CLINICAL STUDY PROTOCOL

Protocol Title:	A First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Healthy Subjects
Protocol Identifier:	BGB-DXP593-101
Phase:	1
Investigational Product:	BGB-DXP593
Proposed Indication:	Not Applicable
Sponsor:	BeiGene, Ltd. c/o BeiGene AUS Pty Ltd. 1C/528 Compton Road Stretton Queensland 4116, Australia
Sponsor Medical Monitor	[redacted]
Original Protocol Version 0.0:	04 August 2020

FINAL PROTOCOL APPROVAL SHEET

A First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Healthy Subjects

BeiGene, Ltd., Approval:

[redacted]

4-Aug-2020

Date

Senior Medical Director

INVESTIGATOR SIGNATURE PAGE

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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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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 Product: BGB-DXP593

Title of Study: A First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Healthy Subjects

Protocol Identifier: BGB-DXP593-101

Phase of Development: 1

Number of Subjects: up to 30 healthy subjects

Study Centers: 1 center in Australia

Study Objectives

Primary Objective

- To investigate the safety and tolerability of BGB-DXP593 administered intravenously as a single dose in healthy subjects

Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects
- To evaluate the potential immunogenicity of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects

Study Endpoints

Primary Endpoint

- Incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs)

Secondary Endpoints

- Changes in vital signs and 12-lead electrocardiogram (ECG) parameters from baseline
- Incidence and magnitude of clinical laboratory abnormalities
- Characterize PK concentration-time profile and PK parameters for BGB-DXP593: 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 infinity (AUC_{inf}), AUC from time zero to Day 29 (AUC_{0-29}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z) as appropriate
- Clinical immunogenicity of BGB-DXP593 evaluated through the detection of antidrug antibodies (ADA) over time

Study Design

This is a first-in-human, randomized, double-blind, placebo-controlled, single dose escalation study to investigate the safety, tolerability, PK, and immunogenicity of BGB-DXP593 in healthy subjects.

After providing written informed consent, subjects will complete all the screening assessments. After being confirmed as eligible, subjects will be sequentially enrolled for different dose levels. Two dose levels are planned for eligible subjects to receive a single intravenous dose of study drug (ie, BGB-DXP593 or placebo) at 10 mg/kg or 30 mg/kg, respectively. Another higher dose level will be allowed for dose escalation.

Enrollment will begin at the 10 mg/kg dose level. Escalation to the next dose level will occur 7 days after the last subject at the current dose level has received the study drug, and the safety, laboratory data have been reviewed.

At each dose level, eligible subjects will be randomized at a 3:1 ratio (6 active: 2 control) to the active arm for receiving BGB-DXP593 or to the control arm for receiving the same volume of placebo (ie, normal saline), respectively. The sentinel dosing will be adopted for each dose level. In the other words, 2 eligible subjects will be randomized at a 1:1 ratio (1 active: 1 control) to receive BGB-DXP593 or placebo on Day 1; and the remaining subjects will be randomized at a 5:1 ratio (5 active: 1 control) to receive BGB-DXP593 or placebo at least 48 hours later, provided satisfactory safety and tolerability is demonstrated for the first 2 subjects randomized and dosed at the dose level.

Dose Level	Number of Subjects [b]	
	Active Arm (BGB-DXP593)	Control Arm (Normal Saline)
A – 10 mg/kg	6	2
B – 30 mg/kg	6	2
C [a]	6	2

Abbreviation: PK, pharmacokinetic.

[a] Besides the 2 planned dose levels, one higher dose level will be allowed. The higher dose level will be triggered based on the review of PK data from the first 2 dose levels.

[b] Enrollment up to 30 subjects is permitted if additional subjects are necessary for safety or PK evaluations.

Subjects are expected to be available for follow-up visits until Day 113 of the study. Subjects will be replaced if they cannot complete the infusion. Subjects may be replaced if they discontinue from the study before Day 29.

The administration of the study drug and the enrollment of new subjects will pause for the dose level, if any of the following events occurs:

- One or more ≥ Grade 4 TEAEs or treatment-emergent SAEs related to study drug as assessed by the investigator in any subject or
- Grade 3 TEAEs related to study drug as assessed by the investigator in 2 or more subjects at the same dose level.

The Safety Monitoring Committee (SMC) will review the safety and laboratory data at each dose level. The SMC may recommend keeping the current enrollment plan, opening a repeated cohort at the same dose level, de-escalating to a lower dose level, or terminating the study. For the scenarios of repeated dose level and lower dose level, the number of subjects and randomization ratio will be the same as planned dose levels.

If a repeated cohort evaluation of the same dose level confirms the AE profile previously observed at the dose level, no higher dose level will be tested in this study.

Study Assessments:

Subjects will be monitored for safety, tolerability, PK, and immunogenicity of BGB-DXP593 throughout the study.

Assessments of safety will include adverse events (AEs), SAEs, clinical laboratory tests, physical examinations, vital signs, and 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. A SMC will periodically monitor safety data.

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

Key Eligibility Criteria

Subjects to be included in this study will be adults between 18 and 60 years of age at the time of informed consent and in good general health.

Test Product, Dose, and Mode of Administration

BGB-DXP593 will be administered intravenously at a dose of 10 mg/kg or 30 mg/kg for 30-60 minutes.

Reference Therapy, Dose, and Mode of Administration

Normal saline (ie, solution of 0.9% sodium chloride) will be administered intravenously for 30-60 minutes.

Statistical Methods

The focus of this first-in-human study is to evaluate the safety, tolerability, PK and immunogenicity of BGB-DXP593. No formal statistical hypotheses will be tested.

Analysis Sets:

The Safety Analysis Set will include all the subjects who received the study drug.

The PK Analysis Set will include all the subjects who received the study drug and had any measurable concentration of study drug.

The ADA Analysis Set will include all the subjects who received the study drug and in whom both baseline ADA and at least 1 postbaseline ADA results are available.

Safety Analyses:

Adverse events, ECGs, vital signs, and laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Descriptive statistics will be used to analyze all safety data.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline on or after the administration of study drug and up to 30 days after the dose of study drug. Only those AEs that were treatment emergent will be included in the summary tables. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by system organ class and preferred term. The treatment-emergent SAEs and treatment-related TEAEs will also be summarized. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Changes from baseline for the ECG parameters and vital signs will be summarized by visit and dose level.

Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Laboratory parameters and their changes from baseline will be summarized by visit and dose level.

Pharmacokinetic Analyses:

Noncompartmental 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 subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for evaluable subjects. The effect of immunogenicity on PK, and safety may be evaluated if data allow.

Sample Size Consideration:

A sample size of 8 subjects at each dose level (6 active and 2 control) totaling up to 30 subjects (including possible replacement) is not based on any statistical considerations. The sample size is based on the clinical consideration to provide safety and tolerability information as well as pharmacological considerations with the need to minimize exposure of healthy subjects at each dose level. No formal inferential statistics will be applied to the safety or PK data.

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
BGB-DXP593	code name for monoclonal antibody BGB-DXP593, also named DXP593, BD-368-2, and WBP2281
CL	clearance
C_{max}	maximum observed concentration
COVID-19	Coronavirus Disease 2019
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
GCP	Good Clinical Practice
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA®	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PT	preferred term
RBD	receptor-binding domain
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMC	Safety Monitoring Committee
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to maximum observed concentration
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 P et al 2020). As of July 2020, over 16 million confirmed cases of COVID-19 worldwide have been reported to World Health Organization. COVID-19 is threatening the global public health, and the ongoing spread of COVID-19, which has resulted in a worldwide pandemic, demands effective interventions against SARS-CoV-2 infections. Unfortunately, there is no vaccine and no prescription drug regimen which has demonstrated significant efficacy in the treatment of COVID-19 patients in clinical studies so far (Jean et al 2020).

Currently, several strategies are used in the clinic or are under development, such as viral-targeting therapeutics and host-targeting agents (such as anti-interleukin 6 antibodies, and glucocorticoids) for the treatment of COVID-19. Convalescent plasma therapy has been used to treat COVID-19 by providing passive immune responses to the viral infection. However, the outcomes of passive plasma therapy are unpredictable due to the variability of sera from different patients (Zhou GY et al 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 et al 2020).

Neutralizing monoclonal antibodies (mAbs), generated from the plasma from convalescent patients, provide a more specific immune response. In addition, the antibodies with a high affinity to the virus can be selected. No clinical studies with SARS-CoV-2-specific neutralizing mAbs have been completed to date, therefore, neutralizing antibodies that effectively block virus entry into host cells are urgently needed (Cao et al 2020).

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

BGB-DXP593 (also named DXP593, BD-368-2, and WBP2281) is a highly potent neutralizing mAb identified by high-throughput single-cell sequencing of convalescent patients' B-cells. BGB-DXP593 binds to the S protein receptor-binding domain (RBD) of SARS-CoV-2 with high specificity and affinity, preventing the virus from entering cells.

1.2.1. Summary of Relevant Nonclinical Data with BGB-DXP593

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 angiotensin-converting enzyme 2 (ACE2) as its receptor with a concentration for 50% inhibition of maximal activity (IC_{50}) of 0.81 nM in a competition enzyme-linked immunosorbent assay.

The crystal structure of BGB-DXP593 fragment antigen-binding (Fab) in complex with RBD suggests that BGB-DXP593 would interfere with the interaction between RBD and ACE2. [redacted]

[redacted] In addition, the structure also suggests that BGB-DXP593 would clash with both protomers in the ACE2 dimer.

In cell-based assays, BGB-DXP593 potently inhibits SARS-CoV-2 infections in both pseudovirus and authentic virus systems with IC_{50} of 8 pM (0.0012 µg/mL) and 0.1 nM (0.015 µg/mL), IC_{99} of 0.6 nM (0.09 µg/mL) and 1.08 nM (0.162 µg/mL), respectively. BGB-DXP593 has wild-type immunoglobulin G1 (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 therapeutic efficacy and 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 to undetectable levels in the prophylactic model of treatment, where BGB-DXP593 was injected 24 hours before the virus infection. Consistent with that, the body weights of the treated mice remained stasis while that of the control mice dropped by > 5% at 5 days post infection. Similarly, BGB-DXP593 reduced the virus load by over 1000 folds in the therapeutic model of treatment (Cao et al 2020), where BGB-DXP593 was injected 2 hours after the infection. And the body weights remained unchanged over a course of 5 days, comparable to those in the prophylactic model of treatment, suggesting that BGB-DXP593 maintained the fitness of the infected mice.

In the hamster therapeutic model of treatment, BGB-DXP593 injection led to dose-dependent lung viral reduction at 7 days post infection, with the best response observed with the highest tested dose group (ie, 20 mg/kg). All dose groups showed improved body weight loss comparing with the control group. BGB-DXP593 (20 mg/kg) also demonstrated preventive effect in hamster model when injected 1 day or 3 days before infection, while the earlier 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. The study for tissue cross-reactivity was evaluated in the normal frozen tissues from both cynomolgus monkeys and humans. The study for cytokine release responses was 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 toxicity study. Based on the available data, the missing information is not considered to have an impact on the toxicity results and data interpretation. The 14-day repeat-dose toxicity study was conducted in cynomolgus monkeys at the doses of 30 mg/kg, 100 mg/kg, or 300 mg/kg, no mortality or morbidity was observed throughout the study; no treatment-related findings or changes were

observed, 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 functions of cardiovascular, respiratory, or central nervous systems were observed.

The systemic exposure, which was 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 obvious drug accumulation or changes were found after weekly repeated doses. The no observed adverse effect level (NOAEL) is considered as 300 mg/kg in this study based on the available data, which was approximately 30-fold of the proposed first in human dose level (10 mg/kg) and 10-fold of the proposed highest human dose level (30 mg/kg) based on body weights.

In the study for tissue cross-reactivity, no specific binding of BGB-DXP593 was detected in either normal cynomolgus monkey or human tissues with the 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. Summary of Relevant Clinical Experience with BGB-DXP593

This is the first-in-human study of BGB-DXP593. No clinical data are available.

1.3. Study Rationale

1.3.1. Rationale for Matching Placebo as the Comparator

In this study, normal saline (ie, solution of 0.9% sodium chloride) will be used as placebo. The volume of normal saline will be identical to the volume of BGB-DXP593. A placebo is being used to preserve the scientific integrity of the study and reduce any potential observational or performance bias.

1.3.2. Rationale for BGB-DXP593 Starting Dose

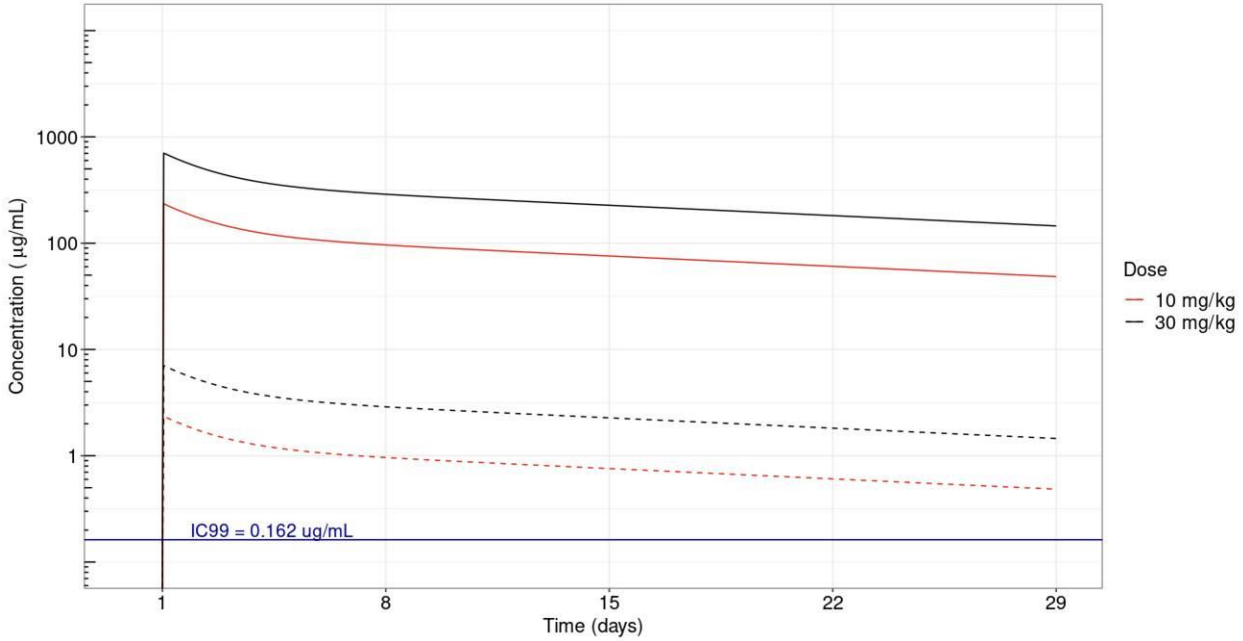
1.3.2.1. Allometric Scaling for Human Pharmacokinetics Projection

Serum concentration-time profiles from 36 cynomolgus monkeys that received either a single dose of BGB-DXP593 at 10 mg/kg or repeated doses of BGB-DXP593 at 30 mg/kg, 100 mg/kg, or 300 mg/kg once every 2 weeks for 2 doses (Section 1.2.1.2) were used in a population PK analysis with NONMEM® Version 7.3 (ICON plc; Dublin, Ireland).

A 2-compartment model with first-order elimination described the PK data well. Between animal variability was estimated for clearance (CL) and volume of distribution (V_z). A proportional error model was used. Human PK parameters were obtained by scaling respective cynomolgus monkey PK parameters multiplied by the ratio of body weight (human to monkey) and taken to the power of 0.75 for clearance and intercompartmental clearance and 1.0 for the central and peripheral compartment volumes (Mahmood and Balian 1999).

The serum concentration-time profiles in humans for BGB-DXP593 were simulated using software R Version 3.4.4 (Figure 1). The cynomolgus monkey PK parameters and projected human PK parameters are shown in Table 1.

Figure 1: Simulated BGB-DXP593 Serum 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
Notes: More details on the IC_{99} results are provided in Section 1.2.1.1.
The solid lines represent for projected serum concentrations. The dashed lines represent for projected lung concentrations assuming 1% biodistribution. Please refer to the BGB-DXP593 Investigator's Brochure for more detailed information on assuming 1% biodistribution.

Table 1: BGB-DXP593 Population PK Parameter Estimates in Cynomolgus Monkeys and Projected PK Parameters in Humans

Parameter (units)	Cynomolgus Monkey		Human Projection
	Estimate	%RSE	
CL (L/hr)	0.00068	4.9	0.0075
V_c (L)	0.121	3.9	2.96
Q (L/hr)	0.00299	7.5	0.033
V_p (L)	0.0984	3.8	2.41
IIV CL (%)	26.9	14.6	NA
IIV V_c (%)	24.1	13.5	NA
Residual variability (%)	14.2	5.1	NA

Abbreviations: CL, clearance; hr, hour; IIV, inter-individual variability; NA, not applicable; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; V_c, volume of central compartment; V_p, volume of peripheral compartment.

1.3.2.2. Recommendation of the First-in-Human Dose of BGB-DXP593 in Healthy Subjects

A single dose of BGB-DXP593 at 10 mg/kg as the starting dose level is proposed in this first-in-human study for BGB-DXP593. The selection of this starting dose level was based on the NOAEL approach and supported by safety margins as described below.

Based on the toxicology evaluation in a 14-day repeat-dose study in cynomolgus monkeys, the NOAEL was determined to be 300 mg/kg (Section 1.2.1.2). Applying a safety factor of 10, the maximum recommended starting dose (MRSD) is estimated as 30 mg/kg (body-weight based) (FDA CDER 2005). The proposed starting dose level of 10 mg/kg is 3 times lower than the MRSD.

In addition, based on the AUC from time zero to infinity (AUC_{inf}) and C_{max} after the second dose at 300 mg/kg (ie, NOAEL in the toxicity study) in cynomolgus monkeys, the projected safety margins at the proposed starting dose of 10 mg/kg are 15.1 and 33.2, respectively (Table 2), which reflects favorably on the safety profile of BGB-DXP593.

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

Table 2: Projected Safety Margins at Proposed Doses in Humans

Safety Margin	BGB-DXP593 Dose (mg/kg)		
	10	30	60
AUC based	[redacted]		
C_{max} based			

Abbreviations: AUC, area under concentration-time curve; C_{max}, maximum observed concentration
Note: The proposed dose levels are 10 mg/kg and 30 mg/kg, safety margins to 60 mg/kg dose are provided for reference.

1.3.3. 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}, time to maximum observed concentration (t_{max}), AUC from time zero to the time of the last quantifiable concentration (AUC_t), AUC_{inf}, AUC from time zero to Day 29 (AUC_{0-29}), terminal half-life ($t_{1/2}$), CL, and V_z.

1.4. Benefit-Risk Assessment

This is a first-in-human study and the side effects of BGB-DXP593 in humans are unknown.

The healthy subjects in this study will not receive any health benefit from participating in the study other than an assessment of their medical status.

The subjects might have some discomfort from blood collection and other study procedures. Other than that, the risks of study participation include possible adverse reactions associated with BGB-DXP593 such as infusion-related reactions. However, since BGB-DXP593 is a human protein selected from recovered COVID-19 patients, it is unlikely to have any pharmacodynamic

effect in healthy subjects. Therefore, the risks are generally low under the current safety monitoring planned for this study.

To further minimize the risk to the subjects, the method of sentinel dosing will be adopted for this study and each healthy subject in the study will receive only a single dose of study drug.

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 STUDY ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To investigate the safety and tolerability of BGB-DXP593 administered intravenously as a single dose in healthy subjects

2.1.2. Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects
- To evaluate the potential immunogenicity of BGB-DXP593 administered intravenously as a single dose at each dose level in healthy subjects

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs)

2.2.2. Secondary Endpoints

- Changes in vital signs and 12-lead electrocardiogram (ECG) parameters from baseline
- Incidence and magnitude of clinical laboratory abnormalities
- Characterize PK concentration-time profile and PK parameters for BGB-DXP593: C_{max}, AUC_t, AUC_{inf}, AUC_{0-29}, t_{max}, $t_{1/2}$, CL, and V_z as appropriate
- Clinical immunogenicity of BGB-DXP593 evaluated through the detection of ADA over time

3. STUDY DESIGN

3.1. Summary of Study Design

This is a first-in-human, randomized, double-blind, placebo-controlled, single dose escalation study to investigate the safety, tolerability, PK, and immunogenicity of BGB-DXP593 in healthy subjects.

After providing written informed consent, subjects will complete all the screening assessments. After being confirmed as eligible, subjects will be sequentially enrolled for different dose levels.

Two dose levels are planned for eligible subjects to receive a single intravenous dose of study drug (ie, BGB-DXP593 or placebo) at 10 mg/kg or 30 mg/kg, respectively. Another higher dose level will be allowed for dose escalation.

Enrollment will begin at the 10 mg/kg dose level. Escalation to the next dose level will occur 7 days after the last subject at the current dose level has received the study drug, and the safety, laboratory data have been reviewed.

At each dose level, eligible subjects will be randomized at a 3:1 ratio (6 active: 2 control) to the active arm for receiving BGB-DXP593 or to the control arm for receiving the same volume of placebo (ie, normal saline), respectively.

The sentinel dosing will be adopted for each dose level. In the other words, 2 eligible subjects will be randomized at a 1:1 ratio (1 active: 1 control) to receive BGB-DXP593 or placebo on Day 1; and the remaining subjects will be randomized at a 5:1 ratio (5 active: 1 control) to receive BGB-DXP593 or placebo at least 48 hours later, provided satisfactory safety and tolerability is demonstrated for the first 2 subjects randomized and dosed at the dose level.

The planned dose levels and number of subjects are provided in Table 3. Up to 30 subjects (including possible replacement) will be enrolled in the study, which will be conducted in 1 center in Australia.

Subjects are expected to be available for follow-up visits until Day 113 of the study. Subjects will be replaced if they cannot complete the infusion. Subjects may be replaced if they discontinue from the study before Day 29.

Table 3: Planned Dose Levels and Number of Subjects

Dose Level	Number of Subjects [b]	
	Active Arm (BGB-DXP593)	Control Arm (Normal Saline)
A – 10 mg/kg	6	2
B – 30 mg/kg	6	2
C [a]	6	2

Abbreviation: PK, pharmacokinetic.
[a] Besides the 2 planned dose levels, one higher dose level will be allowed. The higher dose level will be triggered based on the review of PK data from the first 2 dose levels (see Section 3.2.2.2).
[b] Enrollment up to 30 subjects is permitted if additional subjects are necessary for safety or PK evaluations.

Study Assessments

Subjects will be monitored for safety, tolerability, PK and immunogenicity of BGB-DXP593 throughout the study.

Assessments of safety will include adverse events (AEs), SAEs, clinical laboratory tests, physical examinations, vital signs, and ECGs. A Safety Monitoring Committee (SMC) will periodically monitor safety data.

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. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

PK and ADA sampling will be collected at specific intervals from Day 1 to Day 113 (Appendix 3).

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. Specific details regarding dose escalation are described in the following sections.

3.2. Details of Dose Escalation

3.2.1. Starting Dose and Dose Escalation Approach

Dose escalation will occur sequentially in increasing dose levels of study drug. Each dose level of study drug evaluated may be referred to as a cohort or dose level. This is a single dose escalation study, therefore, only 1 dose of BGB-DXP593 or placebo will be administered to each subject.

The starting dose level will be 10 mg/kg. This dose level was chosen based on an overall assessment of toxicology data in cynomolgus monkeys (more details are provided in Section 1.3.2).

Two ascending dose levels for study drug at single doses of 10 mg/kg and 30 mg/kg, are included in the study. Besides the 2 planned dose levels, one higher dose level will be allowed (see details in Section 3.2.2). The projected safety margins at the proposed dose levels reflect favorably on the safety profile of BGB-DXP593 and show that a dose up to 60 mg/kg is expected to provide adequate (> 2 fold) safety margins (Table 2).

3.2.2. Rules for Dose Escalation

The study design allows a gradual dose escalation with intensive safety monitoring to ensure the safety of the subjects. In this single dose escalation study with healthy subjects, the maximum factor for the first dose escalation step will be 4, the maximum factor for the following potential dose escalation step will be 3.

3.2.2.1. Escalation From Dose Level A to Dose Level B

Dose escalation will occur in sequential order after reviewing at least 7 days of safety and laboratory data by the SMC and in the absence of meeting any prespecified pausing criteria (more details are provided in Section 3.3).

An appropriate interval (at least 7 days) between dose levels will require a timely review and evaluation of safety data (eg, AE profile, vital signs, 12-lead ECG, cardiac telemetry, and clinical laboratory safety tests) prior to proceeding to a higher dose level.

The data will be reviewed by the SMC (Section 11.1) who will decide on the next dose level. The data from all the subjects in the previous dose level will be reviewed. Proceeding to the next higher dose level will only occur if the previous dose level was deemed by the SMC to be safe and well tolerated.

Following the review of data from subjects under a dose level, the timing of assessments and/or blood samples may be adjusted for subsequent dose level(s). Additional assessments or sampling times may be added or removed if indicated by the data; however, the maximum blood volume taken from each subject will not exceed 450 mL.

3.2.2.2. Potential Escalation From Dose Level B to Dose Level C

There is an option to explore a third dose level that is higher than 30 mg/kg in this study. The conduct of the third dose level will be triggered based on the review of PK data from the first 2 dose levels.

Pharmacokinetic data from a minimum of 3 subjects per dose level, up to Day 29, will be evaluated to ensure that the PK of BGB-DXP593 is approximately dose proportional and in line with the predicted concentrations and safety margins. The predicted exposure for Dose Level C, based on PK data from the first 2 dose levels, will not exceed the cynomolgus monkey exposure based on C_{max} and combined AUC of the repeat doses at the NOAEL (ie, 300 mg/kg). The data will be reviewed by the SMC (Section 11.1).

3.3. Criteria for Pausing Drug Administration and New Enrollment

The SMC will review the safety and laboratory data at each dose level. If an increased risk for the subjects is suspected during the study, the SMC will recommend to immediately suspend the recruiting of additional participants.

The administration of the study drug and the enrollment of new subjects will pause for the dose level, if any of the following events occurs:

- One or more ≥ Grade 4 TEAEs or treatment-emergent SAEs related to study drug as assessed by the investigator in any subject or
- Grade 3 TEAEs related to study drug as assessed by the investigator in 2 or more subjects at the same dose level.

The SMC may recommend keeping the current enrollment plan, opening a repeated cohort at the same dose level, de-escalating to a lower dose level, or terminating the study. For the scenarios of repeated dose level and lower dose level, the number of subjects and randomization ratio will be the same as planned dose levels.

If a repeated cohort evaluation of the same dose level confirms the AE profile previously observed at the dose level, no higher dose level will be tested in this study.

4. SELECTION OF STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Male and female subjects, 18 to 60 years of age inclusive, at the time of signing the informed consent
2. Subjects are in good general health as determined by the investigator or medically qualified designee, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring
3. Body weight ≥ 50 kg and body mass index (BMI) within the range 18 to 32 kg/m^2 (inclusive)

   Note: BMI = weight [kg] / (height [m])^2
4. Negative serum IgG to the SARS-CoV-2
5. Negative for COVID-19 based on the nasopharyngeal or oropharyngeal swab with the method of real-time reverse transcription-polymerase chain reaction (rRT-PCR)
6. Female subjects of childbearing potential must be willing to use a highly effective method of birth control (see Appendix 5) from the time of study enrollment until 4 months after the single dose of study drug.
7. Male subjects with female partners of childbearing potential must be willing to use a highly effective method of birth control (see Appendix 5) from the time of study enrollment until 4 months after the single dose of study drug.
8. 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

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

Medical Histories or Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs, constituting a risk to the subject when taking the study drug; or interfering with the interpretation of data
2. Systolic blood pressure > 150 mmHg at screening
3. Any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

4. Any history of a severe allergic reaction prior to enrollment that has a reasonable risk of recurrence during the study
5. Have a medical history of SARS infection
6. Any acute fever disease or infections
7. Any chronic or clinically significant medical condition that, in the opinion of the investigator, would jeopardize the safety or rights of the subject, including but not limited to: diabetes mellitus type I, chronic hepatitis; or clinically significant forms of: drug or alcohol abuse, asthma (except for childhood asthma), autoimmune disease, psychiatric disorders, or heart disease
8. Platelet disorder or other bleeding disorder may cause injection contraindication
9. Alanine aminotransferase and/or aspartate aminotransferase > 1.5 x upper limit of normal (ULN)
10. Bilirubin >1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
11. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
12. Average Fridericia's formula (QTcF) > 450 msec (based on triplicate ECGs)
    - NOTE A: The QTc is the QT interval corrected for heart rate according to QTcF, and/or another method. It is either machine-read or manually over-read.
    - NOTE B: The specific formula used to determine eligibility or discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant.

Prior/Concomitant Therapy

13. Previous receipt of a licensed or investigational biologic agent (such as, monoclonal antibodies) within 3 months or 5 half-lives (whichever is longer) prior to the randomization
14. Previous receipt of a licensed or investigational nonbiologic agent (such as, those derived from chemical synthesis) within 1 month or 5 half-lives (whichever is longer) prior to the randomization
15. Past or intended use of over-the-counter or prescription medication, including herbal medications, within 28 days prior to the randomization. Use of paracetamol, ibuprofen, and/or vitamins at the recommended dose will be allowed at the investigator's discretion within 28 days prior to the randomization.

Prior/Concurrent Clinical Study Experience

16. Participation in ≥ 4 clinical studies within 12 months prior to the randomization

Diagnostic Assessments

17. Positive human immunodeficiency virus (HIV) antibody test
18. Presence of hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (HBcAb) at screening or within 3 months prior to the randomization
19. Positive hepatitis C antibody test result at screening or within 3 months prior to the randomization

    NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
20. Positive hepatitis C RNA test result at screening or within 3 months prior to the randomization

    NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
21. Positive pre-study alcohol/drugs screen

Other Exclusions

22. Immediate family history of seizures, epilepsy, brain or mental disease at the investigator's discretion
23. The total volume of blood loss > 500 mL within 3 months prior to the randomization
24. Sensitivity to any of the study drug or components thereof, or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study
25. Heavy smokers who have ≥ 15 cigarettes per day

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. Five 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(s) or designated personnel are 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 ºC and 8ºC 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 matching BGB-DXP593 is the normal saline (ie, solution of 0.9% sodium chloride) to the required volume. The normal saline will be sourced and provided by the site.

For further details, refer to the Pharmacy Manual for the matching placebo.

5.2. Dosage, Administration, and Compliance

All eligible subjects will be assigned to one of the dose levels. Each subject will receive a single intravenous dose of BGB-DXP593 or matching placebo for 30-60 minutes. The dose of study drug will be based on the subject's actual body weight on the day of study administration.

As a routine precaution, subjects 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.

For safety reasons, dose administration for the first 2 subjects randomized and dosed at each dose level will be monitored for at least 48 hours prior to the remaining subjects receiving the same dose level.

After the starting dose of study drug, the decision to proceed to each subsequent dose level will be made by the SMC at 7 days after the last subject at the current dose level has received the study drug, and all the safety, laboratory data have been reviewed.

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

5.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

At each dose level, eligible subjects will be randomized at a 3:1 ratio (6 active: 2 control) to receive BGB-DXP593 or placebo, respectively. The sentinel dosing will be adopted for each dose level and the randomization ratios for sentinel dosing are provided in Section 3.1.

Site personnel will access the Interactive Response Technology (IRT) system to randomize the treatment assignment. A subject for replacement will receive a unique study subject number and will be assigned to the same treatment as the subject he/she replaces.

Blinding

The study is designed as double-blind for the subjects and the investigator (as well as the site personnel) in order to eliminate observational or performance bias. This is to avoid the systematic differences in assessments on the subject's treatment (ie, BGB-DXP593 or placebo).

The single dose of study drug will be prepared by unblinded pharmacist(s) and administered by blinded study nurse(s). Both the intravenous infusion of BGB-DXP593 and placebo will be colorless. All the follow-up evaluations will be performed by blinded clinic staff.

At the study site, access to the treatment information for each subject is restricted to the unblinded pharmacist(s). Persons directly involved in the clinical conduct of the study will not have access to the treatment allocation prior to database lock.

Regarding the sponsor, the database of this study will be handled as open-label, meaning that the study functions of the sponsor are unblinded (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate). The objectives of the study are expected not to be affected.

Unblinding

1. Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if the unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. Emergency unblinding for AEs may be performed through an IRT system.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor before unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the sponsor must be notified immediately.

2. Inadvertent unblinding

Every effort will be made to blind both the subject and the investigator to the identity of BGB-DXP593 or placebo, but inadvertent unblinding of a subject may occur. If an investigator,

site personnel performing assessments, or subject is unblinded, the unblinding will not be the sufficient cause for that subject to be discontinued from study or excluded from any analyses.

5.4. Incorrect Administration

Any incorrect administration of the study drug should be noted in the subject's medical record and on the appropriate electronic case report form (eCRF).

Adverse events due to 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 should be administered as appropriate.

5.5. Dose Interruption or Modification

There will be no dose reduction of study drug.

A subject may temporarily interrupt their infusion of study drug or discontinue their infusion of study drug due to infusion-related reactions or other medical events.

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

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

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that:

- subjects must not have received any licensed or investigational biologic agent (such as, monoclonal antibodies) within 3 months or 5 half-lives (whichever is longer) prior to the randomization
- subjects must not have received any licensed or investigational nonbiologic agent (such as, those derived from chemical synthesis) within 1 month or 5 half-lives (whichever is longer) prior to the randomization
- subjects must not have received any over-the-counter or prescription medication, including herbal medications, within 28 days prior to the randomization. Use of paracetamol, ibuprofen, and/or vitamins at the recommended dose will be allowed at the investigator's discretion within 28 days prior to the randomization.

6.2. Concomitant Therapy

As the healthy subjects are enrolled in the study, concomitant therapy is not allowed during the study. If medical events (such as, infusion-related reactions, or severe hypersensitivity) occur during the study period, the subjects may receive appropriate medical treatment. The management of infusion-related reactions and severe hypersensitivity is provided in Section 9.7.

All concomitant medications taken during the study will be recorded in the eCRF with indication and dates of administration.

6.3. Potential Interactions Between BGB-DXP593 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 evaluation will be performed within 28 days before the single dose of study drug. A subject 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.

7.1.1. Informed Consent

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled subjects and for subjects who are screened but not enrolled will be maintained at the study site. Consent must be obtained using the most current version of the form approved by the IEC/IRB.

For subjects who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before the single dose of study drug is administered, study site personnel should document the screen failure in the subject's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

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

7.2.2. Subject Numbering

After obtaining informed consent, a unique subject number will be assigned to a potential study participant.

7.3. Check-in (Day -1)

The enrolled subjects will be admitted at least 12 hours prior to the single dose of study drug. On the day of admission, the screening of alcohol/drugs and safety assessment of vital signs will be performed. Smoking will be not allowed during the inpatient stay.

7.4. Randomization

Site personnel will access the IRT system to randomize the treatment assignment. Randomization will occur after the admission on Day -1 and before the dose of study drug on Day 1.

7.5. Treatment (Day 1)

The enrolled subjects will be treated as described in Section 5.2. The study procedures on Day 1 are provided in Appendix 2. Refer to Section 7.7 for additional considerations regarding treatment withdrawal.

7.6. Follow-up Period

The follow-up period starts with the next day following the infusion of study drug and continues until Day 113 of the study. All AEs, including SAEs, will be collected as described in Section 9.6.

7.6.1. Check-out (Day 8)

The subjects will be discharged 7 days after the single dose of study drug. Before the discharge, the procedures and assessments specified in Appendix 1 should be completed.

7.6.2. End-of-Study Visit

Subjects who permanently discontinue from the study will be asked to return to the study center for the End-of-Study (EOS) Visit, which is required to be conducted within 7 days after the premature study discontinuation. The Day 113 Visit is the EOS Visit for subjects who complete all the previously planned study visits.

If a subject refuses to return for the EOS Visit or is unable to do so, every effort should be made to contact the subject by telephone to determine their health status.

7.6.3. Safety Follow-up Visit for Premature Study Discontinuation

If a subject discontinues the study within 30 days after the dose of study drug, a Safety Follow-up Visit will be conducted on 30 days after the dose of study drug. If the premature discontinuation from study occurs within 7 days prior to the timepoint of 30 days after the dose of study drug, the Safety Follow-up Visit could be combined with the EOS Visit as appropriate. A visit window of ± 3 days will be allowed for Safety Follow-up Visit.

7.6.4. Lost to Follow-up

If attempts to contact a subject by telephone are unsuccessful, additional attempts should be made during the study to complete study-related assessments and record outstanding data. It may be possible to obtain the information from other contacts, such as referring physicians, or primary care providers.

Attempts to contact should be documented in the subject's source documents. If a subject cannot be contacted despite all attempts, the subject will be considered lost to follow-up.

7.7. Discontinuation From Study Treatment or From the Study

7.7.1. Subject Discontinuation From the Study Treatment

Eligible subjects will receive a single dose of study drug and they have the right to discontinue the study drug at any time for any reason during the study treatment. In addition, the investigator

has the right to discontinue a subject from the study drug at any time during the study treatment. Subjects who discontinue the study treatment should follow the procedures and the assessments specified in EOS Visit (Section 7.6.2). The subject who could not complete the infusion should be replaced.

The primary reason for discontinuation from the study treatment should be documented on the appropriate eCRF. Subjects may discontinue from the study treatment for reasons that include, but are not limited to, the following:

- Withdraw of consent
- The investigator or sponsor determines it is in the best interest of the subject
- Significant or persistent AE(s) as described in Section 9.7.

7.7.2. Subject Discontinuation From the Study

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

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Completion of all study assessments
- Positive for COVID-19

Subjects may voluntarily withdraw consent from the study at any time. The subject who discontinues from the study before Day 29 may be replaced.

7.8. 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 subject 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 on BGB-DXP593 indicates a potential health hazard to subjects
- Overall subject enrollment is unsatisfactory

The sponsor will notify the investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued subjects must be seen for an EOS Visit as described in Section 7.6.2.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the subject'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. Subjects will be closely monitored for safety and tolerability throughout the study. All assessments will be performed on the day of the specified visit and documented in the medical record for each subject.

Where applicable, the single dose of study drug will be administered only if the clinical assessment and laboratory test values have been reviewed and found to be acceptable per protocol guidelines.

8.1. Screening Assessments

Screening evaluations will be performed within 28 days before receiving the study drug. The screening period begins on the first day that a screening assessment is conducted. The investigator will assess subject eligibility according to the latest screening assessment results.

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, surgery history, reproductive status (ie, no childbearing potential or childbearing potential), and smoking history.

Prior medications include all medications (eg, prescription drugs, over-the-counter drugs, herbal medications) used by the subject within 28 days prior to the single study dose.

8.2. Safety Assessments

8.2.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the subject is in a supine position after resting for 10 minutes.

Height and weight will be measured at screening and weight will be measured again 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

Samples for protocol-specified clinical chemistry, hematology, urinalysis, and coagulation profiles will be evaluated by a local laboratory.

Pregnancy test will be performed for female subjects of childbearing potential during the study. Samples for pregnancy testing will also be assessed locally. The serum pregnancy test will be performed at the Screening Visit, and the next serum pregnancy test will be conducted after the admission on Day -1 and before the dose of study drug on Day 1. Female subjects of childbearing potential with negative results will be eligible to receive the study drug. Afterwards, urine pregnancy test will be performed. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

See Appendix 4 for the list of clinical laboratory tests to be performed and Appendix 1 for the timing and frequency. Additional tests may be performed at any time during the study as deemed necessary by the investigator or as required by local regulations. If required by local regulations, clinical laboratory evaluations performed by a local (instead of a central) laboratory are acceptable.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all materials such as test tubes and labels are provided in the Laboratory Manual.

8.2.4. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings (per local practice) will be kept as part of the subject's permanent study file at the site.

The subject 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.

At each timepoint (see Appendix 1), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to calculate heart rate and measure QT and QTcF intervals.

8.2.5. Cardiac Telemetry

The cardiac telemetry will be performed from approximately 1 hour predose to 24 hours post dosing. Full disclosures will be maintained as part of the subject's source documents and will be reviewed in detail.

8.2.6. 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 .

8.2.7. Serology

The testing of HBV/HCV serology (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], and HCV antibody) will be performed at screening. In the case of positive HCV antibody, the test of HCV RNA will be followed.

Blood from all subjects will be collected and tested for HIV antibody at screening. Those subjects with negative results can be enrolled.

Specific IgG antibodies against SARS-CoV-2 in the serum of all subjects will be measured by quantitative or qualitative antibody testing. Those subjects with negative results can be enrolled.

The tests mentioned above will be performed at a local laboratory.

8.2.8. Virology

The nasopharyngeal or oropharyngeal swab will be collected during the Screening and at the visit on Day 29. The nasopharyngeal or oropharyngeal swab will be tested by the method of rRT-PCR in a local laboratory for the qualitative detection of nucleic acid from SARS-CoV-2 in upper respiratory specimens. During the screening, those subjects who have negative results can be enrolled.

If any subject has positive or suspected result during the study, the subject will be discontinued from the study and treated by following local practice. If the subject is unable to complete the EOS Visit, please see the procedures in Section 7.6.2 and Section 7.6.4.

8.3. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood will be collected to characterize the PK profile of BGB-DXP593 using validated immunoassays. Blood samples will be collected for characterization of ADA. 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 the PK and immunogenicity sampling schedule (Appendix 3).

The PK and ADA assays for BGB-DXP593 will be managed through a central laboratory. 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.

8.4. Visit Windows

The PK sampling schedule allows for a visit window of ± 1 day for the visits at Day 15, Day 22 and Day 29, and a visit window of ± 2 days for the visits at Day 43, Day 57, Day 71, Day 85, and Day 113 (Appendix 1 and Appendix 3). All assessments will be performed on the day of the specified visit.

8.5. Unscheduled Visits

Unscheduled visits may be performed at any time at the subject's or investigator's request if there are any safety concerns. 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 recorded 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

This is the first-in-human study of BGB-DXP593. No clinical data are available yet and no risk associated with BGB-DXP593 has been identified. In the 14-day repeat-dose toxicology study, no apparent toxicity was observed in cynomolgus monkeys at weekly repeated doses of 30 mg/kg, 100 mg/kg, or 300 mg/kg.

9.2. General Plan to Manage Safety Concerns

9.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of subjects in this study. Results from the nonclinical toxicology data from BGB-DXP593 and nonclinical data from other SARS-CoV-2 neutralizing mAbs were considered. Subjects with any history of a severe allergic reaction that has a reasonable risk of recurrence are excluded from the study. Subjects with acute fever disease or infection are also 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 subjects will be evaluated clinically and with standard laboratory tests at specified intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1.

Blood samples will be drawn for determining of ADAs to BGB-DXP593 in subjects who received the study drug. 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 (Section 5.2).

As described in Section 9.6, AEs will be recorded during the study (AE from the time of single study dose and SAEs from the time of signing of informed consent). At the end of study, AEs considered related to study drug will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the subject is lost to follow-up, the subject withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Investigators are instructed to report all AEs. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

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 study drug or not.

Examples of an AE 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.
- New condition(s) detected or diagnosed after study drug administration even though it may 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 these instances, all subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.3.2. Assessment of Severity

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

Toxicities that are not specified in the 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 (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- 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 (for example, 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 9.6.2.1.

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 also consult the BGB-DXP593 Investigator's Brochure in the determination of his/her assessment.

There may be situations when a 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 prior to 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." 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 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 subject's clinical condition or other concomitant AEs).

9.3.4. Following Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject'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 subject is lost to follow-up, or the subject 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 subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided to the site within the time frames outlined in Section 9.6.2.1.

9.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, cardiac telemetry, 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 laboratory test abnormalities or other abnormal assessments that:

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

9.4. Definition of a Serious Adverse Event

A 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 subject was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject 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 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 judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered 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 transfusion support or convenience

9.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), 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 Reporting Period

After informed consent has been signed but prior to 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 the dose of study drug 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.

9.6.2. Reporting of 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 a SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 4.

Table 4: Timeframe and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making 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 a SAE has occurred in a subject, he/she is to report the information to the sponsor within 24 hours as outlined in Section 9.6.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding a 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 promptly 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 product 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 SUSARs (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 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. Death

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

9.6.5. Pregnancies

If the partner of a male subject becomes pregnant within 30 days after the single dose of study drug, a pregnancy report form is required to 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 be always reported as a SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as a SAE.

9.6.6. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and 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 documents:

- BGB-DXP593 Investigator’s Brochure

9.6.7. Reporting 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 Reactions

As a routine precaution, following completion of the study drug administration, subjects 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 of 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 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.

Subjects should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit 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 the study drug are provided in Table 5.

Table 5: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug

NCI-CTCAE grade	Treatment modification for Study Drug
Grade 1 - mild 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 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 subject 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 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. The subject should be withdrawn from study drug treatment.

NCI-CTCAE grade	Treatment modification for Study Drug
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The subject should be withdrawn from study drug treatment. 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 subject 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). Subjects 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 subject 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 subject will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The subject should then be placed on monitor immediately and an Intensive Care Unit should be alerted for possible transfer if needed.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

10.1. Statistical Analysis

10.1.1. Randomization Method

As discussed in Section 7.4, subjects will be randomized using the IRT system for this study.

10.1.2. Analysis Sets

The Safety Analysis Set will include all the subjects who received the study drug.

The PK Analysis Set will include all the subjects who received the study drug and had any measurable concentration of study drug.

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

10.1.3. Subject Disposition

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

Major protocol deviations will be summarized and listed by each category.

10.1.4. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Analysis Set using descriptive statistics. Summary statistics will be presented for continuous demographic and baseline characteristic variables by dose level. The number (percentage) of subjects in each category will be presented for categorical variables by dose level. Continuous variables include, but are not limited to age, weight, height, and BMI. Categorical variables include, but are not limited to, sex, race, and ethnicity.

10.1.5. Prior and Concomitant Therapy

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized by dose level.

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

10.2. Efficacy Analyses

There is no efficacy analysis planned for this study.

10.3. Safety Analyses

Adverse events, ECGs, vital signs, and laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Descriptive statistics will be used to analyze all safety data.

10.3.1. Extent of Exposure

The extent of study drug exposure will be summarized descriptively for the single dose administered by dose level. The number (percentage) of subjects with dose interruption and infusion rate decreased will be summarized with the respective reasons by dose level.

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

10.3.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to MedDRA by the lowest level term, preferred term (PT), and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline on or after the administration of study drug and up to 30 days after the dose of study drug. Only those AEs that were treatment-emergent will be included in summary tables.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to NCI-CTCAE version 5.0 within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. Treatment-emergent SAEs and treatment-related TEAEs will also be summarized. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

10.3.3. Laboratory Analyses

Clinical laboratory (clinical chemistry, hematology, 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. Laboratory parameters and their changes from baseline will be summarized by visit and dose level. Change from baseline will only be summarized for subjects with both baseline and postbaseline measurements.

10.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and changes from baseline will be summarized by visit and dose level.

10.3.5. Electrocardiogram

Descriptive statistics for ECG parameters and changes from baseline will be summarized by visit and dose level.

10.4. Pharmacokinetic Analyses

Noncompartmental analysis will be carried out for BGB-DXP593 serum concentrations. The PK analyses will include only subjects with enough data to enable estimation of key parameters.

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). 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 subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for evaluable subjects. The effect of immunogenicity on PK, and safety may be evaluated if data allow.

10.6. Sample Size Consideration

A sample size of 8 subjects at each dose level (6 active and 2 control) totaling up to 30 subjects (including possible replacement) is not based on any statistical considerations. The sample size is based on the clinical consideration to provide safety and tolerability information and pharmacological considerations with the need to minimize exposure to healthy subjects at each dose level. No formal inferential statistics will be applied to the safety or PK data.

10.7. Interim Analysis

There is no formal interim analysis planned for this study.

11. STUDY COMMITTEE

11.1. Safety Monitoring Committee

An SMC will be established and will include both the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate) and investigators.

The SMC will review safety, laboratory data and make recommendations on dose escalations for this study. The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study.

A separate charter will outline the details for the composition and responsibility of the SMC.

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 subject 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 subject 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 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, subjects' 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[s]) are responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition), subject drug dispensation records, and returned or destroyed study drug. Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to subjects, including batch/lot number, date dispensed, subject 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 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 monitor over the course of the study.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

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 subject. 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 subject, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any subject 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 subjects 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 subjects 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 subject or the subject's legally authorized representative before his or her participation in the study. The case history or clinical records for each subject 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 subject to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Subjects 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 subject 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 subject or the subject's legally authorized representative. All signed and dated ICFs must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

14.4. Subject 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 subjects' personal and medical information.

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

Subject 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 subject), unless permitted or required by law.

In the event of a breach of the confidentiality of a subject'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 subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the Therapeutic Goods Administration in Australia 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 subjects' 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 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 subject, 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 subject 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 or a clinical research associate will make site visits to review protocol compliance, compare eCRFs against individual subject'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 subject 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, PT, and primary SOC. 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) subject 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.

Subject 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: subject 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 subject, 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 subject 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 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
- 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 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 subject'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 subject
- 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.

16. REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Period	**Screening**	**Admission to Unit**	**Treatment**	**Follow-up**													
Day	**-28 to -1**	**-1**	**D1 [a]**	**D2**	**D3**	**D4**	**D5**	**D8**	**D 15**	**D 22**	**D 29**	**D 43**	**D 57**	**D 71**	**D 85**	**D113 / EOS [b]**	**Safety Follow-up Visit [c]**
Visit Window (day)	--	--	--	--	--	--	--	--	± 1	± 1	± 1	± 2	± 2	± 2	± 2	± 2	± 3
Informed consent [d]	X																
Inclusion/exclusion criteria [e]	X																
Demography/prior medications	X																
Medical history	X																
Randomization [f]		X															
BGB-DXP593 single dose administration [g]			X														
Discharge								X									
Safety Assessments																	
Vital signs/ height and weight [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination [i]	X																
Targeted physical examination [i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac Telemetry [k]			X	X													

Period	**Screening**	**Admission to Unit**	**Treatment**	**Follow-up**													
Day	**-28 to -1**	**-1**	**D1 [a]**	**D2**	**D3**	**D4**	**D5**	**D8**	**D 15**	**D 22**	**D 29**	**D 43**	**D 57**	**D 71**	**D 85**	**D113 / EOS [b]**	**Safety Follow-up Visit [c]**
Visit Window (day)	--	--	--	--	--	--	--	--	± 1	± 1	± 1	± 2	± 2	± 2	± 2	± 2	± 3
Prior/Concomitant medications review	X																
Adverse event review [l]	X																
Laboratory Assessments																	
Hematology [m]	X		X	X	X		X	X	X	X		X		X	X	X	X
Clinical chemistry [m]	X		X	X	X		X	X	X	X		X		X	X	X	X
Coagulation [m]	X		X	X	X		X	X	X	X		X		X	X	X	X
IgG to SARS-CoV-2	X																
rRT-PCR test for COVID-19 (nasopharyngeal or oropharyngeal swab)	X										X						
Urinalysis [n]	X		X	X	X		X	X	X	X		X		X	X	X	X
Alcohol/drugs screen [o]	X	X															
PK and ADA blood sampling			See Appendix 3														
Hepatitis B and C testing	X																
Pregnancy test (if applicable) [p]	X	X									X		X		X	X	
HIV test	X																

Abbreviations: ADA, antidrug antibody; AEs, adverse events; COVID-19, Coronavirus Disease 2019; D, day; ECG, electrocardiogram; EOS, End-of-Study; HIV, human immunodeficiency virus; Ig, immunoglobulin; IRT, Interactive Response Technology; PK, pharmacokinetic; rRT-PCR, real-time reverse transcription-polymerase chain reaction; SAEs, serious adverse events.

[a] The schedule of assessments for Day 1 under different timepoints are provided in Appendix 2.

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

[c] The Safety Follow-up Visit is only for subjects who discontinue the study within 30 days after the dose of study drug. The Safety Follow-up Visit will be conducted on 30 days after the dose of study drug (± 3 days). If the premature discontinuation from study occurs within 7 days prior to the timepoint of 30 days after the dose of study drug, the Safety Follow-up Visit could be combined with the EOS Visit as appropriate.

[d] The 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/Institutional Review Board.

[e] Follicle-stimulating hormone and estradiol assessments will be performed on female subjects who are < 55 years of age with no spontaneous menses for ≥ 12 months to identify the status of no childbearing potential. Female subjects of no childbearing potential, and female subjects of childbearing potential who are willing to use a highly effective method of birth control are eligible to participate.

[f] Subjects will be randomized into either the active arm or control arm via IRT. Randomization will occur after the admission on Day -1 and before the dose of study drug on Day 1.

[g] The dose will be based on the subject's actual body weight on the day of receiving the study drug (Day 1).

[h] Height and weight will be measured at screening, and weight will be measured again before the single dose of study drug on Day 1.

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

[j] At each timepoint, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to calculate heart rate and measure QT and QTcF intervals.

[k] The cardiac telemetry will be performed from approximately 1 hour predose to 24 hours post dosing.

[l] After informed consent has been signed but prior to 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 the dose of study drug 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.

[m] Hematology, clinical chemistry and coagulation will be evaluated by a local laboratory. The list of hematology, clinical chemistry and coagulation parameters is provided in Appendix 4.

[n] Collect sample for urine analysis as well as urine microscopy. The urine microscopy will be performed if the urinalysis parameter, such as leukocyte esterase, is out of normal range.

[o] During the screening, a urine sample will be collected for the screening of drugs; a breath test will be performed for the screening of alcohol.

[p] Pregnancy test will be performed for female subjects of childbearing potential during the study. The serum pregnancy test will be performed at the Screening Visit, and the next serum pregnancy test will be conducted after the admission on Day -1 and before the dose of study drug on Day 1. Female subjects of childbearing potential with negative results will be eligible to receive the study drug. Afterwards, urine pregnancy test will be performed. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

APPENDIX 2. SCHEDULE OF ASSESSMENTS FOR DAY 1

Study Day	**Day 1**				
Timepoint (Window Period)	**Predose**	**Dosing**	**1-hour postdose**	**6-hours postdose**	**12-hours postdose**
BGB-DXP593 single dose administration		X			
Vital signs/ height and weight	X (- 15 min)		X (± 15 min)	X (± 15 min)	X (± 15 min)
Targeted physical examination	X (- 30 min)				
12-lead ECG	X (- 15 min)		X (± 15 min)	X (± 15 min)	X (± 15 min)
Cardiac telemetry	X				
Prior/Concomitant medications review	X				
Adverse event review	X				
Hematology	X (- 60 min)				
Clinical chemistry	X (- 60 min)				
Coagulation	X (- 60 min)				
Urinalysis	X (- 60 min)				

Abbreviations: ECG, electrocardiogram; min, minutes.

APPENDIX 3. PHARMACOKINETIC AND ANTIDRUG ANTIBODY BLOOD SAMPLING

Study Day	**Day 1**			**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113/ EOS**
Hours post the start of infusion	**0 (predose)**	**EOI**	**6**	**24**	**48**	**72**	**96**	**168**	**336**	**504**	**672**	**1008**	**1344**	**1680**	**2016**	**2688**
Window Period (hours)	**-60 min to predose**	**Within 30 min after EOI**	**±2**	**±6**	**±6**	**±6**	**±6**	**±6**	**±24**	**±24**	**±24**	**±48**	**±48**	**±48**	**±48**	**±48**
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA sampling	X								X		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.

APPENDIX 4. CLINICAL LABORATORY ASSESSMENTS

Clinical chemistry	Hematology	Coagulation	Urinalysis [a]
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium Creatinine Glucose Lactate dehydrogenase Total protein Magnesium Lipase Amylase	Red blood cell count Hematocrit Hemoglobin Platelet count White blood cell count with differential (both absolute count and percentage) • Lymphocyte count • Neutrophils • Monocytes • Eosinophils • Basophils	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase

Other Screening Tests

- Follicle-stimulating hormone and estradiol (as needed for female subjects who are < 55 years of age with no spontaneous menses for ≥ 12 months to identify the status of no childbearing potential)
- Urine (drugs screen [to include at minimum: amphetamines, barbiturates, benzodiazepines , cocaine, opiates, methamphetamines, methadone, methyl enedioxy methamphetamine, phencyclidine, and tetrahydrocannabinol])
- Breath test (alcohol screen)
- Highly sensitive (serum/urine) human chorionic gonadotropin pregnancy test (as needed in female subjects of childbearing potential)
- Serology:
  - HIV antibody
  - hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody
  - IgG antibodies against SARS-CoV-2
- Virology: nasopharyngeal or oropharyngeal swab for COVID-19 rRT-PCR test

The results of each test must be entered into the CRF.

Abbreviations: COVID-19, Coronavirus Disease 2019; CRF, case report form; HIV, human immunodeficiency virus; Ig, immunoglobin; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; rRT-PCR, real-time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] The urine microscopy will be performed if the urinalysis parameter, such as leukocyte esterase, is out of normal range.

APPENDIX 5. 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 subject'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 subjects who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female subjects 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.

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Approval	[redacted] Clinical Development 04-Aug-2020 14:37:18 GMT+0000

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