BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-DXP593-102
Study Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Patients With Mild-to-Moderate COVID-19
Date:	March 4, 2021
Version:	2.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AUC	area under the plasma or serum concentration-time curve
CI	confidence interval
CL/F	clearance after oral administration
ECG	electrocardiogram
eCRF	electronic case report form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
SAP	Statistical Analysis Plan
IDMC	Independent Data Monitoring Committee
SOC	system organ class
TEAE	treatment-emergent adverse event

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1   INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the protocol BGB-DXP593-102, A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody BGB-DXP593 in Patients With Mild –to Moderate COVID-19.

Reference materials for this statistical plan include the protocol BGB-DXP593-102 (original version, 2020-08-14, protocol amendment 1.0, 2020-09-03, protocol amendment 2.0, 2020-10-19). If the protocol or case report forms are amended or updated then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved before database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

2   STUDY OVERVIEW

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

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

After providing written informed consent, completing all the screening assessments, and being confirmed as eligible for study participation, patients will be randomized in a 1:1:1:1 ratio to receive placebo, BGB-DXP593 5 mg/kg, BGB-DXP593 15 mg/kg, or BGB-DXP593 30 mg/kg. Patient randomization will be stratified by country and disease severity (mild versus moderate COVID-19). The patients will receive a single intravenous infusion of placebo or BGB-DXP593 over 30 to 60 minutes. The patients will then be followed to Day 113 (± 7 days) to assess the efficacy, safety, PK, and immunogenicity. Nasopharyngeal swabs will be collected for RT-qPCR testing of SARS-CoV-2 to assess the change in viral load after study treatment. Approximately 172 patients will be randomized.

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

The study schema is provided in Figure 1.

Figure 1: **Study Schema**
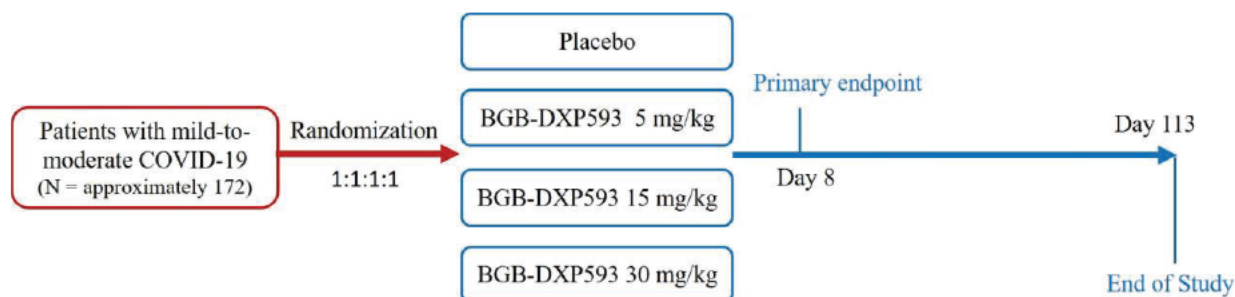
Patients will be monitored for safety, tolerability, efficacy, PK, and immunogenicity during the study.

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

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

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

PK and ADA sampling will be conducted at specific timepoints specified in the protocol.

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

3   STUDY OBJECTIVES

3.1   PRIMARY OBJECTIVES

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

3.2   SECONDARY OBJECTIVES

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

3.3   EXPLORATORY OBJECTIVES

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4   STUDY ENDPOINTS

4.1   PRIMARY ENDPOINTS

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

4.2   SECONDARY ENDPOINTS

- Time-weighted average change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples
- Proportion of patients requiring hospitalization due to worsened COVID-19
- Time to resolution of all COVID-19-related symptoms
- All-cause mortality rate at Day 29
- Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- PK parameters: maximum observed concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_t), AUC from time zero to Day 29 (AUC_{0-29}), AUC from time zero to infinity (AUC_{inf}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z) as appropriate
- Immunogenic responses to BGB-DXP593 evaluated through the detection of antidrug antibodies (ADAs)

4.3   EXPLORATORY ENDPOINTS
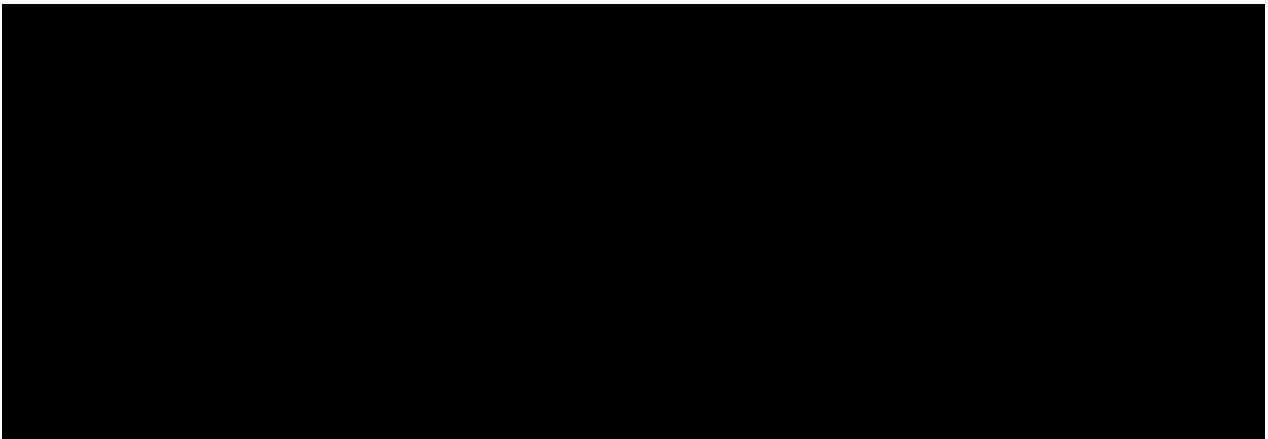
5   SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on the following assumptions:

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- The primary endpoint "change from baseline to Day 8 in SARS-CoV-2 viral shedding" is normally distributed

- One-sided significance level $\alpha = 5\%$

- True maximum treatment effect size of BGB-DXP593 versus placebo is -1.5 $\log_{10}$ copies per mL

- Standard deviation is 3.2 $\log_{10}$ copies per mL (Wang et al 2020)

- Prespecified candidate models listed in Section 6.4.1

Forty-one patients are needed with primary endpoint data per arm to provide at least 82% power to detect non-flat dose-response relationship. MCPMod approach is used. In order to ensure 41 patients per arm with primary endpoint data, at least 43 patients per arm need to be randomized to account for potential dropout rate of 5%.

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

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

- The Intent-to-Treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to the treatment assigned at randomization. This will be the primary analysis set for efficacy analyses.
- The Safety Analysis Set includes all patients who have received the study drug (BGB-DXP593 or placebo). Patients will be analyzed according to their actual treatment received. The Safety Analysis Set will be used for all safety analyses.
- The PK Analysis Set includes all patients who received the study drug (BGB-DXP593) per the protocol and for whom any postdose PK data are available.
- The ADA Analysis Set includes all the patients who received the study drug and in whom both baseline ADA and at least 1 postbaseline ADA results are available.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day is calculated in reference to the date of randomization. For assessments conducted on or after the date of randomization, study day will be calculated as assessment date – date of randomization + 1. For assessments conducted before the date of randomization, study day is calculated as assessment date – date of randomization. There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 10.1.

Baseline is defined as the last non-missing value collected before the administration of the study drug.

All calculations and analyses will be conducted using SAS version 9.4 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal place.

- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.

- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25

- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.

- Time-to-event or duration of event endpoints will be based on the actual date the test was obtained rather than the associated visit date.

- Missing efficacy or safety data will not be imputed unless otherwise specified.

- For laboratory results collected as > x, the value of the laboratory results will be set as x. For laboratory results collected as < x, the value of the laboratory results will be set as x divided by 2.

- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.

- Unscheduled measurements and retested measurements will not be included in by-visit table summaries and graphs but will contribute to the best/ worst case value where required (e.g. shift table). Listings will include scheduled, unscheduled and retest data.

- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).

6.2.3 Handling of Missing Data

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

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

Sensitivity analyses using method of last observation carry forward (LOCF) may be considered to assess the potential impact from missing data for MMRM in primary analysis.

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 10.1.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

Censoring rules for analyses of time-to-event endpoints are determined as in Table 1.

Table 1 Censoring Rules for Analyses of Time-to-event Endpoints

No.	Situation	Date of Event or Censoring	Outcome
1	Target event documented	Date of occurrence of target event	Event
2	Multiple target events documented	Date of first occurrence of target event	Event
3	No target event or death occurred by the time of the End-of-Study Visit or data cut-off, whichever comes first	Date of the End-of-Study Visit or data cut-off, whichever comes first	Censored
4	Death and no target event prior to death	Date of data cutoff	Censored

6.2.4 Multiplicity Adjustment

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one-sided α of 5%). No additional multiplicity adjustments will be made in this study. Two-sided 90% confidence interval will be used to describe the precision of the rate estimate whenever appropriate.

6.2.5 Data Integrity

Before pre-specified interim or final statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data should be completed and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be completed.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Patient Disposition

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

6.3.2 Protocol Deviations

Important protocol deviation criteria will be established and patients with important protocol deviations will be identified and documented before the database lock.

Important protocol deviations will be summarized for all patients in the Safety Analysis Set and

listed by each category.

6.3.3   Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the ITT Analysis Set and descriptive statistics. Continuous variables include but are not limited to age, weight for determining drug administration, and time from first COVID-19 symptom to date of drug administration. Categorical variables include but are not limited to age group, gender, country, race, disease severity, serology status, baseline viral load level group in nasopharyngeal swab samples, and risk status.

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥ 35

- Have chronic kidney disease

- Have diabetes

- Have immunosuppressive disease

- Are currently receiving immunosuppressive treatment

- Are ≥ 65 years of age

- Are ≥ 55 years of age AND have

    o   cardiovascular disease, OR

    o   hypertension, OR

    o   chronic obstructive pulmonary disease/other chronic respiratory disease

6.3.4   Prior and Concomitant Medications

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

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

6.3.5   Medical History

Medical History will be coded using MedDRA (version 23.0 or newer). The number (percentage) of subjects reporting a history of any medical condition, as recorded on the eCRF, will be summarized by system organ class and preferred term in the safety analysis set. A listing of medical history will be provided.

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6.4   EFFICACY ANALYSIS

6.4.1   Primary Endpoint Analyses

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

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

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

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

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

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

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

The model assumptions and resulting graphs were selected to cover both plausible and a diverse range of dose response patterns. These are shown in Figure 2. The parameters for each model shape are listed in Table 2.

Figure 2:   **Shape of the Considered Dose Response Patterns for the MCPMod Analysis**
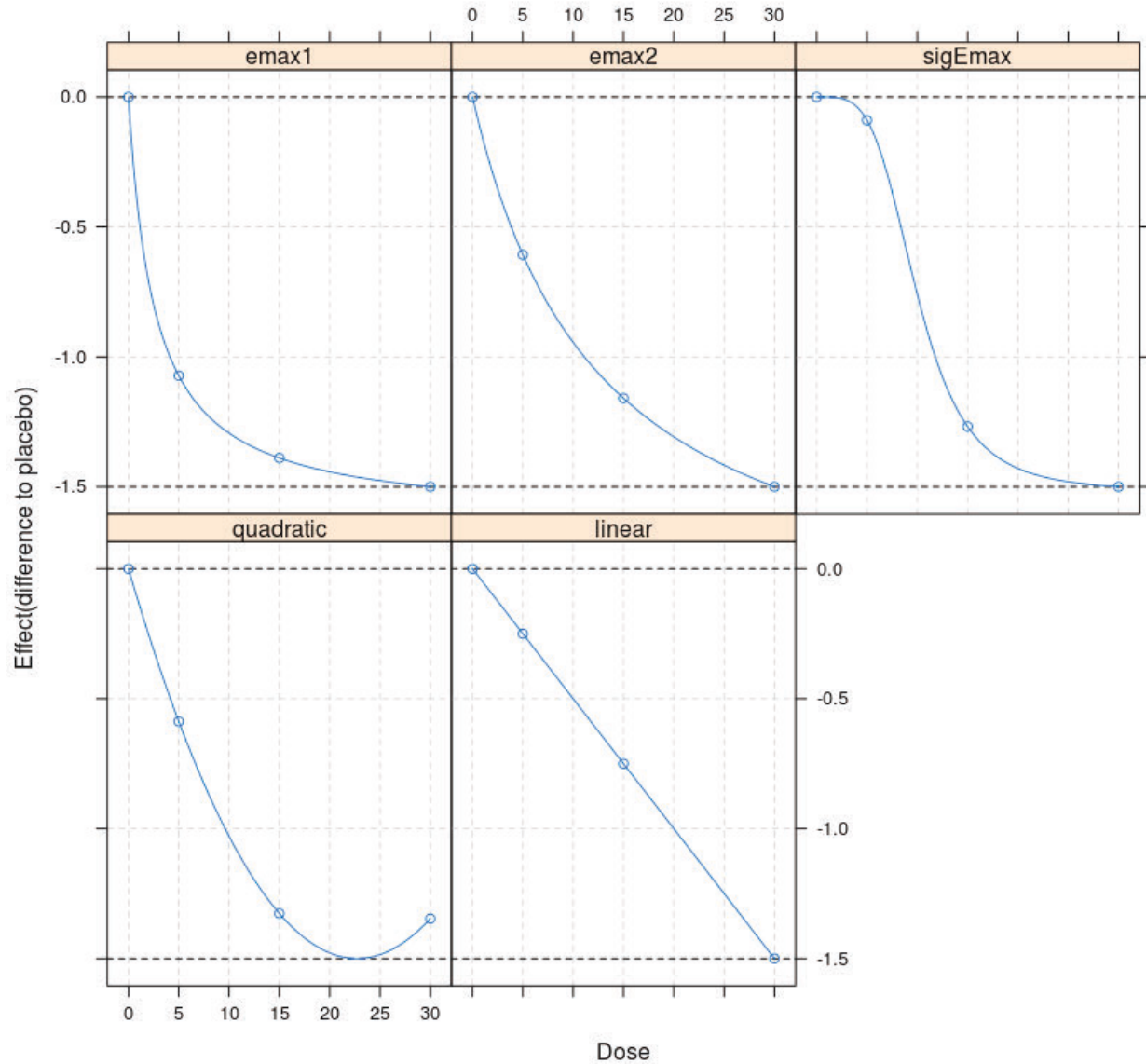
Abbreviation: MCPMod, multiple comparison procedures and modelling approaches

Table 2:   **Parameter(s) in Each Model**

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

If at least one model is statistically significant, then we will reject the null hypothesis of a flat dose response relationship over viral shredding change at Day 8, with a multiple contrast test controlled for the family-wise type I error rate at one-sided $\alpha = 5\%$. A one-sided p-value that corresponds to the most significant model will be calculated.

Bootstrap method with treatment effect resamples is used to induce dose-response relationship. Four candidate models (Emax, sigEmax, Quadratic, and Linear) are fitted and the one with lowest gAIC is selected separately for each resample. The target dose(s) can be estimated from the average model using bootstrap method by incorporating information on the target treatment effect and by accounting for safety. Denote by U_d the upper 0.95 percentile of confidence limit of the predicted mean value p_d at dose d based on the dose-response relationship, where $d = d_1$ (placebo), d_2 (5mg/kg), d_3 (15mg/kg), and d_4 (30mg/kg). The target dose can be found by

$$TD = argmin_{d \in (d_1, d_k]} \{p_d < p_{d_1} + \Delta, U_d < p_{d_1}\}$$

where $k = 1, 2, 3$, and 4. The target treatment effect, Δ, is set to -1 $\log_{10}$ copies/ml.

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

6.4.2 Secondary Endpoint Analyses

Secondary efficacy endpoints will include:

- Time-weighted average change in viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15

- Change in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples from baseline to Day 15

- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples

- Proportion of patients requiring hospitalization due to worsened COVID-19

- Time to resolution of all COVID-19-related symptoms

- All-cause mortality rate at Day 29

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

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

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

The same MMRM analysis for primary endpoint will be used to analyze the change in SARS-CoV-2 viral shedding from baseline to Day 3 and Day 15. Comparisons of active doses to placebo (90% CIs and p-values) will be provided.

The negative RT-qPCR is defined as the value that is below the lower limit of detection. Kaplan-Meier method will be used to assess the time to negative RT-qPCR. The corresponding quartiles (including the median) will be reported and a two-sided 90% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method for each dosing group. Patients who have died prior to experiencing the event of interest will be censored on the day of data cutoff. Patients for whom the RT-qPCR value is still positive by the time of end of study visit or data cutoff, whichever comes first, will be censored on the last RT-qPCR sample date.

The number of patients who require hospitalization due to worsened COVID-19 will be counted. Corresponding proportion will be derived and a two-sided binomial exact 90% CI of proportion will be constructed.

Time to resolution of all COVID-19-related symptoms is defined as the days from randomization to the first day when all symptoms were resolved. Kaplan-Meier method will be used to assess the time to resolution of all COVID-19 related symptoms. The corresponding quartiles (including the median) will be reported and a two-sided 90% CI of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method for each dosing group. Patients who have died prior to experiencing the event of interest will be censored. Their follow-up length will be arbitrarily set as (data cutoff date – first patient in date). This approach is to count death as the worst possible outcome without possibility of recovery. Patients who have ongoing symptoms will be censored at the time of end of study visit or data cutoff, whichever comes first.
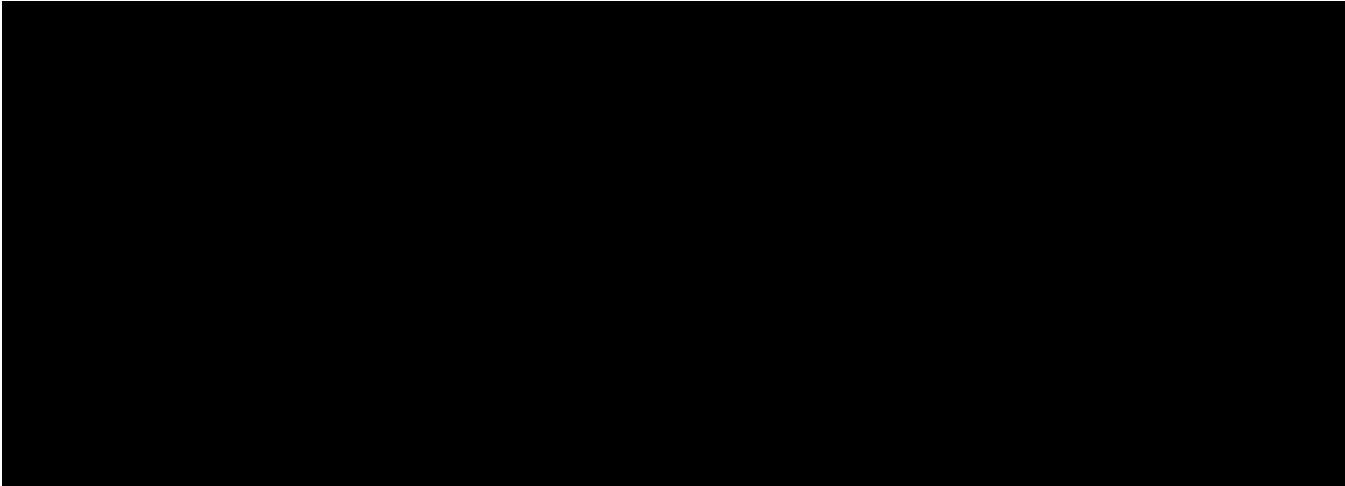
Kaplan-Meier method will be used to assess all-cause mortality rate at Day 29. A two-sided 90% CI of this rate, if estimable, will be constructed using the Greenwood's formula. Patients who do not die will be censored at the time of end of study visit or data cutoff, whichever comes first .

6.4.3   Exploratory Endpoint Analyses
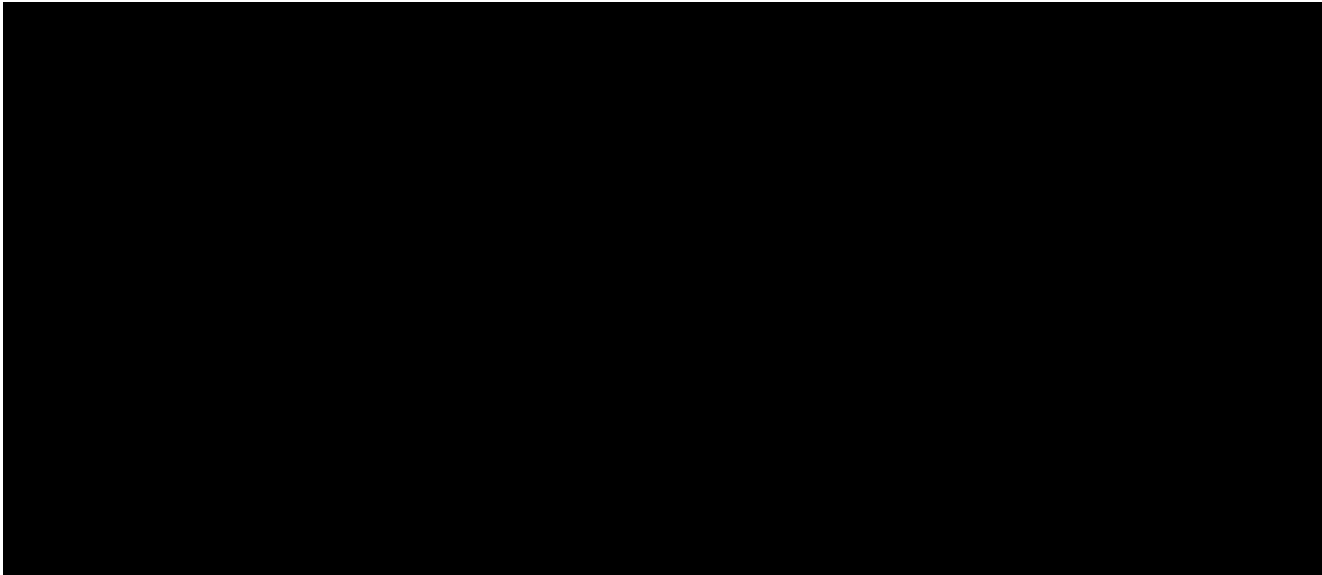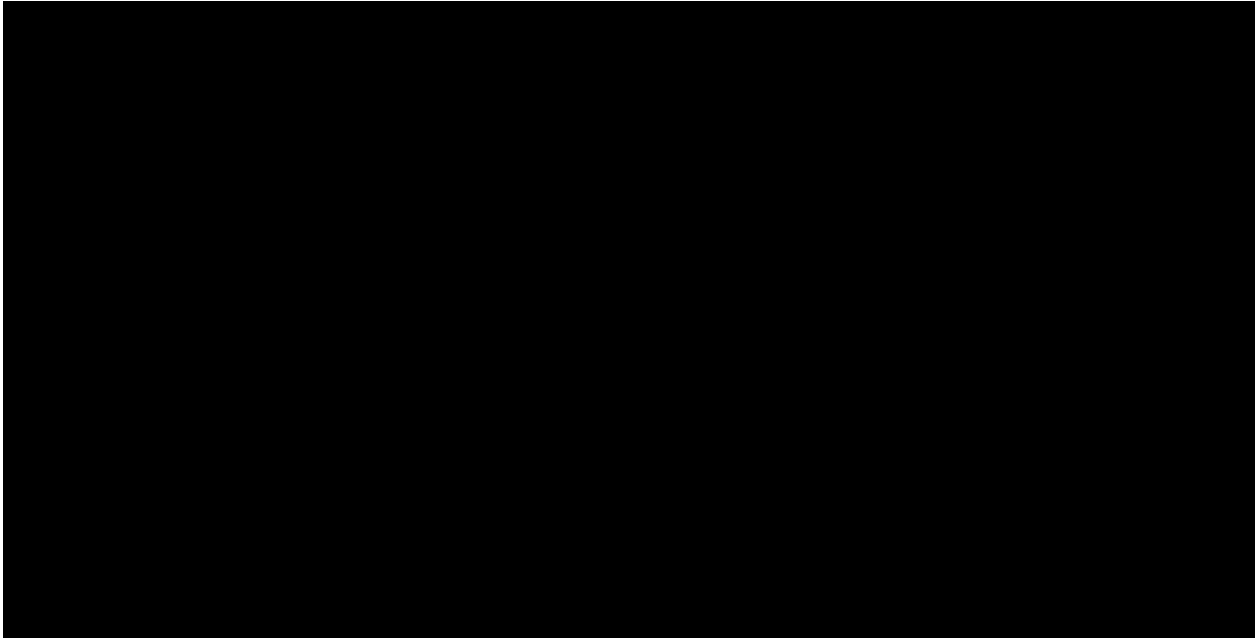
6.4.4 Subgroup Analyses

6.5 SAFETY ANALYSES

6.5.1 Extent of Exposure

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

- Total dose (mg): the sum of all actual doses of the study drug

- Relative dose intensity (RDI) in % is defined as:

$$100 \times \frac{\text{Total Dose (mg)}}{\text{Planned Dose Level (mg/kg)} \times \text{Weight}}$$

where planned dose level equals to 5 mg/kg, 15 mg/kg or 30 mg/kg according to treatment arm assignment. For patients in placebo arm, the planned dose level is set to 15 mg/kg. The weight is based on a patient's actual body weight on the day of drug administration.

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

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

6.5.2 Adverse Events

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

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

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

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

An overview table of patients with at least one TEAE will be presented with the incidence of:

- patients with any TEAE
- patients with any TEAE with grade 3 or higher
- patients with any serious TEAE
- patients with any TEAE leading to death
- patients with any TEAE leading to treatment discontinuation
- patients with any TEAE leading to drug interruption
- patients with any TEAE leading to infusion rate decreased

- patients with any treatment-related TEAE
- patients with any treatment-related TEAE with grade 3 or higher
- patients with any treatment-related serious TEAEs

- patients with any treatment-related TEAE leading to death

- patients with any treatment-related TEAE leading to treatment discontinuation

- patients with any treatment-related TEAE leading to drug interruption

- patients with any treatment-related TEAE leading to infusion rate decreased

Treatment-related AEs also include those events with missing assessment of the causal relationship.

The incidence of following TEAEs will be reported by SOC and PT, sorted by decreasing order of the frequency of the SOC first and then by decreasing order of the frequency of the PT within the SOC:

- patients with any TEAE

- patients with any serious TEAE

- patients with any TEAE leading to death

- patients with any TEAE leading to treatment discontinuation

- patients with any TEAE leading to drug interruption

- patients with any treatment-related TEAE

A patient will be counted only once by the highest grade according to NCI-CTCAE, version 5.0, within a SOC and PT, even if the patient experienced more than one TEAE within a specific SOC and PT.

The incidence of following TEAEs will be reported by SOC, PT and Worst Grade:

- patients with any TEAE

- patients with any treatment-related TEAE

Subject data listings of all AEs, SAEs, treatment-related AEs, grade 3 or above AEs, AEs that led to death and AEs that led to treatment discontinuation, dose interruption will be provided.

6.5.3   Laboratory Values

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Reference (normal) ranges for laboratory parameters will be provided.

Laboratory parameters are graded by NCI-CTCAE Version 5.0 or higher and will be summarized through shift tables from baseline to the worst postbaseline grade. Grade 3 or 4 laboratory toxicity will be summarized, and parameters with NCI-CTCAE grading in both high and low directions will be summarized separately.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, SpO2, respiratory rate, pulse rate, and body temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

6.6 PHARMACOKINETIC ANALYSES

The following analysis plan provides the framework for the summarization of the PK data from study BGB-DXP593-102. The objective is to assess BGB-DXP593 PK and characterize PK parameters following a single IV dose. The PK analyses will be based on the BGB-DXP593 PK analysis set. Additional PK analyses (such as modeling and simulation using nonlinear mixed effects modelling) may be conducted if deemed necessary and will be described in a separate analysis plan.

6.6.1 Calculation of Serum Pharmacokinetic Parameters

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized by dose level using descriptive statistics.
The following plasma PK parameters will be calculated for BGB-DXP593, as appropriate for the data collected. Other PK parameters may be calculated if supported by the data.

Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

Parameter (Units)	Definition	Method of Determination
AUC_{0-29} ($\mu g \cdot hr/mL$)	Area under the serum concentration versus time curve from 0 to Day 29	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{inf} ($\mu g \cdot hr/mL$)	AUC from zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_t ($\mu g \cdot hr/mL$)	AUC from time zero to time t	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} ($\mu g/mL$)	Maximum observed drug concentration during a dosing interval	Observed value
t_{max} (h)	Time to reach C_{max}	Actual elapsed time for observed C_{max} in each period.
$t_{1/2}$ (hr)	half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL (L/h)	clearance	Calculated as $Dose/AUC_{inf}$
V_z (L)	volume of distribution during the terminal phase	Calculated as CL/λ_z, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve

6.6.2   Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots. BGB-DXP593 concentration and time data will be listed individually and summarized by dose level using descriptive statistics.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.

- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term "BLQ" with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics.

- If a concentration at a given time point is missing it shall be reported as a missing value. Missing values may be defined in a bioanalytical source as "NS" (no sample), "NR" (no result), "IS" (insufficient sample), etc. If missing data are not identified in the bioanalytical source (i.e., the record is missing), the reporting convention of "NS" shall be utilized.

- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and %CV shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

6.6.3   Plots of Pharmacokinetic Concentrations

BGB-DXP593 concentration versus time data will be plotted individually and summarized graphically using arithmetic mean (±SD) plots by dose level. Arithmetic mean concentrations that are BLQ shall be set to "missing" for plotting on both linear scale and log-linear scale.

6.6.4   Reporting of PK Parameters for Descriptive Statistics

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters except t_{max} should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%; t_{max} should be presented as median, range (minimum, maximum) , and sample size (n) when presenting the summary statistics.

- Geometric mean (geometric CV%) will be the default method of reporting PK parameters within in-text tables.

- For any parameters that n ≤ 2, SD should not be presented.

- The units for all PK parameters will be provided.

- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g. AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.

  In this scenario, for reporting PK parameters such as AUC and C_{max}, the following guidance is provided for rounding:

  – If the numerical value is below 100 then one decimal place may be used e.g. 0.1 or 99.9.

  – For values ranging from >100, whole numbers should be used e.g. 100 or 9999.

  – If > 10,000 the clinical pharmacologist may decide on changing units e.g. from μg/ml to mg/ml.

  – For reporting times e.g. for t_{max} or $t_{1/2}$, if <1 hr use 2 decimals; time up to 24 hr should be reported to one decimal place e.g. 23.5 hr, time >24 hr should be rounded to nearest whole number e.g. 105 hr.

6.6.5 Software

For the calculations of PK parameters Phoenix® WinNonlin® Version 7.0 or higher (Certara, NJ. USA) will be used.

6.7 IMMUNOGENICITY ANALYSES

The scope of reporting conventions and calculation methodologies used for characterizing clinical immunogenicity depends on the incidence and kinetics of anti-drug antibodies detected (ADA). Additional ADA analyses (such as the effect of immunogenicity on PK, and safety) may be conducted if deemed necessary and will be described in a separate analysis plan.

The immunogenicity results will be listed and summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs. If data permit, the incidence of positive and neutralizing ADAs will be reported for ADA-evaluable subjects according to the following definitions:

- ADA-evaluable subject: Number of subjects with reportable non-missing baseline result and at least one reportable sample taken after drug administration during the treatment or follow-up observation period with reportable result (used for computing treatment-induced ADA incidence).

- Treatment-emergent ADA: Treatment-boosted ADA subject or treatment-induced ADA subject. Synonymous with "ADA Incidence".

- Treatment-induced ADA: ADA-evaluable subjects that were ADA-negative at baseline and ADA-positive following administration of biologic product.

- Treatment-boosted ADA: Baseline-positive ADA-evaluable subject with significant increases (4-fold or higher) in ADA titer after biologic drug administration. [Baseline-positive ADA-evaluable subject: an ADA-evaluable subject with positive ADA result].

- Persistent ADA: Persistent ADA: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer.

- Transient ADA: Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period, or two or more time points during the treatment, where the first and last ADA-positive samples are separated by a period of less than 16 weeks, and the subject last sampling time point is ADA-negative.

- Neutralizing ADA: patients with positive nab.

6.8 OTHER EXPLORATORY ANALYSES

7 INTERIM ANALYSIS

A primary analysis of efficacy and safety is planned after all patients have finished Day 8 visit or discontinued the study earlier. Pharmacokinetic, immunogenicity and exploratory biomarkers will not be a part of the primary analysis.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9 REFERENCES

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10 APPENDIX

10.1 IMPUTATION OF PARTIAL DATES FOR AEs/MEDICATIONS/THERAPIES/PROCEDURES

Imputation for AEs with missing or partial dates

If AE start (onset) date/end are missing or partial missing, the following imputation rules apply.

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed start date > death date, then set to death date

If year of the start date is missing or start date is completely missing, do not impute.

If the imputed start date > the end date (or the imputed end date), set the imputed start date = end date (or the imputed end date).

Imputation for medications/therapies/procedures with missing or partial dates

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medication/therapy/procedure:

If start date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > death date, then set to death date

If end date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

- If the imputed end date > death date, then set to death date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.