

STATISTICAL ANALYSIS PLAN

A FIRST-IN-HUMAN, PHASE 1A/1B, OPEN-LABEL, DOSE-ESCALATION AND EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY OF THE RAF DIMER INHIBITOR BGB-3245 IN PARTICIPANTS WITH ADVANCED OR REFRACTORY TUMORS

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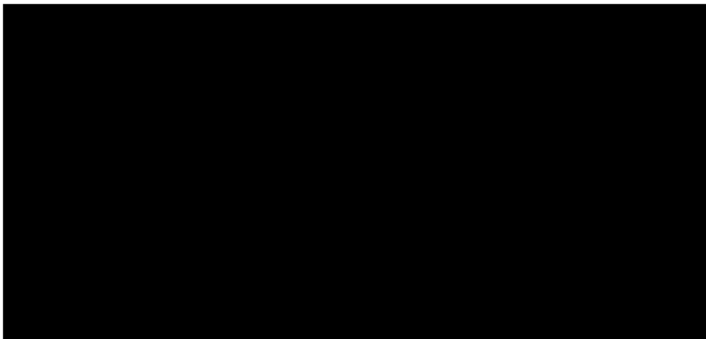
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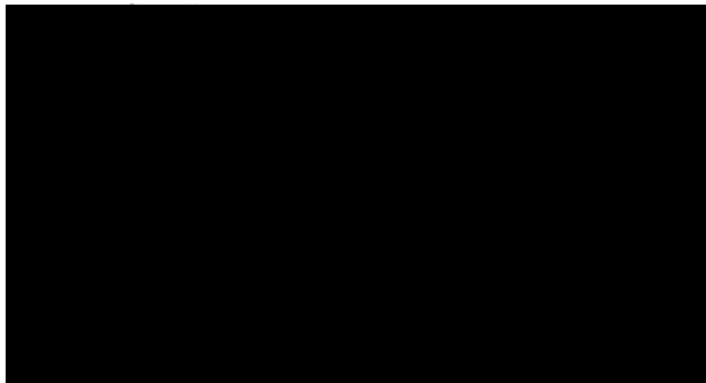


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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
AUC	Area Under the Plasma Concentration Time Curve
AUC _{0-∞}	Area Under the Plasma Concentration Time Curve from Zero to Infinity
AUC _{last}	Area Under the Plasma Concentration Time Curve from Zero to the Last Measurable Concentration
AUC _{last,ss}	Area Under the Plasma Concentration Time Curve from Zero to the Last Measurable Concentration at Steady State
BRAF	v-RAF Murine Sarcoma Viral Oncogene Homolog B
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CL/F	Apparent Clearance
C _{max}	Maximum Observed Plasma Concentration
C _{max,ss}	Maximum Observed Plasma Concentration at Steady State
CPK	Creatine Phosphokinase
CR	Complete Response
CRAF	Raf-1 Proto-Oncogene, Serine/Threonine Kinase
CRC	Colorectal Cancer
CRF	Case Report Form
CS	Clinically Significant
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Trough Plasma Concentration
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DOR	Duration Of Response
DSD	Duration of Stable Disease
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
ERK	Extracellular Signal-regulated Kinase
FDA	Food and Drug Administration
FIH	First-In-Human
HRAS	Harvey Rat Sarcoma Virus Oncogene
ICF	Informed Consent Form

ICH	International Council for Harmonisation
ID	Identification
IRB	Institutional Review Board
IRT	Interactive Response Technology
KRAS	Kirsten Rat Sarcoma Virus Oncogene
MAPK	Mitogen Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated Protein Kinase Kinase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI-2	Modified Toxicity Probability Interval-2
NCA	Non-Compartmental Analysis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NCS	Not Clinically Significant
NE	Not Evaluable
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
OCT	Optical Coherence Tomography
ORR	Objective Response Rate
OS	Overall Survival
PCS	Potentially Clinically Significant
PD	Progressive Disease
PDx	Pharmacodynamic
PFS	Progression-Free Survival
pERK	Phosphorylated extracellular signal-regulated kinase (phospho-ERK)
PIK3CA	Phosphoinositide 4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred term
QD	Once a day
QTc	Corrected QT interval
QTcB	Corrected QT Interval by Bazett's Formula
QTcF	Corrected QT Interval by Fridericia's Formula
RAF	Rapidly Accelerated Fibrosarcoma
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
SS	Steady State
STD	Standard Deviation
t _{1/2}	Elimination Half-Life

TBD	To Be Determined
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T _{max}	Time To Maximum Observed Plasma Concentration
T _{max,ss}	Time To Maximum Observed Plasma Concentration at Steady State
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
V _z /F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

1. Introduction

This document is the statistical analysis plan (SAP) for BGB-3245-AU-001, a first-in-human, Phase 1a/1b, open-label, dose-escalation and expansion study to investigate the safety, pharmacokinetics, and antitumor activity of the RAF dimer inhibitor BGB-3245 in participants with advanced or refractory tumors. The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures produced by SpringWorks Therapeutics and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. It is based on protocol Version 7.0 dated 22 April 2024.

The sponsor, MapKure, has decided on 29 January 2025 to stop further enrollment in Phase 1b of the study and proceed to close the study on 08 April 2025. On 03 February 2025, the sponsor has made the decision to have an abbreviated clinical study report (CSR), instead of a full CSR, for the study. In particular, efficacy-related analyses will be abbreviated due to lack of clinical benefit. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the abbreviated CSR for this trial.

This SAP will also outline all the differences in the currently planned analytical objectives and analyses relative to those planned in the study protocol if there is any. This analysis plan is to be finalized before the planned database lock.

2. Summary of Study Protocol

2.1 Study Objectives and Endpoints

The study objectives and corresponding analysis endpoints are listed below.

Phase 1a (Dose Escalation Part)	
Primary Objectives	Primary Endpoints
- To assess the safety and tolerability of BGB-3245 in participants with solid tumors. - To determine the maximum tolerated dose (MTD), if any, and recommended Phase 2 dose (RP2D) for BGB-3245.	- Incidence of serious adverse events (SAEs) and the incidence and severity of adverse events (AEs) (coded to preferred term [PT] and system organ class [SOC]), physical examination, Eastern Cooperative Oncology Group (ECOG), vital signs, electrocardiograms (ECGs), ophthalmological examination, and laboratory tests. - MTD as determined by an SMC based on the occurrence of DLTs, safety, and tolerability. The sponsor defined the RP2D based on safety, preliminary efficacy, and other complementary data. The RP2D was to be confirmed by the SMC

Secondary Objectives	Secondary Endpoints
- To characterize the pharmacokinetics of BGB-3245 after single-dose and multiple-dose administration. - To assess the preliminary antitumor activity of BGB-3245.	- For a single-dose profile: area under the plasma concentration (AUC) from zero to the last measurable concentration (AUC_{last}), AUC from zero to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (Vz/F), as available data allowed. In addition, area under the plasma concentration time curve from zero to the last measurable concentration at steady state ($AUC_{last,ss}$), area under the concentration time curve for the dosing interval at steady state (AUC_{tau}), maximum observed plasma concentration at steady state ($C_{max,ss}$), and time to maximum observed plasma concentration at steady state ($T_{max,ss}$) were calculated at steady state, as available data allow. - ORR, DOR, CBR, PFS, Duration of SD (DSD)
Exploratory Objectives	Exploratory Endpoints
- To determine potential predictive biomarkers of molecular response. - To assess potential pharmacodynamic (PDx) biomarkers of target engagement, biological activity, and mechanism of action. - To explore mechanisms of treatment resistance in participants who fail to respond or develop resistance.	- Potential biomarkers of molecular response - Potential biomarkers of resistance
Phase 1b (Dose Expansion Part)	
Primary Objectives	Primary Endpoints
Evaluate the optimal RP2D for BGB-3245	Optimal RP2D

Primary Objectives (cont.)	Primary Endpoints (cont.)
To determine the objective response rate (ORR) as assessed by initial investigator review using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) of BGB-3245 at the RP2D when given orally in participants with mutational selected solid tumors.	ORR (confirmed CR+PR)
Secondary Objectives	Secondary Endpoints
- To determine the progression-free survival (PFS); disease control rate (DCR) as assessed by initial investigator review using RECIST v1.1; duration of response (DOR); clinical benefit rate (CBR); and overall survival (OS) of BGB-3245 as a single agent. - To further assess the safety and tolerability of BGB-3245. - To further characterize the pharmacokinetics of BGB-3245.	- PFS, DCR (confirmed CR, PR, or SD), DOR, CBR (confirmed CR or PR or durable SD [SD ≥ 24 weeks]), and DSD, OS - Incidence of AEs, SAEs, physical examination, ECGs, and laboratory measurements. - Pharmacokinetics assessment, including but not limited to steady-state trough plasma concentration C_{trough}.
Exploratory Objectives	Exploratory Endpoints
- To determine potential predictive biomarkers of molecular response. - To assess potential PDx biomarkers of target engagement, biological activity, and mechanism of action. - To explore mechanisms of resistance in participants who fail to respond or develop resistance.	As described for Phase 1a.

2.2 Study Design

This is a FIH, Phase 1a/1b (dose escalation and expansion) study of BGB-3245 in participants with tumors harboring BRAF or KRAS/NRAS/HRAS mutations that are likely to respond to a RAF dimer inhibitor.

The Phase 1a portion of the study consisted of a dose-escalation and dose-finding component to establish the MTD and/or RP2D and to evaluate the pharmacokinetics of BGB-3245. Phase 1b will consist of an expansion component to further evaluate the safety, tolerability, pharmacokinetics, and dose optimization of BGB-3245 at the RP2D and to assess the preliminary antitumor activity of the compound in participants in each of the treatment groups.

This study will consist of 3 periods:

1. Screening Period represents 28 days between the date of signing the informed consent until the first administration of study drug.
2. Treatment Periods for Phase 1a and Phase 1b will be as follows:
 - a. In Phase 1a, the first treatment cycle will be 30 days, with a 2-day treatment-free period on Days 2 and 3. After the first treatment cycle, participants will be treated by repeated treatment cycles of 28 days. In Phase 1b, all treatment cycles will be 28 days of continuous BGB-3245 treatment.
 - b. All participants will receive study drug until
 1. disease progression;
 2. cessation of study treatment due to death, intolerance, or withdrawal of consent from the study;
 3. completion of 2 years of treatment (unless the investigator's benefit-risk assessment supports continued treatment);
 4. Investigator's decision; or
 5. the study is stopped by the sponsor for any reason.
3. Safety Follow-up Period consists of a follow-up visit at approximately 30 (+ 7) days after last dose of the study drug.
 - a. Beyond 30 days, investigators should report any serious adverse events (SAEs) that are believed to be related to study drug or deaths irrespective of the cause if they become aware of them.
 - b. Participants who discontinue study drug due to a Grade ≥ 3 drug-related adverse event (AE) will be followed until the resolution of the AE (to $\leq$ Grade 1, baseline, or stabilization) or initiation of a new treatment, whichever comes first.

Approximately 28 to 60 participants were planned to be enrolled in Phase 1a dose escalation. Approximately 72 participants were planned to be enrolled in Phase 1b to achieve 60 evaluable participants.

Further details of the study design are described in the study protocol and its amendments.

i. Phase 1a

Planned dose levels for Phase 1a are:

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- Level 1: BGB-3245, 5 mg
- Level 2: BGB-3245, 10 mg (100% increase)
- Level 3: BGB-3245, 15 mg (50% increase)
- Level 4: BGB-3245, 25 mg (67% increase)
- Level 5: BGB-3245, 40 mg (60% increase)
- Level 6: BGB-3245, 60 mg (50% increase)
- Subsequent Dose Levels: to be determined (TBD)

Dose cohort size management and dose-escalation decisions were made in accordance with the modified toxicity probability interval-2 (mTPI-2) design (Ji et al 2010) and had to be confirmed by the Safety Monitoring Committee (SMC). The mTPI-2 used a Bayesian statistics framework and a beta-binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflected the relative difference between the toxicity rate of each dose level. The target toxicity rate for the MTD was $\phi = 0.30$. The maximum sample size was to be 60 participants. The Phase 1a portion of the trial enrolled and treated participants in minimum cohorts of 3 participants. Being a model-assisted design, mTPI-2 automatically and appropriately tailored dose escalation and de-escalation decisions with the acceptable toxicity probability interval of (0.25, 0.33). All the dose-escalation decisions were pre-calculated under the mTPI-2 design and presented in a 2-way table. The decision rules to “dose escalate” (E), “no change in dose” (S), “dose de-escalate” (D) or “dose de-escalate, unacceptable toxicity” (DU) are described in Table 1

Cohorts of participants could have received doses already tested but a dose that was associated with decision “Dose de-escalate, unacceptable toxicity” could not have been revisited and no additional participants should have been treated at this dose or higher doses for the remainder of the trial.

Table 1 Dose Escalation/De-Escalation Rule for the mTPI-2 Design

Maximum sample size/dose level = 15, Target toxicity probability = 0.30, epsilon 1 =0.05, epsilon 2 =0.03

Number of DLTs	n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12	n=13	n=14	n=15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	S	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	D	D	S	S	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	D	S	S	S	E	E	E
4				DU	DU	DU	D	D	D	D	D	D	S	S	S
5					DU	DU	DU	DU	DU	D	D	D	D	D	D
6						DU	DU	DU	DU	DU	DU	D	D	D	D
7							DU	DU	DU	DU	DU	DU	DU	D	D
8								DU	DU	DU	DU	DU	DU	DU	DU

Column indicates the number of participants treated. Row indicates the number of participants with DLTs.

*E: Escalate to the next higher dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose was never used again in the trial; S: Stay at the same dose.

The study enrolled and treated participants in minimum cohorts of 3 participants. The design was described as follows:

1. Participants in the first cohort were treated at dose level 1.
2. To assign a dose to the next cohort of participants, conduct dose escalation/de-escalation according to Table 1. When using Table 1, please note the following:
 - a. “DU” means the current and higher doses from the trial are eliminated to prevent treating any future participants at these doses.
 - b. When a dose is eliminated, de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
 - c. If the current dose is the lowest dose and the rule indicates dose de-escalation (D), continue to treat the new participants at the lowest dose unless the number of dose-limiting toxicities (DLTs) reaches the elimination boundary (ie, DU), at which point terminate the trial for safety.
 - d. If the current dose is the highest dose, which may be higher than the predefined dose level of 60 mg, and the rule indicates dose escalation, treat the new participants at the highest dose (or the dose that is recommended by SMC).
3. Repeat step 2 until the maximum sample size of 60 is reached or stop the trial if the number of participants treated at the current dose reaches 15.

Due to binomial data variability in small samples, DLTs could have been observed in lower dose levels by chance even when the true probability was fairly low. This could have resulted in the estimated posterior DLT rate to exceed the targeted very early in the trial, triggering an early stop when very few participants (eg, 3) had been treated. To prevent stopping the trial prematurely in such cases, a dose de-escalation option with a lower dose of 5 mg or current dose level could have been added to the dose grid.

Estimating the MTD and RP2D:

An MTD was identified at 40 mg QD (SMC Meeting Minutes, June 2021). RP2D was not established in this study.

MTD has been identified with sufficient accuracy: at least 6 to 12 participants have been treated on a dose that is currently estimated to be the MTD and/or RP2D; or

1. All doses explored appeared to be overly toxic.
2. The maximum number of participants reached 60.
3. The highest planned dose was reached and there were no more doses to test.

ii. Phase 1b

Phase 1b is a multicenter, open-label, parallel-group, dose expansion study, and this phase will investigate RP2D to examine the potential efficacy as well as safety and tolerability of BGB-3245 in several solid tumor indications. The following treatment groups were planned for the dose expansion cohort.

- Group 1: Participants with tumor types other than colorectal cancer (CRC) that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or mitogen-activated protein kinase kinase (MEK) inhibition. Participants must start BGB-3245 treatment within 90 days from last treatment with prior BRAF and/or MEK inhibitors (n=40).
 - Participants will be randomized in 1:1 via IRT to receive either 25 mg QD or 40 mg QD dose of BGB-3245 for a total of 20 participants evaluable for each dose level.
 - RP2D for further development will be determined by comparing the safety, tolerability, efficacy, dose intensity (as noted by dose interruptions and dose reductions), and PK of the 25 mg and 40 mg dosing levels.
 - Results of the participants who were already enrolled in Group 1 before Protocol version #6 was implemented will be included in the final evaluation and summarized separately as supportive analysis.
- Group 2: Participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation (n=20).
 - Examples of Class II mutations include P367L/S, G464V/E, G469V/S/R/I/A/T170delinsAK, L485W/F, N486_A489delinsK, N486_P490del, L525R, E586K, L597V/S/R/Q/P/K, A598V/T599insV, T599I/dup/V600insT, T599I/K, T599TT/TS, V600_K601D/E/N, V600_K601del, V600_K602delinsDT, V600_W604delinsDQTDG, K601_S602delinsNT, K601E/N/T, BRAF kinase duplication. Additional Class II mutations were considered upon medical monitor approval.
 - Participants in Group 2 will be treated with 40 mg QD dose of BGB-3245. Treatment will be managed via the IRT system.

iii. Dose-Limiting Toxicity Definition

All toxicities or AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version (v) 5.0. The occurrence of any of the following toxicities was considered a DLT during dose escalation if it occurred within 30 days of receiving BGB-3245 on Cycle 1 Day 1, with the exclusion of toxicities clearly related to disease progression or intercurrent illness.

Hematologic:

1. Any Grade ≥ 4 hematological toxicity
2. Grade ≥ 3 febrile neutropenia (defined as absolute neutrophil count [ANC] $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ [101°F] or a sustained temperature of $\geq 38^\circ\text{C}$ [100.4°F] for > 1 hour)
3. Grade 3 neutropenia lasting > 7 days
4. Grade 3 thrombocytopenia with clinically significant bleeding

Nonhematologic:

1. Any death not clearly due to the underlying disease or extraneous causes and for any toxicity requiring permanent discontinuation of study drug(s)
2. Any Grade ≥ 4 nonhematologic event unless otherwise noted below
3. Grade 3 total bilirubin (TBIL) (except in participants with Gilbert's Syndrome) or transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST])
4. Confirmed occurrence of Hy's law or the United States Food and Drug Administration (FDA)'s definition of potential drug-induced liver injury not explained by any other cause(s) (eg, viral hepatitis, exposure to other hepatotoxins), without evidence of cholestasis and include the following laboratory abnormalities:
 - Participants with AST or ALT and TBIL baseline values within the normal range who subsequently presented with AST or ALT values $\geq 3 \times$ upper limit of normal (ULN) concurrent with a TBIL value $\geq 2 \times$ ULN with no evidence of hemolysis and an ALP value $\leq 2 \times$ ULN or other findings indicating an absence of cholestasis
 - For participants with baseline ALT or AST values above the ULN, AST or ALT value $\geq 2 \times$ the baseline values should have been used in the definition mentioned above.

Note that this specific category of DLT uses ULN rather than common terminology criteria for adverse events (CTCAE) grade for definition.

5. Grade ≥ 3 rash that did not begin to resolve within 7 days of initiating optimal medical and supportive care
6. Grade ≥ 3 significant neurologic toxicity (eg, seizure, hallucination, confusion, or delirium)
7. Grade ≥ 3 generalized muscle weakness
8. Grade ≥ 3 creatine phosphokinase (CPK) with or without symptoms
9. Grade ≥ 3 nonhematologic treatment-related toxicity not listed above that did not resolve to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy

Clinically important or persistent toxicities that were not included above could also have been considered a DLT following review by the sponsor in consultation with investigators or following review by the SMC. Additionally, any clinically significant toxicities that occurred after the DLT observation period for a given dose level could have been taken into account regarding subsequent dose escalation and/or RP2D decisions.

The following toxicities were not considered a DLT:

- Isolated Grade 3 or Grade 4 laboratory abnormalities not listed above that had no clinical correlation and resolved to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy
- Grade ≥ 3 nausea, vomiting, or diarrhea that resolved to Grade ≤ 1 within 3 days
- Grade ≥ 3 fatigue that resolved to Grade ≤ 1 within 5 days
- Grade ≥ 3 asymptomatic increase of lipase or amylase without pancreatitis that resolved to Grade ≤ 1 within 3 days

In such cases where participants had been safely dosed at the next dose level, additional dose-escalation criteria (eg, increase minimum number of participants, expand the DLT observation period, etc.) for subsequent dose levels were considered by the sponsor in consultation with participating investigators.

Participants must have met 1 of the following during the DLT observation period to be considered DLT evaluable: 1) received $\geq 80\%$ of the assigned doses of BGB-3245 and remained on study for 30 days from Cycle 1 Day 1 administration of BGB-3245 or 2) experienced a DLT during Cycle 1. Participants who failed to meet 1 of the above criteria could have been replaced.

iv. Data Monitoring Committee

There is no Data Monitoring Committee for this study.

3. Analysis Sets

The following analysis populations will be evaluated and used for presentation of the data. Participant assignments to the analysis populations will be finalized prior to the database lock.

- The Safety Population will include all participants who received at least 1 dose of study drug. This population will be used for safety analyses and presentation of all data listings. Summary for PFS and OS will also be based on Safety Population.
- The DLT Evaluable Population included participants who received at least 80% of the assigned dose of BGB-3245 and remained on study for 30 days from Cycle 1 Day 1 administration of BGB-3245 during the dose-escalation phase (Phase 1a), or who

experienced a DLT during the dose-escalation phase (Phase 1a). Refer to Section **Error! Reference source not found.** for the definition of DLT. This population will be used for DLT related analyses.

- The PK Concentration Population will include all participants who received BGB-3245 and have at least one evaluable PK concentration (including values below the lower limit of quantification). Summaries and listings of PK concentrations will be based on the PK Concentration Population.
- The PK Parameter Population will include all participants who received BGB-3245 and have sufficient pharmacokinetic data to calculate at least one PK parameter. Summaries and listings of PK parameters will be based on the PK Parameter Population.
- The Efficacy Evaluable Population will include all dosed participants who have radiologically confirmed evaluable disease at baseline and at least 1 evaluable postbaseline radiological tumor response assessment. This population will be used for the efficacy analyses except for endpoints PFS and OS.

4. Study Endpoints

4.1 Study Endpoints for Dose Escalation Phase 1a

i. Primary Endpoints

- Safety and tolerability of BGB-3245 were assessed by the incidence of serious adverse events (SAEs) and the incidence and severity of adverse events (AEs) (coded to preferred term [PT] and system organ class [SOC]), physical examination, Eastern Cooperative Oncology Group (ECOG), vital signs, electrocardiograms (ECGs), ophthalmological examination, and laboratory tests.
- The MTD was determined by an SMC based on the occurrence of DLTs, safety, and tolerability. The sponsor defined the RP2D based on safety, preliminary efficacy, and other complementary data. The RP2D was to be confirmed by the SMC.

ii. Secondary Endpoints

- For a single-dose profile: area under the plasma concentration (AUC) from zero to the last measurable concentration (AUC_{last}), AUC from zero to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F), as available data allowed. In addition, area under the plasma concentration time curve from zero to the last measurable concentration at steady state ($AUC_{last,ss}$), area under the concentration time curve for the dosing interval at steady state (AUC_{tau}), maximum observed plasma concentration at steady state ($C_{max,ss}$), and time to maximum observed plasma concentration at steady state ($T_{max,ss}$) were calculated at steady state, as available data allow.
- ORR was defined as the proportion of participants who had confirmed complete response (CR) or partial response (PR).
- DOR was defined as the time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death due to any cause, whichever occurs first.
- CBR was defined as the proportion of participants with best overall response (BOR) of confirmed CR, PR, or stable disease (SD) lasting ≥ 24 weeks.
- PFS was defined as the time from the date of the first administration of study drug to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first.
- Duration of SD (DSD) was defined as the time interval, in the absence of either confirmed CR or PR, between the date of the first administration of study drug and the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurred first.

iii. Exploratory Endpoints

- Potential biomarkers of molecular response, including phosphorylated mitogen-activated protein kinase 1 (MAPK1), phosphorylated-ERK (pERK); mutational status of BRAF, KRAS proto-oncogene, GTPase (KRAS), NRAS proto-oncogene, GTPase (NRAS), A-Raf proto-oncogene serine/threonine kinase (ARAF), NF1; BRAF or Raf-1 proto-oncogene, serine/threonine kinase (CRAF) fusion, amplification of and other aberrations in, or affecting, the MAPK pathway. Refer to panel mutation testing described in the Laboratory Manual for a full list of genes.
- Identification of potential biomarkers of resistance: optional tumor biopsy samples (International Conference on Harmonisation [ICH] E18 guidelines) taken at disease progression were used to identify potential biomarkers of resistance, including but not limited to expression or mutations (protein and ribonucleic acid [RNA]) of MAPK or parallel, redundant signaling pathways.

4.2 Study Endpoints for Dose Expansion Phase 1b

i. Primary Endpoint/Estimand

- Determination of the optimal RP2D
- ORR (confirmed CR+PR) as described in Section 4.1.2 above in participants with selected tumors.
- The primary estimand for ORR consists of:
 - The target study population, which is participants with tumor types other than colorectal cancer (CRC) that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition.
 - The variable of interest, which is ORR, defined as a best overall response of CR or PR according to RECIST 1.1.
 - The summary measures, which are the rate of participants with objective confirmed response between the 2 dose levels of 25 mg QD or 40 mg QD dose of BGB-3245
 - The intercurrent events, which are discontinuation of BGB-3245 or start of new anti-cancer therapy before achieving an objective response. Participants who discontinue BGB-3245 or start new anti-cancer therapy prior to achieving an objective response are considered as non-responders (i.e., a while-on-treatment strategy is applied).

ii. Secondary Endpoints/Estimands

- PFS as described above, **DCR** (confirmed CR, PR, or SD), DOR, CBR (confirmed CR or PR or durable SD [SD $\geq$ 24 weeks]), and DSD.
- OS is defined as the time from the date of the first administration of study drug to the date of death due to any cause.
- Safety and tolerability assessment of AEs, SAEs, physical examination, ECGs, and laboratory measurements.
- Pharmacokinetics assessment, including but not limited to steady-state trough plasma concentration C_{trough} .
- For the estimands of these secondary endpoints similar attributes apply specifically for DOR, PFS and OS. The censoring rules to account for intercurrent events are described in detail in section 6.3.

iii. Exploratory Endpoints

As described for Phase 1a (Section [iii](#)).

5. Statistical Methodology

5.1. Statistical and Analytical Issues

i. Statistical Methods

Statistical methodology and analyses are in accordance with the principles outlined by the ICH E9 (R1) guidelines. Statistical analyses will be carried out by using statistical analysis system (SAS) Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.

By-participant data listings will be produced for data collected through the study (e.g., case report form [CRF], PK, lab). All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

Tabulations will be produced for appropriate demographic, disease characteristic, baseline, exposure, safety, PK, and efficacy parameters. Unless otherwise stated in the analysis sections below, continuous variables will be summarized by reporting the number of observations, mean, standard deviation (STD), median, minimum (Min), maximum (Max) and first quartile (Q1) and third quartile (Q3). Categorical variables will be summarized using frequency tables showing the number and percentage of participants within a particular category. Time-to-event data will be

summarized using the Kaplan-Meier method, the number and percentage of participants with an event or censored, and the 25th percentile, median and 95% CI, and 75th percentile of the duration will be reported at a minimum. In addition, landmark survival at 6 months and 12 months will be presented as probability of survival and 95% CI.

Formal statistical hypothesis testing will not be performed for this Phase 1a/1b dose-escalation and expansion trial. Although exploratory confidence intervals (CIs) will be presented as described below, these data will be used for exploratory conclusions only.

All toxicities or adverse events will be graded by the investigator based on the NCI-CTCAE Version 5.0. Medical histories, prior anti-cancer procedure/surgery, and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Prior and concomitant medications, as well as prior systemic anti-cancer treatment will be coded using the World Health Organization (WHO) Drug Dictionary. The dictionary version will be presented in the footnote of the statistical outputs.

Baseline will be defined as the last evaluable/non-missing observation/assessment prior to the first dose of study drug.

ii. Dose Level, Study Part, and Group Assignment

Data from Phase 1a and Phase 1b will be tabulated separately and overall. Analyses will be presented by dose level for Phase 1a, and by group and dose level for Phase 1b. Analyses presentation for all Phase 1a and Phase 1b Safety Population participants who took the selected dose of 40 mg will also be done. Data from both Phases will be combined in tabulations and data listings.

For Phase 1a only, participants with intra-participant dose change will be summarized and listed on their initial dose level. For Phase 1b only, participants who were enrolled under protocol version 4.0 will be summarized and listed as a separate group.

iii. Visit Windows

All data will be tabulated per the evaluation visit as recorded on the electronic Case Report Form (eCRF), even if the assessment is outside of the visit window. For by visit summaries, data captured on EOT or Safety Follow-up visit will be mapped to protocol scheduled visits using the visit windows, wherever applicable. Visit windows specified in Protocol Tables 11 and 13 (Study Assessments and Procedures Schedule) will be used.

Unscheduled visits will not be presented in the by visit/timepoint summary tables but will be included in data listings. However, unscheduled data will be included in the “worst case post baseline” and “last post baseline assessment” summaries which will capture a worst case or last assessment across all scheduled and unscheduled visits after the first dose of study drug.

iv. Handling of Dropouts and Missing Data

Unless indicated otherwise, summary statistics will be reported for observed data only and missing data will not be imputed.

v. Pooling of Investigative Sites

As this is a Phase 1a/1b study, no by-site analyses are planned.

vi. Determination of Sample Size

No formal statistical calculation of sample size will be used, and the sample size is empirical.

The study plans to enroll

- Phase 1a: Up to 60 participants for the dose escalation until MTD and/or RP2D determination.
- Phase 1b: Approximately 72 participants will be treated to achieve 60 evaluable participants in the 2 groups (40 evaluable participants in Group 1 and 20 in Group 2). Groups 1 and 2 will be evaluated separately. Each group may be closed due to futility or clinical efficacy based on statistical evaluation or insufficient participant recruitment. If promising preliminary efficacy results have been observed in any of the arms after treating all planned participants (ie, higher ORR or longer PFS), more participants could be added to that arm to further assess the efficacy before moving into Phase 2/3 clinical development. This additional enrollment in the expansion cohort may occur only after the amendment to the protocol supporting this action is approved by the institutional review board (IRB) or the Ethics Committee.

5.2. Participant Characteristics

All participant characteristics analysis results will be presented for the Safety Population. For Phase 1a, presentation will be by dose level and overall, and for Phase 1b, by group, dose level, and overall. In addition, an overall presentation for all participants from both phases will also be done.

i. Participant Disposition

Participant disposition tabulation will include the following:

- Number of participants screened (i.e., who signed the informed consent)
- Number of participants failed screening
- Number of enrolled participants
- Number (%) in each participant population for analysis
- Number (%) of participants completed the study
- Number (%) of participants who discontinued from treatment / study and reason(s)
- Number (%) of participant survival status at data cutoff date (alive, dead, withdrawn consent, or lost to follow-up) for Phase 1b

** Percentages are based on the Safety Population.*

Phase 1a participants will be considered as having completed the study if the eCRF ‘End of Study’ page indicates completion for Phase 1a. For the Phase 1b participants, they will be considered as having completed the study once they complete the safety follow-up visit, or if they proceed to avail the post trial access of BGB-3245.

Participants excluded from the various analysis populations will be listed as well as the reasons for exclusion. All participant disposition data will be provided in a by-participant listing.

ii. Protocol Deviations

The number and percentage of participants with major protocol deviation will be presented. The determination of major protocol deviations will occur prior to database lock and analysis and will be based on the definition from ICH E6 (R2) or ICH E3 R1) Q&A “Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being”.

All protocol deviations will be provided in a by-participant listing with the categorization of minor or major.

iii. Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be presented. The following variables will be listed and summarized descriptively: Country (%), Age (years), Sex (%), Ethnicity (%), Race

(%), Height (cm), Weight (kg), Body Mass Index (BMI) (kg/m²), ECOG Performance Status (%), Alcohol Use (%), and Frequency of Alcohol Use (%).

iv. Prior and Concomitant Medications

Prior medication will be defined as any medication that stopped before the first administration of study medication. Concomitant medication is defined as any medication taken that (1) started before the first administration of study medication and were continuing at the time of the first administration of study medication, or (2) started on or after the date of the first administration of study medication up to 30 days after the participant's last dose.

Medications missing both start and stop dates or having a start date prior to 30 days after the participant's last dose and missing the stop date or having a stop date on or after the first administration of study medication and missing start date will be counted as concomitant.

Medications with partial stop date will be considered as concomitant if one of the following criteria is met, unless the start date is more than 30 days after the participant's last dose.

- 1) Stop date has month and year but day is missing, and the month and year of medication stop date is on or after month and year of treatment start date;
- 2) Stop date has year but month and day are missing, and the year of medication stop date is on or after year of treatment start date.

Prior and concomitant medications will be coded using the WHO Drug Dictionary, and participant incidence of concomitant medications will be tabulated by Anatomic Therapeutic Class (ATC) 2nd level and preferred term (PT) on Safety Population. Participants will be counted only once for each ATC or PT in case of multiple records of the same ATC or PT in the database.

Medications started more than 30 days after the participant's last dose, if any, will be considered as subsequent medications, and will be listed only.

All prior, concomitant, and subsequent medications will be included in a by-participant data listing using the Safety Population.

v. Medical Histories (Non-Cancer Related)

Medical history will be coded using MedDRA.

A by-participant data listing of medical history (non-cancer related) will be provided

vi. Cancer-Related Medical History

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior medication therapy, including start and stop dates, best response, and reason for discontinuation.

Descriptive statistics on cancer-related medical history characteristics will be presented for the following:

- Primary tumor site
- Solid tumor current stage
- Number of prior lines of systemic cancer therapy
- Time since initial cancer diagnosis in months = (Date of informed consent – Date of initial diagnosis)/30.4375
- Time since metastatic disease diagnosis in months = (Date of informed consent – Date of first metastatic disease)/30.4375
- Participants with prior anti-cancer surgery
- Participants with prior systemic anti-cancer therapy
- Participants with prior radiotherapy

And for the time calculation, if only month and year are provided, the day=1 will be assumed. If only year is provided, month=1 and day=1 will be assumed.

Cancer history data will be presented in data listings by group/dose level and participant.

vii. Anti-cancer Surgery, Systemic Anti-Cancer Treatment, and Radiotherapy

Prior anti-cancer procedure/surgery during treatment, coded using MedDRA coding system will be tabulated by SOC and PT. Similarly, prior systemic anti-cancer treatment, coded using WHO Drug, will be tabulated by ATC and PT. Systemic anti-cancer treatment after study treatment discontinuation will be listed only.

Prior radiotherapy and radiotherapy during treatment will be listed only for all participants in Safety Population.

viii. Treatment Exposure and Compliance

Study drug exposure will be presented descriptively. The number of cycles received will be summarized using both continuous and categorical descriptive statistics. In addition, the total cumulative dose (mg) as well as the average daily dose received and the duration of exposure will be summarized. The duration of exposure (months) will be calculated as (treatment end date or database cutoff date for ongoing participants – treatment start date +1) / 30.4375.

For Phase 1a, dose intensity will be presented for each cycle and for whole treatment period. For Phase 1b, dose intensity and overall study drug compliance will be presented for whole treatment period. Dose intensity and compliance will be calculated as follows:

- Dose intensity during whole treatment period will be calculated as: (total number of mg taken during treatment period) / (duration of exposure in days * initial assigned dose level at enrollment in mg)
- Cycle-specific dose intensity will be calculated as: (total number of mg taken during cycle) / (28 days * initial assigned dose level at enrollment in mg)
- Overall study drug compliance will be calculated as: (total dosed capsule quantity / total dispensed quantity)

For Phase 1a participants, duration of exposure doesn't include the 2-day treatment-free period in Cycle 1 when calculating compliance. Furthermore, study drug compliance and relative dose intensity (%) will be summarized descriptively as categories:

- Less than 80%
- 80% ~ 120%
- Greater than 120%

In addition, the number of participants with dose interruptions, reductions, and dose delays will be presented.

Day 1 for each cycle will be identified using the Visit eCRF and the total number of mg taken during each cycle will be calculated (for example, the total number of mg taken during Cycle 1 is the total of all doses recorded between Day 1 of Cycle 1 and the day before the first day of Cycle 2). Some participants may have less than or greater than the expected number of days (i.e., 28 days are expected for cycle compliance). Participants with discontinuation dates that fall within cycles will have their expected days adjusted in the compliance calculation for that cycle. For example, if a participant discontinues within Cycle 2, the expected number of days will be calculated based on the date of the last dose within Cycle 2.

All dosing data will be presented in a data listing for participants in Safety Population.

5.3. Efficacy Analysis

Generally, efficacy analysis results will be presented for all Efficacy Evaluable Population, unless stated otherwise. For Phase 1a, presentation will be by dose level and overall; for Phase 1b, by group, dose level, and overall. In addition, an overall presentation for participants from both phases will also be done.

PFS and OS will be analyzed using the Safety Population. ORR will be also be analyzed using Safety Population, if the number of participants in the Efficacy Evaluable and Safety populations differ.

For participants in both Phase 1a and Phase 1b, tumor imaging will be performed within 28 days prior to first dose of study drug, and while on study approximately every 8 (- 1) weeks in the first year and approximately every 12 (- 1) weeks thereafter. After the first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later (≥ 4 weeks) after the first response or at the next scheduled assessment time point. The primary analysis of efficacy will be based on confirmed responses, but the analysis of unconfirmed response will be provided as a secondary analysis. Participants who discontinue study treatment early for reasons other than radiographic disease progression (e.g., toxicity) will continue to undergo tumor assessments following the original plan until the participant begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

i. Tumor Response

Tumor response will be assessed by the investigators using RECIST v1.1 (Eisenhauer et al, 2009). For participants with ovarian cancer, tumor response will also be assessed by investigators based on Gynecological Cancer Intergroup CA-125 criteria. The investigator's assessment of the tumor response will be used for treatment decisions (continue vs. discontinue the treatment) in both phases of the study.

ii. Overall Response

The possible overall responses at a specific visit, from best to worst, are as follows.

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)

If no assessment is done or a response cannot be determined, it is designated as not evaluable (NE).

The date of the assessment of the overall RECIST response at a specific visit is defined as the earliest of the actual dates of the tumor assessment scan of the target lesions, non-target lesions, and new lesions at that visit.

Tumor response measured by RECIST including CA-125 criteria will be listed only, all efficacy endpoints will be derived using the tumor response data based on RECIST criteria.

iii. Best Overall Response

The confirmed BOR is the best response recorded from the start of the study drug treatment until the last tumor assessment considering any requirement for confirmation and will be derived based on the RECIST 1.1 guideline (Eisenhauer et al, 2009). For Phase 1a and 1b participants, BOR will be derived based on investigator reported overall time point response

Unconfirmed BOR is defined as the best response across all time points. A best response of SD requires the interval from first administration of study drug to SD to be at least 6 weeks (42 days). Classification of best confirmed response is done according to the following hierarchy and rules:

1. CR: requires two consecutive CR response assessments a minimum of 4 weeks (28 days) apart
2. PR: requires two consecutive PR response assessments OR a PR response immediately followed by a CR response assessment (a minimum of 4 weeks (28 days) apart)
3. SD: requires only one SD response assessment at a minimum interval (not less than 6 weeks (42 days))
4. PD: requires only one PD response assessment

The frequency distribution of unconfirmed and confirmed BOR will be presented with number and percentage of participants in each category (CR, PR, SD, durable SD (≥ 24 weeks) and PD)., ORR, DCR, and CBR will be presented with number and percentage of responders, as well as the 2-sided exact 95% CI using Clopper-Pearson method. Analysis in both Phase 1a and Phase 1b, responses are based on investigator assessment.:-

- ORR is defined as the proportion of participants who have confirmed CR or PR.
- DCR is defined as the proportion of participants with BOR of confirmed CR, PR, or SD.
- CBR is defined as the proportion of participants with BOR of confirmed CR, PR, or durable SD (SD lasting ≥ 24 weeks).

As part of RECIST 1.1, the sum of the diameters of all target measurable lesions will be recorded in eCRF. The maximum percent decrease from Baseline in sum of diameters in target lesions will be calculated for each participant, and a waterfall plot will present these percentages by participant.

All response assessments will be listed. The sum of the longest diameters, the decrease from baseline in sum of diameters as well as the percent decrease from baseline will be also listed.

iv. Duration of Response

DOR is defined as the time from the first determination of a confirmed objective response per RECIST v1.1 until the first documentation of progression or death due to any cause, whichever comes first. Participants who are alive and progression-free as of the analysis cutoff date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. This endpoint will only be evaluated for participants that have a confirmed BOR of CR or PR.

DOR data will not be tabulated and will only be presented in a by-participant listing.

v. Duration of Stable Disease

DSD is defined as the time interval, in the absence of either confirmed CR or PR, between the date of the first administration of study drug and the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurred first. Participants who are alive and progression-free as of the analysis cutoff date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. This endpoint will only be evaluated in participants not achieving a confirmed CR or PR.

DSD data will only be presented in a by-participant listing.

vi. Progression-Free Survival

PFS is defined as the time from the date of the first administration of study drug to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. PFS will be evaluated for all participants in Safety Population.

PFS in months will be analyzed using the same Kaplan-Meier methodology. The following table demonstrates how to determine the outcome with respect to censoring for PFS in various situations:

Table 2 Censoring mechanism for PFS

Hierarchy	Situation	Date of Event/Censoring	Outcome
1	Objectively documented PD	Date of assessment showing PD	Event
2	Death due to any cause (if no documented PD)	Date of death	Event
3	No baseline assessments	Date of first study drug administration	Censor
4	Treatment discontinuation with no PD	Date of last assessment	Censor
5	New anticancer treatment started with no PD beforehand	Date of last assessment prior to anticancer therapy	Censor
6	No death, PD, anticancer therapy, or treatment discontinuation	Date of last assessment	Censor

Abbreviations: PD=progressive disease

vii. Overall Survival (Phase 1b only)

OS is defined as the time from the date of first administration of study drug to the date of death due to any cause. Participants who remain known to be alive at the date of data cutoff will be censored at their date last known to be alive. Participants who are lost to follow-up will be censored at the date of last contact. OS will be evaluated for all participants in Safety Population.

The date of first dose, disease progression, death, last tumor assessment, last contact, and DOR, DSD, PFS, OS durations will be reported in data listings.

OS data will only be presented in a by-participant listing.

5.4.Safety Analysis

Safety assessments will include AEs, laboratory values, vital signs, physical examinations, ECOG Performance Status, Ophthalmologic Examination, and ECG. All safety analyses (other than DLTs) will be performed using the Safety Population..

All safety analysis results will be presented by dose level and overall for Phase 1a Safety Population. They will be presented separately for Phase 1b Safety Population by group, dose level,

and overall. In addition, an overall presentation for all Safety Population participants from both phases will also be done.

i. Adverse Events

Adverse events will be graded according to the NCI-CTCAE Version 5.0, coded using the MedDRA coding system, and displayed in tables and data listings by SOC and PT.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent (TEAE) is defined as any AE that started or worsened after the first dose of study treatment was taken, including those that occurred or increased in severity up to 30 days after the last dose of study treatment. A condition present at baseline that worsens after initiation of study treatment will be captured as an AE with the onset date as the date the event worsened.

The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will be excluded as being treatment-emergent only if the start month/year is before the month/year of study drug administration or if the stop date/time is before study drug administration.
- If the start day and month are missing but the start year is complete, an AE will be excluded as being treatment-emergent only if the start year is before the year of study drug administration or if the stop date/time is before study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before study drug administration.

For summaries by SOC and PT, a participant will be counted only once at the SOC level and once at each PT level within the SOC level, even if the participant experienced more than one AE within a specific SOC and PT. The summary tables will include the number and percentage of participants and the number of events.

An overall AE incidence summary table will be produced and will include:

- The number and percentage of participants reporting at least 1 TEAE
- The number and percentage of participants reporting at least 1 TESAE
- The number and percentage of participants reporting at least 1 BGB-3245-related TEAE
- The number and percentage of participants reporting at least 1 BGB-3245-related TESAE
- The number and percentage of participants reporting at least 1 TEAE with toxicity Grade 3 or higher
- The number and percentage of participants reporting at least 1 TEAE classified as a DLT (only for Phase 1a)

- The number and percentage of participants reporting at least 1 TEAE classified as an adverse event of special interest (AESI)
- The number and percentage of participants reporting a TEAE leading to treatment discontinuation
- The number and percentage of participants reporting a TEAE leading to dose reduction
- The number and percentage of participants reporting a TEAE leading to drug interruption
- The number and percentage of participants with a TEAE leading to death

Tabulations by SOC and PT will be produced for all TEAEs, TESAEs, BGB-3245-related TEAEs, BGB-3245-related TESAEs, TEAEs leading to discontinuation of study treatment, TEAEs with toxicity Grade 3 or higher, TEAEs classified as DLTs, TEAEs leading to dose reduction or drug interruption, and treatment-emergent AESIs. TEAEs will also be summarized by worst AE severity/grade and AE relationship to study treatment. Missing relationship is considered related to study treatment.

In addition, all TEAEs will also be summarized by PT in descending frequencies.

AESIs are defined as nonserious or serious AEs that are of scientific and/or medical concern specific to BGB-3245. AESIs for BGB-3245 are given in [Appendices 2](#). AESIs will be identified through programming based on the preferred terms and toxicity grade.

All AEs occurring on-study will be provided in data listings. Additional listings will be provided for serious AEs, AESIs, AEs leading to dose reduction or interruption and AEs leading to discontinuation of study treatment.

A by-participant listing of deaths will be presented.

For Phase 1a only, tabulation by SOC and PT will be produced for all DLTs using the DLT Evaluable Population. By-participant listings will also be provided for the DLTs.

ii. Laboratory Evaluations

Local laboratory assessments will be performed for serum chemistry, hematology, coagulation, and urinalysis (all parameters reported in [Table 3](#)) on the following protocol scheduled visits. Laboratory values will be graded according to NCI-CTCAE V5.0.

- Serum chemistry and hematology (except CPK and thyroid function testing): Screening; Day 1, 8, 15, and 22 (Phase 1b only) of Cycle 1; Day 1 and 15 of Cycle 2; Day 1 of Cycle 3 and subsequent cycles; and EOT/Safety Follow-up visit.
- CPK: Screening; Day 1, 4 (Phase 1a only), 8, and 15 of Cycle 1; Day 1 of Cycle 2 and subsequent cycles; and EOT visit.
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, and free T4): Screening; Day 1 of every 3 cycles thereafter starting with Cycle 4 (eg, Cycles 4, 7, 10, etc); and Safety follow-up visit.

- Coagulation and Urinalysis: Screening; and EOT/Safety Follow-up visit.

Values at baseline and change from baseline to worst case (worst decrease and/or worst increase) for the serum chemistry and hematology, parameters will be summarized descriptively and presented as stated in Section 5.4. Microscopy data, if available, will be listed only. All presentation of the results of tests in the different laboratory parameters will be based on results in the International System of Units (SI units); conversion will be performed prior to the transfer to SpringWorks Therapeutics.

Furthermore, shift from baseline to the worst case post baseline in CTCAE toxicity grade (decrease or increase) will be summarized for each serum chemistry and hematology parameter.

Laboratory results in original and SI units will be included in by-participant listings with values that fall outside of the normal ranges will be flagged as: H (High) and L (Low). Coagulation, urinalysis, and pregnancy test data will only be presented in by-participant listings.

Table 3 Clinical Laboratory Assessments

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	RBC count	Prothrombin time	pH
Alanine aminotransferase	Hematocrit	Partial thromboplastin time	Specific gravity
Aspartate aminotransferase	Hemoglobin	International Normalized Ratio	Glucose
Albumin	Monocyte count		Protein
Total bilirubin	Basophil count		Ketones
Blood urea nitrogen or equivalent (uric acid or urate)	Eosinophil count		Blood
Potassium	Platelet counts		
Sodium	WBC count with 5-part differential ^a		
Calcium	Neutrophil count		
Creatine phosphokinase	Lymphocyte count		
Creatinine ^b			
Glucose			
Lactate dehydrogenase			
Phosphate			
Total protein			
Testosterone ^c			

Thyroid-stimulating hormone			
free T3			
free T4			

Abbreviations: pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RBC, red blood cell; WBC, white blood cell.

- Both the absolute number and the proportion (%) of each cell type will be reported for the 5-part differential WBC.
- Creatinine will be used for calculation of creatinine clearance and estimated glomerular filtration rate using the equation provided in protocol Appendix 16.8.
- Testosterone test is only applied for participants with metastatic castration-resistant prostate cancer. However, the testosterone levels do not need to be checked if the participant has undergone surgical castration for > 4 months. Participants receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM).

iii. Vital Signs and Weight

Vital signs including temperature (°C/°F), heart rate (bpm), pulse oximetry (%), respiratory rate (breaths/min), and systolic and diastolic blood pressure (mmHg) will be collected at the following protocol scheduled time points.

- Phase 1a: Screening; pre-dose and at 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours post first dosing on Day 1 in Cycle 1; pre-dose and at 1, 2, 3, 4, 6, and 8 hours post first dosing on Day 1 in Cycle 2; pre-dose and post-dose on Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 15, Day 1 of Cycle 3 and each cycle thereafter, and EOT/Safety Follow-up.
- Phase 1b: Screening; Day 1, 8, 15, and 22 of Cycle 1; Day 1 and 15 of Cycle 2; Day 1 of Cycle 3 and each cycle thereafter; and EOT/Safety Follow-up.

Weight will be collected at Screening; Day 1 of each Cycle; and EOT/Safety Follow-up visit. Weight collected in unit lb will be converted to unit kg using formula $1 \text{ lb} = 2.20462 \text{ kg}$.

Vital signs, including weight, will be summarized descriptively as the value at each protocol scheduled time point and change from baseline.

In addition, vital signs and weight data will be listed for all participants in Safety Population.

iv. Physical Examination

A complete physical examination will be conducted at Screening, which includes an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.

Newly occurring or worsening clinically significant abnormalities identified on physical examination will be captured as AEs, and physical examination data will not be summarized nor

listed separately. Physical examination at Screening will be listed for all participants in Safety Population.

v. 12-Lead Electrocardiogram

ECG assessments will be performed in triplicate at the following timepoints.

- Phase 1a: Screening; pre-dose and at 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours post first dosing on Day 1 in Cycle 1; pre-dose and at 1, 2, 3, 4, 6, and 8 hours post first dosing on Day 1 in Cycle 2; pre-dose on Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, and Day 1 of Cycle 3 and each cycle thereafter; and EOT/Safety Follow-up.
- Phase 1b: Screening; pre-dose and at 1- and 3-hour post-dose on Day 1 of Cycle 1 and Cycle 2; pre-dose on Day 1 of Cycle 3 and each cycle thereafter; and EOT/Safety Follow-up.

For each time point, triplicate ECG recordings must be taken in close succession and not more than 2 minutes apart (total up to 4 minutes for 3 ECGs in a triplicate). The average of the triplicate values for ECG parameters heart rate (bpm), RR interval (msec), PR-interval (msec), QT-interval (msec), QRS-complex (msec), corrected QT interval by Bazett's formula (QTcB) interval (msec), and corrected QT interval by Fridericia's formula (QTcF) interval (msec) will be used for table summary, and the original triplicate values will be presented in the data listing.

ECG data will not be tabulated and will only be presented in a by-participant listing.

In addition, the categorical analysis of QTc outliers (number [%] of maximum individual absolute QTc values and maximum individual QTc change from baseline) will be presented according to the ICH E14 guideline. The summarization of outliers refers to the categories below.

Maximum post Baseline QTc interval prolongation:

- QTc interval ≤ 450 msec
- QTc interval > 450 msec and ≤ 480 msec
- QTc interval > 480 msec and ≤ 500 msec
- QTc interval > 500 msec

Maximum change from baseline in QTc interval:

- QTc interval increases from baseline ≤ 30 msec
- QTc interval increases from baseline > 30 msec and ≤ 60 msec
- QTc interval increases from baseline > 60 msec

vi. Evaluation of ECOG Performance Status

ECOG performance status ([Table 4](#)) will be assessed at Screening, on Day 1 of each treatment cycle, the EOT visit, and the Safety Follow-up visit.

ECOG performance assessments will not be tabulated and will only be presented as by-participant listing in Safety Population.

Table 4 ECOG Performance Status (Oken, 1982)

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, Light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

vii. Ophthalmological Examination

Full ophthalmic assessment, including the visual acuity, intraocular pressure, slit lamp examination, and retinal assessment, should be performed at Screening, every 8 (minus 1) weeks during the first year and every 12 (minus 1) weeks thereafter as well as at the EOT visit.

In case the result of the ophthalmologist's exam is abnormal in only one eye, then the result will be classified as abnormal for the overall eye exam.

The results of the eye examination will not be tabulated and will only be listed by participant, and by eye, for each method (visual acuity, intraocular pressure, slit lamp, dilated funduscopy, optical coherence tomography [OCT]).

5.5. Pharmacokinetics Analysis

One of the secondary objectives of this study is to evaluate the PK profile of BGB-3245 after single and multiple doses. These analyses will be performed based on the PK Concentration and PK Parameter populations and presented for Phase 1a by dose level, and by enrollment indication group and dose level for Group 1 within Phase 1b. The PK Parameter Population will be used for the PK parameter calculations, graphical displays of individual data and the listings of PK parameters, and for all other listings and summarization of PK parameters. Participants with missing PK parameters due to unreliable or missing data will be flagged and excluded from summarization.

5.5.1. Data Handling

i. BLQ

For the calculation of concentration summary statistics: All BLQ values will be set to zero.

For the PK parameter analysis: BLQ values will be set to zero except BLQ values which are between quantifiable concentrations. The pharmacokineticist will review the BLQ value between quantifiable concentrations for imputation of zero on a case-by-case basis.

ii. Handling of Missing Concentrations

A minimum of 3 quantifiable concentrations is recommended to report AUC. If they are all BLQs, AUC will be reported as zero, $C_{\max}$ will be zero and $T_{\max}$ will not be determined.

For PK parameter calculations, missing pre-dose values will be imputed as zero concentrations.

No imputation will be performed for missing post-dose plasma concentrations, and they will be treated as missing. Unless otherwise noted, summary statistics of concentrations will be calculated on non-missing data.

iii. Emesis

Data from subjects who experience emesis at or before 2 times the median $t_{\max}$ among participants at the specific dose level following oral administration will be flagged in the listing and excluded from summary statistics for the concentrations and PK parameters that affected by emesis at the specific visit.

iv. Time Deviations (NOTE: Time Deviation Table to be considered for mock)

If the actual time of blood collection deviated by >10% from the nominal time, these sample concentrations will be flagged as time deviations in the listing. The samples with collection time deviated >20% from the nominal time will be excluded from the concentration summary statistics tables and mean figures and PK parameter summary statistics tables.

v. Incomplete Dosing Information

The samples associated with missing dose dates or times may be imputed using nominal collection times

vi. Missing Sampling Dates and/or Times

Missing actual sampling times may be imputed using nominal collection times.

vii. Changes from Planned Dosing

Subjects with a dose deviation >20% will be excluded from the calculation of summary statistics for concentrations and PK parameters. Such profiles will be included in the PK analysis and individual profiles will also be presented.

In the case where subjects were dosed with study drug but discontinued from the study (early termination), the concentration data will be reported in the concentration tables and included in all summary statistics

viii. Protocol Deviations

The PK concentrations that are impacted by major deviations will be flagged in the listing and excluded from the concentration summary table and mean figures.

The PK parameters that are impacted by major deviations that interfere with absorption, distribution, metabolism and excretion of BGB-3245 will be flagged in the listing and excluded from the PK parameter summary table and mean figures.

ix. Other Data Considerations

After database lock, a visual inspection of concentration-time profiles will be performed to determine dataset integrity and potential outliers. Descriptive statistics of parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by the pharmacokineticist for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

- For single dose administration (the first dose of BGB-3245 in Phase 1a), non-zero pre-dose concentration values will be identified in the study report and included in the computation of PK parameters if the value is not greater than 5% of C_{max} . Subject PK profiles with non-zero pre-dose concentration values greater than 5% of C_{max} will be reviewed by the pharmacokineticist for inclusion/exclusion from the PK analysis on a case-by-case basis.
- Pre-dose concentrations will be excluded from the data summaries and graphs if samples were drawn post-dose.
- Post-dose concentrations will be excluded from summary statistics and NCA analysis if they are taken predose.
- Multiple observations at the same time point will be averaged for the calculation of parameters.
- Any concentrations that cannot be uniquely and unequivocally attributed to a particular subject, treatment, or day and/or time point based on case report form (CRF) records or other observed data records in the study will be treated as incomplete data. Such data will be compiled, commented, and listed separately in the appendix of the report. Incomplete

and/or non-compliant data, if any, will be excluded from analysis datasets; no analyses, summaries or graphs will be produced using these data.

- Profiles and PK parameters of subjects that had increase, interruption or reduction of scheduled doses will be presented but may be excluded from the calculation of summary statistics if >20% dose deviation.
- In the case where subjects were dosed with study drug but discontinued from the study (early termination), the concentration data and PK parameters will be reported in all summary statistics.

5.5.2. PK Parameter Calculations

For the final PK analysis, all PK parameter calculations will be performed using actual sampling times calculated relative to the start of study drug administration in hours. If actual sampling time is not available, nominal sampling times will be used for PK parameter calculation. The sampling time of pre-dose samples relative to dosing will be set to zero. PK parameters will be determined using noncompartmental (NCA) methods based on individual plasma concentration-time data for BGB-3245

The area under the concentration vs. time curve (AUC) will be calculated using the linear/log trapezoidal method. PK parameters will not be calculated for profiles with less than three quantifiable concentrations.

PK parameters will be calculated using a qualified installation of Phoenix® 8.4.0 or later.

The following plasma PK parameters will be derived for BGB-3245 for Phase 1a during Day 1, Day 2, Day 3, Day 4, and Day 15 of Cycle 1 and Day 1 of Cycle 2, 3, and 4, as appropriate:

Parameter	Definition	Method of Determination
AUC _{0-inf}	Area under the concentration-time curve from dosing extrapolated to infinity. $AUC_{inf} = (AUC_{last} + C_{last}/K_{el})$ where C_{last} is the plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and K_{el} is the terminal elimination phase rate constant estimated by linear regression based on observations justified to describe the terminal phase on the log-linear concentration-time profile.	Linear/Log trapezoidal method

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time curve from dosing to time of last quantifiable concentration	Linear/Log trapezoidal method
$AUC_{last,ss}$	Area under the plasma concentration time curve from dosing to time of last quantifiable concentration at steady state	Linear/Log trapezoidal method
AUC_{tau}	Area under the concentration-time curve at steady state from dosing time to time tau (tau=24 hours)	Linear/Log trapezoidal method
CL/F	Apparent oral clearance	Dose/ AUC_{0-inf}
Vz/F	Apparent oral volume of distribution	Dose/($AUC_{0-inf} * k_{el}$)
$t_{1/2}$	Apparent terminal elimination half-life	$Ln2/k_{el}$
C_{max}	Maximum observed plasma concentration	Observed directly from data
C_{trough}	Predose observed concentration	Observed directly from data For Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 4 Day 1.
$C_{max,ss}$	Maximum observed plasma concentration at steady state	Observed directly from data
T_{max}	Time of maximum observed concentration	Observed directly from data
$T_{max,ss}$	Time of maximum observed concentration at steady-state	Observed directly from data

For Phase 1b, only C_{trough} will be obtained for BGB-3245:

Parameter	Definition	Method of Determination
C_{trough}	Pre-dose observed concentration	Observed directly from data. For Day 8 and Day 22 of Cycle 1, Cycle 2 Day 1 and subsequent cycles on Day 1.

5.5.3. Calculation of Terminal Elimination Rate Constant

The terminal elimination rate constant (k_{el}) will be calculated by log-linear regression of the drug concentrations in the apparent terminal elimination phase of the concentration-time profile. The points used in the k_{el} calculation will be automatically selected by Phoenix WinNonlin, manually adjusted as required, and verified by visual inspection of the concentration-time curve. A minimum of the 3 time points with quantifiable concentrations

(the first point must be after $T_{\max}$ so that $C_{\max}$ will not be included) will be used in the k_{el} regression.

Parameters derived from the terminal elimination phase will be reported if they pass the following reporting criteria:

- a positive terminal elimination rate constant ($k_{el} > 0$); and
- the adjusted coefficient of determination (R^2_{adj}) for the log-linear regression of k_{el} is ≥ 0.80

No value for k_{el} and other k_{el} -related parameters (e.g., $AUC_{0-\infty}$, $t_{1/2}$, CL/F , and V_z/F) will be reported for concentration profiles that do not exhibit an elimination phase in the concentration versus time profile (i.e., if $R^2_{adj} < 0.8$ for the log-linear regression analysis of k_{el}).

If the extrapolated portion of $AUC_{0-\infty}$ from T_{last} to infinity ($\%AUC_{extrap}$) for a subject is greater than 20%, the estimated $AUC_{0-\infty}$ value will be flagged when listed in the report. If the $\%AUC_{extrap}$ is greater than 40%, the estimated $AUC_{0-\infty}$ value will not be included in the calculation of summary statistics.

5.5.4. Presentation of PK Data

i. PK Concentration Data

Individual PK concentration data will be listed by participant, time point, part, group (for Phase 1b only), and cycle with day and dose level. A summary of concentrations by part, group (for Phase 1b only), and cycle with day and dose level and nominal time post dose, where the set of statistics include n , mean, median, standard deviation, coefficient of variation (CV), minimum, maximum and the number of concentrations above the lower limit of quantification.

For individual PK concentration, and summary, the following rules will apply:

- BLQ will be displayed in individual listings
- All concentration values that are BLQ will be set to zero while summarizing the concentration
- The sampling time of pre-dose samples relative to dosing will be treated as zero
- Drug concentrations will be summarized by nominal time point
- All concentrations will be presented in original units as reported by the Bioanalytical lab, e.g., ng/mL
- No further imputation will be applied to any missing values.

The following figures will be produced for Phase 1a PK:

1. Individual participant profiles of the plasma concentration-time data of BGB-3245, will be plotted using actual times for Cycle and Day. Overlay of all participants will be presented by separating each figure with dose level. These profiles will be presented on both linear-linear and log-linear scales.
2. Mean $\pm$ SD participants profiles of the plasma concentration-time data of BGB-3245 will be plotted using nominal times by dose level for Cycle and Day. Dose level for mean figure will be plotted in same figure. These profiles will be presented on both linear-linear and log-linear scales.
3. Individual participant trough (predose) profiles of the plasma concentration-time data of BGB-3245 will be plotted. Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 predose concentration will be considered. Overlay of all participants will be presented by dose level. These profiles will be presented on linear-linear scales only.
4. Mean trough (predose) concentration $\pm$ SD participants profiles of the plasma concentration-time data of BGB-3245 figure will be plotted. Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 pre-dose concentration will be considered. Dose level for mean figure will be plotted in same figure. These profiles will be presented on linear-linear scales only.

The following figures will be produced for Phase 1b PK:

1. Individual participant profiles of the plasma concentration-time data of BGB-3245 will be plotted using actual times for Cycle and Day. Overlay of all participants will be presented by group, and dose information. These profiles will be presented on both linear-linear and log-linear scales.
2. Mean $\pm$ SD participants profiles of the plasma concentration-time data of BGB-3245 will be plotted using nominal times by dose level, and group for Cycle and Day. Group with dose information for mean figure will be plotted in same figure. These profiles will be presented on both linear-linear and log-linear scales.
3. Individual participant trough (predose) profiles of the plasma concentration-time data of BGB-3245 will be plotted. Cycle 1 Day 8, Cycle 1 Day 22, Cycle 2 Day 1, and subsequent cycles on Day 1 pre-dose concentration will be considered. Overlay of all participants will be presented by group, and dose information. These profiles will be presented on linear-linear scales only.
4. Mean trough (predose) concentration $\pm$ SD participants profiles of the plasma concentration-time data of BGB-3245 will be plotted. Cycle 1 Day 8, Cycle 1 Day 22, Cycle 2 Day 1, and subsequent cycles on Day 1 pre-dose concentration will be considered. Group with dose

information for mean figure will be plotted in same figure. These profiles will be presented on linear-linear scales only.

Note: For individual and mean plots, all concentration values that are BLQ will be set to zero.

ii. PK parameter Data

PK parameters will be summarized using the following descriptive statistics.

Parameter	Summary Statistic
AUCs, C _{max} , CL/F, V _z /F,	sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), median, minimum (Min), maximum (Max), geometric mean and geometric CV%.
T _{max}	sample size (n), median, minimum (Min), maximum (Max)
t _{1/2}	sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), median, minimum (Min), maximum (Max)

Note: n = non-missing No. of observations

iii. Reporting Rules

Individual concentration values will be reported at the level of precision as received in the source data file. Individual PK parameters will be reported with 3 significant figures, except for T_{max} and T_{last} which are parameters of time that will be reported with 2 decimals.

Unless otherwise noted, data summaries will only include observed data.

Reporting rules for the summary statistics will be as follows:

- N: integer
- Mean and geometric mean: 1 more decimal/significant digit than the individual value
- SD: 1 more decimal/significant digit than the mean
- CV% and Geometric CV%: always 1 decimal
- Median, Min, Max: same number of decimals/significant digits as the individual value

5.6. Interim Analysis

Not Applicable.

5.7. Changes to Methods Planned in the Protocol

- For Safety analysis, shift from baseline summary will be based on Toxicity grade per the SAP and mockup shell, while in protocol the shift categories is within normal limits,” “high,” and “low”.
- The secondary analyses of best overall tumor responses based on central review are not done because central reviews were not performed.
- Changes between the planned analyses from SAP Version 1 to SAP Version 2 are summarized in Section 10 Change History Summary.

6. Tables, Listings, And Figures

6.1. Programming Guidelines

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of SpringWorks Therapeutics will be followed in the creation and quality control of all tables, listings, and figures.

6.1.1. Format of Output

Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: at least 1.25 inches on top (the binding margin [or left for portrait output]), at least 1 inch on right, left, and bottom. All output should have the Sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table). All output should have the following header at the top of the page:

Sponsor Name Protocol XXXXXXXX	Confidential	Page n of N
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1. Output numeration will conform to International Conference on Harmonization (ICH) recommendations. The study population should be identified immediately following the title.
2. Column headings should be in initial upper-case characters.
3. For numeric variables, include “unit” in column or row headings where appropriate.

4. Footnotes should be single spaced but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table.
5. If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 participant represented in 1 or more groups should be included.
6. An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more participants.
7. Listings should be sorted by dose levels and participant numbers.
8. In a listing, display the participant number only once for the participant with multiple records. If a participant's records run into multiple pages, display the participant number once for every page.

6.1.2. Format of Data

1. Unless otherwise specified for continuous variables, the estimated mean, standard deviation and median for a set of values should be printed out to 1 more significant digit than the individual units of measurement. The minimum and maximum should report the same significant digits as the original values.
2. Data in columns of a table should be formatted as follows:
 - Alphanumeric values are left-justified.
 - Whole numbers (e.g., counts) are right-justified.
 - Numbers containing fractional portions are decimal aligned.
3. Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than signs "<0.1%" should be printed when values are >0.0 and <0.1% (not 0.0%).
4. Missing data should be represented on participant listings as either a hyphen ("–") with a corresponding footnote ("– = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.
5. Dates should be printed in SAS DATE9.format ("DDMMYY": 01JUL2000). Missing portions of dates should be represented on participant listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the participant are output as "N/A", unless otherwise specified.
6. Time should be printed in SAS TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on participant listings as dashes (--:30). Times that are

missing because they are not applicable for the participant are output as “N/A”, unless otherwise specified.

7. References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-247.

ICH Guideline. E9 Statistical Principles for Clinical Trials.

ICH Guideline. E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.

ICH Guideline. E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs - Scientific guideline.

ICH Guideline. E18 Guideline on genomic sampling and management of genomic data.

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials*. 2010;7(6):653-663.

Kaplan EL, Meier P. 1958. Nonparametric estimation of incomplete observations. *J Am Stat Assoc* 53:457-481.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-55.

BGB-3245-AU-001_SMC Meeting Minutes_22 Jun 2021.

8. Appendices

Appendix 1: BGB-3245-AU-001_Mockup TLF Version 2.0.docx

Appendix 2: Adverse Events of Special Interest for BGB-3245

Musculoskeletal (reported as AESI if Grade $\geq$ 2)
Rhabdomyolysis
Myalgia
Muscular weakness
Muscle spasms
Musculoskeletal (reported as AESI if Grade $\geq$ 3)
Creatine phosphokinase increased
Cardiac Disorders (reported as AESI if Grade $\geq$ 2)
Atrial fibrillation
Cardiac failure
Renal Disorders (reported as AESI if Grade $\geq$ 2)
Acute kidney injury
Skin Disorders (reported as AESI if Grade $\geq$ 3)
Drug-induced hypersensitivity
Angioedema
Rash
Rash acneiform
Rash maculopapular
Hepatic Disorders (reported as AESI if Grade $\geq$ 3)
Aspartate transaminase increase
Alanine transaminase increase
Hematological Disorders (reported as AESI if Grade $\geq$ 2)
Platelet Count Decreased/Thrombocytopenia
Constitutional (reported as AESI if Grade $\geq$ 2)
Pyrexia
Respiratory Disorders (reported as AESI if Grade $\geq$ 2)
Pneumonitis

Abbreviations: AESI = Adverse Event of Special Interest.

9. SAP Version History

Version	Effective Date	Changes	Author / Modified by
1.0	05-May-2023	NA	[REDACTED]
2.0	19-May-2025	See summary below	[REDACTED]

10. SAP Change History Summary

Version	Modifications
1.0	Initial Version
2.0	References to Syneos were removed. The TEAE is defined as any AE that started or worsened after the first dose of study treatment was taken, including those that occurred or increased in severity up to 30 days after the last dose of study treatment. Tabulations of results will be presented by study overall, in addition to by-phase presentation. Because of the planned abbreviated CSR, the following changes to analyses from SAP Version 1 had been made: • Medical histories (non-cancer related) will not be tabulated and will be presented only in a by-participant listing. • Main efficacy endpoints for tabulation will only be ORR and PFS. • For laboratory parameter analyses, descriptive statistics will be presented for values and change from baseline to worst post-baseline time point only serum chemistry and hematologic parameters. Shift tables from baseline to worst post-baseline time point will also be presented only for serum chemistry and hematologic parameters. • Coagulation and urine analyses will not be tabulated and will only be presented in by-participant listings. • Tabulation of vital signs identifying potentially clinically significant values will not be performed. • No separate PK SAP will be drafted. All calculations and considerations for PK calculations were included in this revised SAP. In addition, the PK Concentration Population and PK Parameter Population were defined for use in the PK analyses. • Section 5.4.9 on “Pharmacodynamic and Biomarker Analysis” has been deleted.