graphs were selected to cover both plausible and a diverse range of dose response patterns. These are shown in Figure 3. The parameters for each model shape are listed in Table 4.

**Figure 3: Shape of the Considered Dose Response Patterns for the MCPMod Analysis**




Abbreviation: MCPMod, multiple comparison procedures and modelling approaches

**Table 4: Parameter(s) in Each Model**

| Model | Prespecified parameters |
|---|---|
| Emax1 | $ED_{50}$ = 2.6 |
| Emax2 | $ED_{50}$ = 12.5 |
| sigEmax | $ED_{50}$ = 10, h = 4 |
| Quadratic | $\delta$ = -0.022 |
| Linear | No assumption needed |

If at least one model is statistically significant, then we will reject the null hypothesis of a flat dose response relationship over viral shredding change at Day 8, with a multiple contrast test controlled for the family-wise type I error rate at one-sided α = 5%.

After rejecting the null hypothesis, the statistically significant model(s) from the above candidate set are selected as reference models. The dose-response relationship is estimated using model average technique to generate the new estimates.

The target dose(s) can be estimated from the average model by incorporating information on the minimum clinically relevant effect and by accounting for safety.

Comparisons of active doses to placebo (90% confidence intervals [CIs] and p-values) based on the mixed effects model will be reported. These are supportive analyses of the primary endpoint to supplement the MCPMod analysis, which is the primary analysis.

### 10.2.2. Secondary Endpoint Analyses

Secondary efficacy endpoints will include:

- Time-weighted average change in viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples
- Proportion of patients requiring hospitalization due to worsened COVID-19
- Time to resolution of all COVID-19-related symptoms
- All-cause mortality rate at Day 29

The time-weighted average change in viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15 is defined as:

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

where $Y_i$ is the change from baseline in viral shedding at Visit $i$, $t$ is the time at the specified timepoint (the actual study day), $a$ is the baseline assessment at Day 1, and $b$ is the last assessment at or prior to Day 15 visit. Analysis of covariance (ANCOVA) model with corresponding baseline viral shedding, disease severity, and treatment as covariates will be used. Comparisons of active doses to placebo (90% CIs and p-values) will be provided.

The same MMRM analysis for primary endpoint will be used to analyze the change in SARS-CoV-2 viral shedding from baseline to Day 15. Comparisons of active doses to placebo (90% CIs and p-values) will be provided.

Kaplan-Meier method will be used to assess the time to negative RT-qPCR. The corresponding quartiles (including the median) will be reported and a two-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method for each dosing group. Patients who have died prior to experiencing the event of interest will be censored on the day of data cutoff.

The number of patients who require hospitalization due to worsened COVID-19 will be counted. Corresponding proportion will be derived and a two-sided binomial exact 95% CI of proportion will be constructed.

Kaplan-Meier method will be used to assess the time to resolution of all COVID-19-related symptoms. The corresponding quartiles (including the median) will be reported and a two-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method for each dosing group. Patients who have died prior to experiencing the event of interest will be censored. Their follow-up length will be arbitrarily set as (data cutoff date – first-patient-in date). This approach is to count death as the worst possible outcome without possibility of recovery.

Kaplan-Meier method will be used to assess all-cause mortalities and corresponding quartiles (including the median) will be reported. A two-sided 95% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method. Patients who does not die will be censored on the last known date alive.

### 10.2.3. Exploratory Endpoint Analyses

[redacted]

[redacted]

[redacted]

Safety will be determined by monitoring AEs and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE Version 5.0. The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized using the Safety Analysis Set.

### 10.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively for the total dose received per patient (mg) and relative dose intensity.

The number (percentage) of patients requiring treatment interruption because of AEs will be summarized for each study drug. Reasons for dose interruption will be summarized as well.

Patient data listings will be provided for all dosing records and for calculated summary statistics.

### 10.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA lowest level term, preferred term, and primary system organ class.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the administration of study drug and up to the 30 days after dosing.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE Version 5.0 within a system organ class and preferred term, even if the patient experienced more than 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug.

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, ≥ Grade 3 TEAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation or treatment interruption will be summarized.

### 10.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by visit with the maximum postbaseline change.

Laboratory parameters that are graded by NCI-CTCAE Version 5.0 or higher will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions will be summarized separately.

### 10.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, and body temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

## 10.4. Pharmacokinetic Analyses

The PK analyses will include patients with sufficient data to enable estimation of key parameters, such as $C_{max}$, $t_{max}$, $t_{1/2}$, $AUC_t$, $AUC_{inf}$, $AUC_{0-29}$, CL, and $V_z$ (as appropriate for data collected), with patients grouped according to treatment received. Non-compartmental or model-based methods will be used as appropriate.

Individual and mean serum BGB-DXP593 concentration versus time data will be tabulated and plotted by dose level. The PK parameters of BGB-DXP593 may be derived and summarized with descriptive statistics (sample size, mean, standard deviation, coefficient of variance, median, minimum, maximum, geometric mean, geometric coefficient of variance). Other PK parameters may be calculated if supported by the data. Individual serum concentration versus time data will be tabulated and plotted by dose level.

Additional PK analyses (such as modeling and simulation using nonlinear mixed effects modelling) may be conducted as appropriate.

## 10.5. Immunogenicity Analyses

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK and safety may be evaluated if data allow.

## 10.6. Other Exploratory Analyses

[redacted]

## 10.7. Sample Size Consideration

The sample size calculation is based on the following assumptions:

- The primary endpoint “change from baseline to Day 8 in SARS-CoV-2 viral shedding” is normally distributed
- One-sided significance level $\alpha = 5\%$
- True maximum treatment effect size of BGB-DXP593 versus placebo is -1.5 $\log_{10}$ copies per mL
- Standard deviation is 3.2 $\log_{10}$ copies per mL (Wang et al 2020)
- Prespecified candidate models listed in Section 10.2.1

Forty-one patients are needed with primary endpoint data per arm to provide at least 82% power to detect non-flat dose-response relationship. MCPMod approach is used. In order to ensure 41 patients per arm with primary endpoint data, at least 43 patients per arm need to be randomized.

The calculation has been performed using R software, version 3.6.1.

## 10.8. Interim Analyses

A primary analysis is planned after all patients have finished Day 8 visit or discontinued the study earlier. A decision will be made based on the interim results about whether a Phase 3 study should be initiated and which dose to be used for the Phase 3 study.

## 10.9. Missing Data Handling and Censoring Rules

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

For MMRM analysis, no imputation will be performed for missing viral shredding. If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random” assumption.

Sensitivity analyses using method of last observation carry forward (LOCF) may be considered to assess the potential impact from missing data, which will be detailed in the statistical analysis plan (SAP).

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures will be provided in the statistical analysis plan (SAP).

Censoring rules for analyses of time-to-event endpoints are determined as in Table 5.

**Table 5: Censoring Rules for Analysis of Time-to-event Endpoints**

| No. | Situation | Date of Event or Censoring | Outcome |
|---|---|---|---|
| 1 | Target event documented | Date of occurrence of target event | Event |
| 2 | Multiple target events documented | Date of first occurrence of target event | Event |
| 3 | No target event or death occurred by the time of the End-of-Study Visit or the Safety Follow-up Visit (whichever is later), or data cut-off, or withdrawal from study, whichever comes first | Date of last adequate event assessment prior to or on the date of the End-of-Study Visit or the Safety Follow-up Visit (whichever is later), or data cut-off, or withdrawal from study, whichever comes first | Censored |
| 4 | Death and no target event prior to death | Date of data cutoff | Censored |

# 11. STUDY COMMITTEES

## 11.1. Independent Data Monitoring Committee

An IDMC will be established; the function and membership will be described in the IDMC Charter.

Regular safety monitoring and efficacy monitoring will be performed by the IDMC. The first IDMC safety review will occur after at least 12 patients (ie, approximately 3 patients per treatment arm) have received study treatment and have been followed up for at least 7 days. The frequency of the subsequent safety reviews will be defined in the IDMC Charter. Preliminary efficacy summaries will be provided to the IDMC when approximately 60 patients have received study treatment and have been followed up for at least 14 days. Preliminary efficacy summaries will be included in the IDMC report and reported monthly afterwards. The frequency of the meetings may be adjusted based on the need for safety monitoring of the study. The IDMC has access to unblinded information to assess the safety and efficacy.

In addition to the planned IDMC review(s), ad hoc reviews may take place based on new information.

The IDMC may recommend modifications to the study procedures or conduct based on available data. After IDMC review and discussion, the sponsor will make all final decisions regarding any change in study conduct. Please see the details in the IDMC Charter.

# 12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

## 12.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

## 12.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene, Ltd., (hereafter referred to as BeiGene) may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

# 13. QUALITY ASSURANCE AND QUALITY CONTROL

## 13.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

## 13.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

## 13.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

## 13.4. Drug Accountability

The investigator or designee (ie, unblinded pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), patient drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the unblinded monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study unblinded monitor over the course of the study.

# 14. ETHICS/PROTECTION OF HUMAN PATIENTS

## 14.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

## 14.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

### 14.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

## 14.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

## 14.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the BGB-DXP593 Investigator's Brochure, this protocol, eCRFs, the Investigational New Drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

## 14.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

# 15. DATA HANDLING AND RECORD KEEPING

## 15.1. Data Collection and Management Responsibilities

### 15.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

### 15.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

### 15.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out with due consideration to data protection and medical confidentiality.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by the lowest level term, preferred term, and primary system organ class. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

## 15.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include but not be limited to documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of a period of up to 10 years or as allowed by your IRB/IEC.

## 15.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

## 15.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

## 15.5. Study and Study Center Closure

Upon completion of the study, the unblinded monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

## 15.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 15.4

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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# 17. APPENDICES

# APPENDIX 1. SCHEDULE OF ASSESSMENTS

| Period | Screening[a] | Treatment | | Follow-up [b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -3 to -1 | Day 1 | | Day 3 | Day 5 | Day 8 | Day 15 | Day 22 | Day 29 | Day 57 | Day 85 | Day 113/EOS Visit[c] | Day 31 Safety Follow-up Visit[d] |
| | | Predose | 2-hour postdose | | | | | | | | | | |
| **Visit Window (day)** | | | ±1 hour | | ±1 | ±1 | ±1 | ±2 | ±2 | ±3 | ±3 | ±7 | ±3 |
| Informed consent [e] | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria [f] | X | | | | | | | | | | | | |
| Demography/Prior medications | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | |
| Review SARS-CoV-2 results [g] | X | | | | | | | | | | | | |
| Randomization [h] | | X | | | | | | | | | | | |
| Study drug administration [i] | | X | | | | | | | | | | | |
| **Safety assessment** | | | | | | | | | | | | | |
| Vital signs/ height and weight [j] | X | X | X | X | | X | X | | X | | X | X | X |
| Complete physical examination [k] | X | | | | | | | | | | | | |
| Targeted physical examination [l] | | X | | X | | X | X | | X | | X | X | X |
| 12-lead ECG [m] | X | X | X | | | | | | X | | X | X | |
| Adverse event [n] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Efficacy assessment** | | | | | | | | | | | | | |
| RT-qPCR for SARS-CoV-2 (nasopharyngeal swab) | | X | | X | | X | X | | | | | | |

| Period | Screening[a] | Treatment | | Follow-up [b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -3 to -1 | Day 1 | | Day 3 | Day 5 | Day 8 | Day 15 | Day 22 | Day 29 | Day 57 | Day 85 | Day 113/EOS Visit[c] | Day 31 Safety Follow-up Visit[d] |
| | | Predose | 2-hour postdose | | | | | | | | | | |
| **Visit Window (day)** | | | ±1 hour | | ±1 | ±1 | ±1 | ±2 | ±2 | ±3 | ±3 | ±7 | ±3 |
| RT-qPCR for SARS-CoV-2 (saliva [u]) | | X | | X | | X | X | | | | | | |
| RT-qPCR for SARS-CoV-2 (blood) | | X | | X | | X | X | | | | | | |
| WHO 8-point ordinal scale [o] | | X | | X | X | X | X | X | X | | | | |
| COVID-19-related symptoms [p]/Disease severity [p] | X | X | | X | X | X | X | X | X | | | | |
| **Laboratory assessments** | | | | | | | | | | | | | |
| Hematology [q] | X[r] | | | X | | X | X | | X | | | | |
| Chemistry [q] | X[r] | | | X | | X | X | | X | | | | |
| Coagulation [q] | X[r] | | | X | | X | X | | X | | | | |
| Urinalysis [q] | X[r] | | | | | X | | | X | | | | |
| Pregnancy test [s] | X[r] | | | | | | | | X | | X | X | |
| PK blood sampling | | See Appendix 2 | | | | | | | | | | | |
| ADA blood sampling | | See Appendix 2 | | | | | | | | | | | |
| SARS-CoV-2 serology sampling [t] | | X | | | | | | | | | | | |
| [redacted] | | [redacted] | | [redacted] | | [redacted] | [redacted] | | [redacted] | | | [redacted] | |

Abbreviations: ADA, antidrug antibody; COVID-19, Coronavirus Disease 2019; ECG, electrocardiogram; EOS, End-of-Study; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; IRT, Interactive Response Technology; PK, pharmacokinetics; RT-PCR, reverse transcription-polymerase chain reaction; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; WHO, World Health Organization.

[a] If the site is able to complete all the screening procedures, randomization, and study treatment in 1 day, the screening assessments can be combined with the Day 1 assessments

[b] Telehealth/remote nurse home visits will be permitted after Day 1 visit (treatment)/discharge from the hospital if circumstances prevent visits to the clinic. Day 5, Day 22, and Day 57 visits will be performed by phone/video.

[c] The EOS Visit will be conducted within 7 days after a premature study discontinuation. The Day 113 visit is the EOS Visit for patients who complete all the previously planned study visits.

[d] The Safety Follow-up Visit is only for patients who prematurely discontinue the study within 30 days after study treatment. The Safety Follow-up Visit will be conducted at 30 days (± 3 days) after study treatment (Day 31 [± 3 days]). If the premature discontinuation from study occurs within 7 days prior to Day 31 (± 3 days), the Safety Follow-up Visit can be combined with the EOS Visit or the Day 29 visit, as appropriate.

[e] Written informed consent must be obtained before performing any study-specific procedures. Consent must be obtained using the current version of the form approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The consent can be obtained via remote consent if approved by local IRB.

[f] Follicle-stimulating hormone (FSH) and estradiol assessments will be performed in female patients who are < 55 years of age with no spontaneous menses for ≥ 12 months to identify the status of no childbearing potential (refer to Appendix 4). Historical test results are allowed.

[g] Positive results of SARS-CoV-2 test (RT-PCR or other tests authorized by local regulatory authorities) ≤ 72 hours prior to screening are required for confirmation of eligibility.

[h] Patients enrolled will be randomized via IRT to receive placebo, BGB-DXP593 5 mg/kg, BGB-DXP593 15 mg/kg, or BGB-DXP593 30 mg/kg on Day 1.

[i] The dose of BGB-DXP593 will be based on the patient's actual body weight on the day of receiving the study drug (Day 1).

[j] Vital signs will be monitored approximately every 15 minutes during the infusion, and then hourly till 2 hours after the infusion; the monitoring will include measurements of body temperature (˚C), pulse rate, respiratory rate, saturation of oxygen ($SpO_2$), and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated or supine position after resting for 10 minutes. Height will be measured at screening only and weight will be measured at Day 1 before study drug dosing.

[k] Complete physical examination includes evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems.

[l] At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

[m] A 12-lead ECG will be performed at the timepoints specified in the table. All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in a semirecumbent or supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation) before each ECG collection.

[n] After informed consent has been signed but before the administration of the study drug, only serious adverse events (SAEs) should be reported. After initiation of the study drug, all adverse events (AEs) and SAEs, regardless of relationship to study drug, will be reported until 30 days after study treatment or EOS Visit, whichever is later. After the period, the investigator should report any SAEs that are considered to be related to the study drug.

[o] Refer to Section 8.3.2 for details regarding WHO 8-point ordinal scale.

[p] The COVID-19-related symptoms include, but are not limited to, fever, cough, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting. Refer to Section 8.3.3 for assessment of disease severity.

[q] Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 3.

[r] laboratory tests (clinical chemistry, hematology, coagulation, urinalysis, and pregnancy test) performed within 3 days prior to screening visit can be used to confirm eligibility.

[s] Urine pregnancy test using highly sensitive human chorionic gonadotropin will be performed in all women of childbearing potential at the specified timepoints. A confirmation serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. Serum pregnancy tests may be substituted for urine pregnancy tests if the site is not able to perform urine testing. Female patients with negative test results will be eligible to receive the study drug.

[t] Peripheral Blood samples will be collected from patients to explore the association of biomarkers with the efficacy of BGB-DXP593, including but not limited to SARS-CoV-2 serology, cytokines and gene expression signatures. Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples.

[u] Saliva samples collected here will also be used for SARS-CoV-2 mutation testing.

# APPENDIX 2. PHARMACOKINETIC AND ANTIDRUG ANTIBODY BLOOD SAMPLING

| Study Day | Day 1 | | Day 3 | Day 8 | Day 15 | Day 29 | Day 113/ EOS Visit [a] |
|---|---|---|---|---|---|---|---|
| **Hours post the start of infusion** | **0 (predose)** | **EOI** | **48** | **168** | **336** | **672** | **2688** |
| **Window Period (hours)** | **-60 min to predose** | **Within 30 min after EOI** | **±6** | **±24** | **±24** | **±48** | **±168** |
| PK blood sampling | X | X | X | X | X | X | X |
| ADA sampling | X | | | | X | X | X |

Abbreviations: ADA, antidrug antibody; EOI, end of infusion; EOS, End-of-Study; min, minutes; PK, pharmacokinetics.
Note: Sample collection must be from the opposite arm that is used for study drug infusion. Refer to laboratory manual for detailed collection instructions. PK and ADA sampling will be performed only in sites that can adequately perform sampling, handling, and processing procedures outlined in the laboratory manual.
[a] The EOS Visit will be conducted within 7 days after a premature study discontinuation; if the EOS Visit occurs then PK and ADA samples should be collected.

# APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

| Clinical chemistry | Hematology | Coagulation | Urinalysis |
|---|---|---|---|
| Alkaline phosphatase<br>Alanine aminotransferase<br>Aspartate aminotransferase<br>Albumin<br>Total bilirubin<br>Direct bilirubin<br>Blood urea nitrogen or urea<br>Potassium<br>Sodium<br>Total calcium[a]<br>Creatinine<br>Glucose<br>Lactate dehydrogenase<br>Total protein<br>Magnesium<br>C-reactive protein | Red blood cell count<br>Hematocrit<br>Hemoglobin<br>Platelet count<br>White blood cell count<br>Lymphocyte count<br>Neutrophil count | Prothrombin time<br>Partial thromboplastin time or activated partial thromboplastin time<br>International normalized ratio<br>D-Dimers | Specific gravity<br>pH<br>Glucose<br>Protein<br>Blood<br>Ketones<br>Bilirubin<br>Urobilinogen<br>Nitrite<br>Leukocyte esterase or leukocyte |
| **Other Tests** | | | |
| • Follicle-stimulating hormone (FSH) and estradiol test (as needed for female patients who are < 55 years of age with no spontaneous menses for ≥ 12 months to identify the status of no childbearing potential)<br>• Highly sensitive human chorionic gonadotropin pregnancy test (in women of childbearing potential)<br>• SARS-CoV-2 RT-qPCR test | | | |

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

[a] Total calcium values will be corrected for patients with hypoproteinemia.

# APPENDIX 4. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral, injectable, or implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for azoospermia has been demonstrated in a semen sample examination as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug(s), and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group 2014.