BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317/BGB-290_Study_001
Study Protocol Title:	A Phase 1/1b, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in Subjects with Advanced Solid Tumors
Date:	September 4, 2020
Version:	1.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITIONS
ADA	anti-drug antibody
AE	adverse event
BGB-290	code name for PARP inhibitor
BGB-A317	code name for monoclonal antibody BGB-A317
BRCA1/2	breast cancer type 1/2 susceptibility gene
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HR	homologous recombination
ICF	informed consent form
irAEs	immune-related adverse events
IV	intravenous
kg	kilogram
mBRAC	BRAC mutation
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival

PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1, programed death receptor ligand-1, Programed Death-1 Ligand-1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
RECIST	Response Evaluation Criteria in Solid Tumors
SAEs	serious adverse events
SCLC	small cell lung cancer
SD	stable disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment emergent adverse event
TNBC	triple negative breast cancer
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary Enhanced

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 protocol BGB-A317/BGB-290-study-001 part B: A Phase 1/1b, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in Subjects with Advanced Solid Tumors. The focus of this SAP is for the final analysis specified in the study protocol part B based on protocol version 3.3.

2 STUDY OVERVIEW

This is a 2-part Phase 1, open label, multiple dose, dose-escalation and expansion study to investigate the safety, pharmacokinetics and antitumor activity of the anti-PD-1 monoclonal antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in patients with advanced solid tumors.

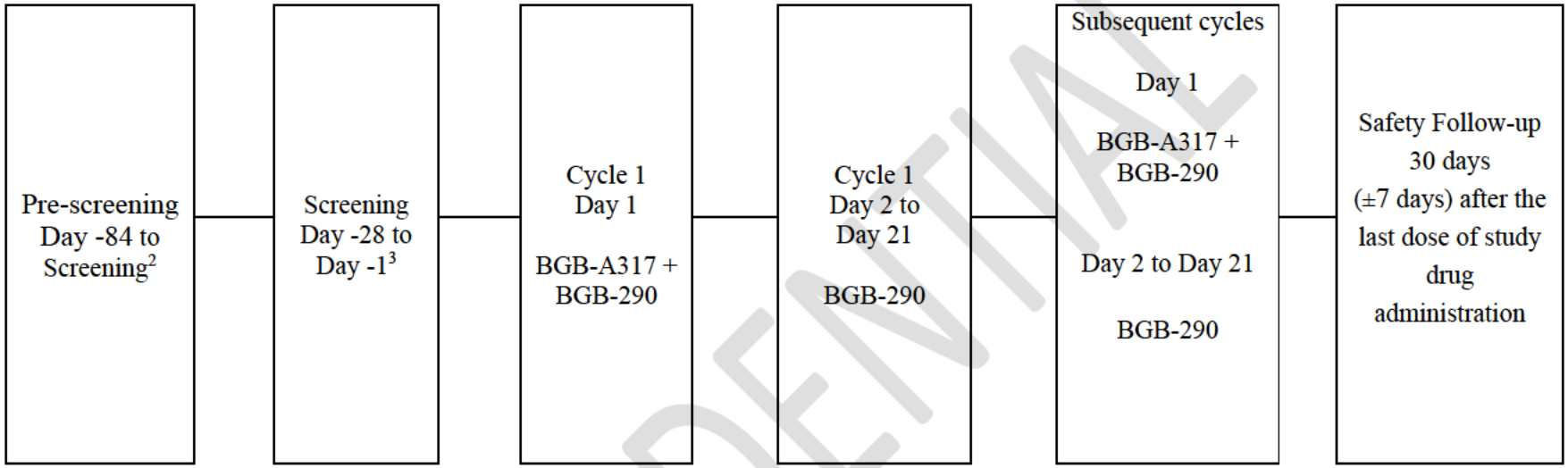
Part A consists of a dose-escalation and dose-finding component to establish the MTD and/or RP2D to evaluate the safety, PK, preliminary anti-tumor activity of BGB-A317 and BGB-290 combination and immunogenicity of BGB-A317. The details of the analysis for part A of the study are in the A317-BGB-290-001 Part A SAP finalized and dated 27 February 2018

Part B will be to further evaluate the PK, safety, and tolerability of the combination of BGB-A317 200 mg and BGB-290 IV Q3W combined with BGB-290 40 mg PO BID, and to assess the preliminary anti-tumor activity of the combination in patients in each of tumor types and the arms specified below (refer to protocol version 3.3 Section 5.1.2). Up to approximately 200 patients (approximately 20 patients/cohort) are planned to be included in Part B.

Arm 1a: Ovarian Cancer, fallopian tube or primary peritoneal cancer with BRCA1/2 mutation (mBRAC) or HRD;
Arm 1b: Ovarian Cancer, fallopian tube or primary peritoneal cancer without mBRCA and HRD;
Arm 2: Triple negative breast cancer (TNBC) with mBRCA or HRD;
Arm 3: Metastatic castration-resistant prostate cancer (mCRPC) with mBRCA or HRD;
Arm 4: Small cell lung cancer (SCLC);
Arm 5: Gastric or gastroesophageal junction cancer;
Arm 6: urothelial cancer;
Arm 7: pancreatic cancer;
Arm 8: non-ovarian gynecological cancer;
Arm 9: Non-small cell lung cancer (NSCLC)

A flow chart of the study design of Part B is presented in Figure 1 below.

Figure 1: Overall Study Design (Part B)



3 STUDY OBJECTIVES

PART B:

3.1 PRIMARY OBJECTIVES

- To assess the preliminary anti-tumor activity of the combination of BGB-A317 and BGB-290 in patients with specific tumor types

3.2 SECONDARY OBJECTIVES

- To further assess the safety and tolerability of the combination
- To further characterize the PK of BGB-A317 and BGB-290 in combination
- To further assess host immunogenicity to BGB-A317

3.3 EXPLORATORY OBJECTIVES

[redacted]

4 STUDY ENDPOINTS

PART B:

4.1 PRIMARY ENDPOINT

- Objective response rate (ORR), defined as the proportion of patients with a documented CR or PR per RECIST v1.1

4.2 SECONDARY ENDPOINTS

- Progressive-free survival (PFS), defined as the time from the date of first dose to the date of the first objectively documented tumor progression, assessed by investigator per RECIST v1.1, or death, whichever occurs first
- Duration of response (DOR), defined as the time from the first determination of an objective response, assessed by investigator per RECIST v1.1, until the first documentation of progression or death, whichever occurs first
- Disease control rate (DCR), defined as the proportion of patients whose best overall response is CR, PR, or SD, assessed by Investigator per RECIST v1.1
- Clinical benefit rate (CBR), defined as the proportion of patients who have CR, PR, or SD of $\geq$ 24 weeks in duration, assessed by Investigator per RECIST v1.1
- Overall survival (OS), defined as the time from the first dose date to death date due to any cause
- Safety and tolerability as assessed by the incidence and nature of AEs

- Pharmacokinetic parameters, including but not limited to Ctrough of BGB-A317 and BGB-290
- Immunogenicity of BGB-A317

4.3 EXPLORATORY ENDPOINTS

- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

Part B will include expansion arms of specific tumor types. Up to approximately 200 patients may be enrolled. The purpose of these expansion arms is to explore signals of clinical efficacy as well as to confirm the safety and tolerability of the combination in each selected tumor type. Anti-tumor activity will be evaluated in Part B. A decision can be made to stop an arm early due to suboptimal clinical anti-tumor activity. Twenty additional patients may be enrolled in any disease cohort to evaluate further the anti-tumor activity if evidence of activity is observed. The probability of observing at least one responder is approximately 88% in an expansion arm (n=20) when the underlying ORR is as low as 10%. Each arm in Part B: 1a, 1b, 2, 3, 4, 5, 6, 7, 8, and 9 may be analyzed independently. All arms will enroll approximately 20 patients.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

The Safety analysis set (SAF) includes all subjects who received any dose of any study treatment. All safety and efficacy analyses will use the safety population.

The PK analysis set (PK) includes all patients with valid PK sampling after treatment with study drug(s).

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of study treatment. For assessments conducted on or after the date of the first dose of study treatment, study day will be calculated as assessment date – date of first dose of study treatment + 1). For assessments conducted before the date of the first dose of study treatment, study day is calculated as (assessment date – date of first dose of study treatment). 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: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the time of first dose.

All calculations and analyses will be conducted using SAS version 9.2 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 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- For laboratory results collected as '<' or '>', a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- 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.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures 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.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

No multiplicity adjustment will be performed.

6.2.6 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

complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Patient Disposition

The number (percentage) of subjects with treatment ongoing, discontinued from the treatment/study, and primary reasons for discontinuation from treatment/study will be summarized in the safety population.

6.3.2 Protocol Deviations

Protocol deviation criteria will be established and subjects with protocol deviations will be identified and documented before the database lock. Major protocol deviations will be summarized by category for safety population.

6.3.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics in the safety population. Continuous variables include age, weight, and height at baseline; categorical variables include age groups (< 65 vs. >=65), sex, race, ethnicity and ECOG PS.

6.3.4 Disease History

The number (percentage) of subjects reporting a history of disease and characteristic, as recorded on the CRF, will be summarized. Disease characteristics include primary diagnosis, duration of disease, stage at initial diagnosis, receptor status, histology/cytology, histologic grade, localization of metastases. A listing of disease history will be provided.

6.3.5 Prior Anti-Cancer Drug Therapies and Radiotherapies

The number (%) of prior anti-cancer systemic therapies, and prior anti-cancer radiotherapy will be summarized. Duration of last systemic therapy, best response of last systemic therapy and time from last therapy to study entry will be summarized.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of subjects reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term by phase in the safety population. Prior medications are defined as medications that started before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after the subject's last dose or initiation of a new anti-cancer therapy. A listing of prior and concomitant medications will be provided.

6.3.7 Medical History

Medical History will be coded using MedDRA (version currently in effect at BeiGene at the time of database lock). The number (percentage) of subjects reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety population. A listing of medical history will be provided.

6.4 Efficacy Analysis

6.4.1 Primary Efficacy Endpoint

Objective Response Rate (ORR)

The primary analysis will be based on safety population. The number and proportion of patients who achieved confirmed objective tumor response (CR or PR) as evaluated by investigator according to RECIST v1.1 will be summarized. Patients without postbaseline tumor assessment will be considered as non-responders. A two-sided exact 95% confidence interval (CI) of ORR will be constructed to assess the precision of the point estimate of ORR. Safety population will be used to estimate ORR.

6.4.2 Secondary Efficacy Endpoints

Disease Control Rate (DCR) and Clinical Benefit Rate (CBR)

DCR and CBR according to RECIST v1.1 will be determined along with exact 2-sided 95% confidence interval by arm.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first study treatment to disease progression or death, whichever occurs first. Median PFS, PFS rate at 3, 6, 9, 12 and18 months and their 95% CI will be estimated using Kaplan-Meier method. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

The PFS derivation rules in this SAP follow Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)" with minor modification.

Table 1 shows the censoring rules for the derivation of PFS using RECIST 1.1 criteria based upon investigator's tumor assessment.

Table 1 The censoring rules for the derivation of PFS Per RECIST 1.1.

No.	Situation	Date of Progression or Censoring	Primary Analysis
1	No baseline tumor assessments	Date of the first dose	Censored

No.	Situation	Date of Progression or Censoring	Primary Analysis
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by the investigator.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 18 weeks + 1 week in the 1st year and 24 weeks + 1 week after the 1st year in this study:

The priority of the censoring rules in the primary analysis is as follows:

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of the first dose. However, if the subject died within 70 days (10 weeks) after the first dose and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed more than one assessment before PD or death (No. 7), the subject will be censored on the date of the last tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

Overall Survival (OS) is defined as the time from the date of first study treatment to death. Subjects who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the last date the subject was known to be alive. Median OS, OS rate at 6, 9, and 12months and their 95% CI will be estimated using Kaplan-Meier method. Kaplan-Meier curves by arm will be constructed to provide a visual description of the OS change with time.

Duration of Response (DOR)

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). Duration of response analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule.

Kaplan-Meier curve will be used to estimate median time and 95% confidence interval for duration of response.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion. The maximum tumor shrinkage based on target lesion used in the plots will be listed. The post-baseline nadir will be summarized using descriptive statistics. These analyses will be performed based on RECIST1.1.

6.5 SAFETY ANALYSES

All safety analyses will be performed by arm and by total (combined cohorts) based on the safety population. The incidence of treatment-emergent adverse events (TEAEs) will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values will be flagged.

6.5.1 Extent of Exposure

The following exposure parameters will be summarized with descriptive statistics for each study drug. One cycle is defined as 21 days of treatment. Specifically:

- The duration of exposure (days) for each study drug will be calculated as below.
  - Total duration of BGB-A317 (days) = last dose date of A317 - first dose date of A317 + 21;
  - Total duration of BGB-290 (days) = last dose date of BGB-290 - first dose date of BGB-290 + 1,

- The number of cycles received defined as the number of cycles with non-missing doses (dose>0) will be summarized for study drug A317.
- The number of doses taken will be calculated as the sum of numbers of non-missing doses (dose>0) for each study drug.

- The number of patients with dose reductions, dose interruptions for BGB-290, dose omissions, dose delays, and infusion interruption for BGB-A317, and treatment discontinuation and their reasons will be summarized by counts and percentages according to study drug. In addition, frequency of above dose modifications will be summarized by categories (0, 1, ≥2).
- Average dose intensity per patient (in mg/21 day for BGB-A317 and in mg/dose for BGB-290) and relative dose intensity per patient (percent of cumulative dose received relative to planned dose) will be summarized by descriptive statistics in each study drug.

  For BGB-A317:
  - Average dose intensity (mg/21 days) = total dose (mg) / duration of treatment (day) * 21;
  - relative dose intensity (%) = average dose intensity (mg/21 days)/200 mg*100%

  For BGB-290:
  - Average dose intensity = total dose (mg) / (duration of treatment (day) * 2);
  - relative dose intensity (%) = average dose intensity (mg/administration) / 40 mg/administration *100%
- Total dose (mg) per subject will be computed as the total of the doses received in all cycles for each study drug.

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

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

TEAE is defined as any AE or SAE with either an onset date or a date of worsening in severity from baseline (ie, pretreatment) occurring after first dose of study drug and up to either 30 days following discontinuation from study drug or start of new anticancer therapy, whichever occurs first. The TEAE classification also applies to irAEs that are recorded up to 90 days after discontinuation from BGB-A317, regardless of initiation of subsequent anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), immune-related AEs, treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction, dose interruption, dose delay and dose omission will be

provided. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study treatment or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and Preferred Term. A patient will be counted only once by the worst severity grade per NCI-CTCAEv.4.03 within an SOC and Preferred Term.

The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drugs.

Serious adverse events, TEAE with grade 3 or above, irAE, related TEAE, related SAE and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, dose delay and dose omission will also be summarized.

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 will be provided.

All deaths and causes of death will be summarized, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation. Subject data listing of all death with the cause of death will be provided.

6.5.3 Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in table 2.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit.

Laboratory parameters that are graded in NCI CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. Number (percentage) of subjects with abnormal postbaseline laboratory values will be summarized.

Subject data listings of selected hematology and serum chemistry parameters, urinalysis and coagulation will be provided.

Table 2. Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Hemoglobin	Prothrombin time	glucose
Alanine aminotransferase	Hematocrit	Activated Partial	protein
Aspartate aminotransferase	Platelet count	Thromboplastin Time	ketones
Albumin	WBC count	International Normalized	blood
Bicarbonate	Neutrophil count	Ratio	24 hour protein[1]
Blood urea nitrogen	Lymphocyte count		Random urine
Calcium			protein to
Chloride			creatinine ratio
Creatinine			
Glucose			
Lactate dehydrogenase			
phosphorus			
Potassium			
Sodium			
Total bilirubin			
Total protein			
Testosterone			

[1] On routine urinalysis, if urine protein is ≥2+ by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio

WBC = white blood cell

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], pulse rate, temperature, and weight) and changes from baseline will be presented by visit. Vital signs will be listed by subjects and visits.

6.5.5 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points (refer the time points to the protocol study assessments and procedures schedule) after the start of treatment. Observed and change from baseline in ECG will be summarized.

6.5.6 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized.

6.6 Pharmacokinetic Analyses

Pharmacokinetic samples were collected in this study as outlined in Section 5.1.3 in Protocol Amendment v4.0 and only from patients randomized to receive BGB-290 or BGB-A317 and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the laboratory manual.

Serum concentration data, including but not limited to C_{trough}, will be tabulated and summarized for each cycle at which PK samples are collected. Descriptive statistics will include means, medians, ranges, standard deviations and coefficient of variation (CV), and geometric mean, geometric CV as appropriate.

Additional PK analyses may be conducted as appropriate

6.7 IMMUNOGENICITY

Human anti-drug antibodies (ADA) to BGB-A317 will be assessed during the study as defined in the protocol.

ADA attributes:

- Treatment boosted ADA is defined as ADA positive at baseline that was boosted to a 4 fold or higher level following drug administration.
- Treatment-induced ADA is defined as ADA negative at baseline and ADA positive post-baseline.
- **Persistent ADA response** is defined as Treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected only in the last time point or at a time point less than 16 weeks before a negative last sample.
- **Transient ADA response** is defined as Treatment-induced ADA detected only at 1 time point during treatment or follow-up, excluding last time point; or detected at 2 or more timepoints during treatment or follow-up, where the first and last positive samples (irrespective of any negative samples in between) are separated by less than 16 weeks and the last time point is negative. Transient ADA is a treatment-induced response that is not considered persistent.
- **Neutralizing ADA** is defined as ADA that inhibits or reduces the pharmacological activity.

ADA response endpoints:

- **ADA incidence** is defined as sum of treatment-emergent ADA, which include both treatment-induced and treatment-boosted ADA-positive patients, as a proportion of the ADA evaluable population.
- **ADA prevalence** is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

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

7 INTERIM ANALYSIS

There will be no formal interim analysis.

8 CHANGES IN THE PLANNED ANALYSIS

Not Applicable.

9 REFERENCES

Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research (2007). FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

10 APPENDIX

10.1 IMPUTATION OF MISSING/PARTIALLY MISSING DATES

Missing data will not be imputed unless otherwise specified. The imputation rule for the safety analyses will be used to address the issues with partial dates.

When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

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

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

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 medications:

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 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 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.