Statistical Analysis Plan

BerGenBio ASA

Protocol: BGBC004

IND Number: 124645

Investigational Product: BGB324

A Multi-Center Open-Label Phase 1/2 Study of BGB324 in Combination with Erlotinib in Patients with Stage IIIb or Stage IV Non-Small Cell Lung Cancer

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Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute myeloid leukemia
APTT	Activated Partial Thromboplastin Time
Ara-C	Cytosine arabinoside
AST	Aspartate Aminotransferase
BM	Bone marrow
BP	Blood Pressure
bpm	Beats per minute
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
°C	Celsius
CI	Confidential Interval
cm	Centimeter
CRF	Case Report Form
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
HR	Heart rate
INR	International Normalized Ratio
IWG	International Working Group
kg	Kilogram
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mmHg	millimeter of mercury
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
NA	Not Applicable
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective response rate
PD	Pharmacodynamic, Progressive Disease
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumours version

RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation, Stable Disease
STLM	Sum of Target Lesion Measurements
SMC	Safety Monitoring Committee
TEAE	Treatment-Emergent Adverse Event
TTP	Time To Progression
WHO	World Health Organization
WBC	White Blood Cells

1 Introduction

This document presents the statistical analysis plan (SAP) for BerGenBio ASA, Protocol No. BGBC004: A Multi-Center Open-Label Phase 1/2 Study of BGB324 in Combination with Erlotinib in Patients with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC). This Statistical analysis plan (SAP) is based on the final protocol dated 16 May 2017 (Version 5.0).

This study is designed primarily to evaluate the safety of the Axl inhibitor BGB324 when administered as monotherapy, and to establish the recommended Phase 2 dose (RP2D) of the combination of BGB324 and erlotinib in patients with Stage IIIb or Stage IV NSCLC.

2 Study Objectives

2.1 Run-In Cohort (Phase 1)

2.1.1 Primary Objective

To explore the safety and tolerability of single agent BGB324 in patients with NSCLC.

2.2 Arm A (Phase 1)

2.2.1 Primary Objective

- To identify the RP2D of BGB324 administered in combination with erlotinib in patients with NSCLC

2.2.2 Secondary Objectives

The **secondary objectives** are:

- To explore the safety and tolerability of BGB324 administered in combination with erlotinib in patients with NSCLC.
- To identify the dose limiting toxicity (DLT) profile of BGB324 administered in combination with erlotinib in this population.
- To assess the pharmacokinetics (PK) of BGB324 and erlotinib and the potential effect of BGB324 on erlotinib.

2.2.3 Exploratory Objective

- To evaluate the pharmacodynamics (PD) effects of BGB324 administered in combination with erlotinib.

2.3 Arm B (Phase 2)

2.3.1 Primary objective

- To explore the safety and tolerability of the combination of BGB324 and erlotinib in patients with NSCLC with an activating Epidermal Growth Factor Receptor (EGFR) mutation and who have progressed after receiving an approved EGFR inhibitor (i.e., prior erlotinib, afatinib or gefitinib).

2.3.2 Secondary Objectives

The **secondary objectives** are:

- To assess the PK of BGB324.

- To explore the clinical efficacy of the combination of BGB324 and erlotinib in this setting.

2.3.3 Exploratory objectives

The **exploratory objectives** are:

- To evaluate the PD effects of BGB324 administered in combination with erlotinib.
- To investigate any correlation between the PD effects of BGB324 administered in combination with erlotinib and clinical efficacy.

2.4 Arm C (Phase 2)

2.4.1 Primary Objective

- To explore the safety and tolerability of the combination of BGB324 and erlotinib in the first-line setting in patients with advanced NSCLC with an activating EGFR mutation.

2.4.2 Secondary Objectives

- To explore the time to progression of the combination of BGB324 and erlotinib in this setting.

2.4.3 Exploratory Objectives

The **exploratory objectives** are:

- To evaluate the PD effects of BGB324 administered in combination with erlotinib.
- To investigate any correlation between the PD effects of BGB324 administered in combination with erlotinib and clinical efficacy.

3 End-points

3.1 Safety End-points

Safety and tolerability will be assessed by conducting the following safety assessments at pre-defined time-points during the study:

- Treatment emergent adverse events (TEAE)
- Physical examination
- Vital signs including blood pressure (BP), heart rate (HR)
- Electrocardiogram (ECG) or multi-gated acquisition (MUGA) scan
- 12-lead triplicate ECG
- Clinical laboratory parameters including clinical chemistry, hematology coagulation and urinalysis
- Eastern Co-operative Oncology Group (ECOG) performance status

The primary objective of Arm A is to identify the RP2D of BGB324 administered in combination with erlotinib in patients with NSCLC. This will be accomplished by evaluation of the safety and occurrence of DLTs at each dose level.

AEs will be assessed using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 criteria during the first cycle (21 days) of treatment for the purposes of establishing the dose of BGB324 that can safely be given in combination with erlotinib.

DLTs will include:

- Any non-hematological toxicity ≥Grade 3 except Grade 3 nausea, vomiting or diarrhea that resolves within 72 hours with optimal therapy;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.
- Grade 4 neutropenia persisting for ≥5 days or Grade 3 or 4 febrile neutropenia.
- Treatment discontinuation or dose reduction for >72 hours during the first cycle as a result of treatment-related toxicity.

A patient must receive all loading doses and miss no more than 3 daily doses in Cycle 1 (21 day cycle of treatment) to be considered as informative to support dose escalation, unless the inability to administer BGB324 was a result of treatment-related toxicity.

If 1 patient in a cohort experiences a DLT during Cycle 1, the cohort will be expanded to 6 patients. If 2 of 3 or 2 of 6 patients in a cohort experience DLT, no further dose-escalation will take place and the prior dose level will be nominated as the RP2D (see section 8.3.2 of the protocol).

3.2 Efficacy End-points

Disease assessment will be performed after every two cycles (6 weeks) of treatment prior to administering study drug in the subsequent cycle. The frequency of scans may be extended to the end of every three cycles after 12 weeks (4 cycles) and every 4 cycles after 24 weeks (8 cycles). Patients who remain on treatment for 12 months or longer may have their scans extended to a frequency of 6 months, unless disease progression is suspected in which case a scan should be conducted at an earlier time point.

Clinical efficacy will be assessed using the Response Evaluation Criteria in Solid Tumors

(RECIST) Version 1.1. Clinical efficacy endpoints will include time to progression.

3.2.1 Objective Response Rate (ORR)

Patients included in the study must be assessed for response to treatment, Overall Response (OR) determined by Investigator based on appropriate radiographic imaging and consistent with RECIST 1.1.

Each patient will be assigned to one of the following ordered categories for OR (from best to worst responses): Complete response (CR), Partial response (PR), Stable disease (SD), Progressive disease, Not Evaluable (NE) or Not Applicable at each timepoint.

The Best Overall Response (BOR) is determined once all the data for the patient is known and is defined as the best overall response recorded from the initiation of treatment until disease progression or date of subsequent therapy across all tumour assessment.

ORR defined as percentage of patients with a BOR assessed as CR or PR, i.e. patients with response, divided by the number of patients in efficacy population.

The one-sided, within-group tests of proportion of responders, against the null hypothesis of a response rate ≤5% (this being the observed response rate under current treatment). Values of p <0.2 will be taken as sufficient evidence of a trend to justify further study.

For analysis of the ORR, summary tables will be generated, presenting the number and percentage of responders (i.e. patients with CR or PR) and non-responders in efficacy population.

3.2.2 Best Percentage change in target lesion

Percentage change in target lesion size from baseline across all tumour assessment, where target lesion size is measured by the sum of the product of diameters of all target lesion sizes by the Investigator.
The Best percentage change is largest percentage change across all tumour assessment.

Patients who die due to progression of their disease prior to the first planned protocol assessment of response will be considered as having BOR of PD.

The first response assessed during the follow-up period will be used to confirm any previous CR or PR observed during the treatment period, provided that no new anti-tumoral treatment has been initiated during the follow-up period.

3.2.3 Time To Progression (TTP)

- The Time to Progression (TTP) will be calculated as the number of days from the date of first administration of BGB324 to the date of radiological progression of disease first observed, according to the overall response evaluation (progressive disease, measurement proven or progressive disease, symptomatic deterioration). If a subject died without any radiological assessment, the progressive disease date is date of death;

Patients who do not have progressive disease at the end of study or withdrawal will have their TPP censored. In these patients, the censoring date is defined as the last date on which progression status was assessed. Censoring general rules for TTP are provided within Table 1 below.

Table 1: Censoring Rules for TTP

Reason for censoring	**Rule**
No baseline evaluable or post-baseline radiological assessment	Date of first treatment administration
Two or more not evaluable (NE) protocol specified assessments, i.e. scheduled assessments, before progressive disease	Date of last evaluable disease protocol specified assessment before the second protocol specified NE assessment
No progressive disease	Date of last evaluable radiological assessment
Treatment discontinuation for undocumented progression	Date of last evaluable radiological assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable radiological assessment

* An assessment is considered NE when no imaging/measurement is done at all at a particular time point, or only a subset of lesion measurements are made at the time point. The participant is considered NE at that time point.

3.3 Pharmacokinetic End-points

Pharmacokinetic analysis will be managed by Bergen Bio then will not be part of this SAP.

3.4 Pharmacodynamic End-points

Pharmacodynamic analysis will be managed by Bergen Bio then will not be part of this SAP.

4 Study Design

4.1 Discussion of Study Design

This is a multi-center open-label Phase 1/2 study of BGB324 as a single agent (Run-in Cohort) and in combination with erlotinib (Arms A, B and C) in patients with Stage IIIb or Stage IV NSCLC.

At time of amendment 5, patient recruitment into the Run-In cohort (BGB324 monotherapy) and Arm A (BGB324 dose escalation in combination with erlotinib) has completed and the RP2D has been confirmed. Patients that remain on treatment in the Run-In cohort or Arm A must be followed up in accordance with the protocol schedule.

This study is anticipated to be conducted at approximately 10 sites in the US and in Europe (the number of sites and the involvement of European sites may be revised to reflect changes in recruitment rates), and will enroll up to approximately 60 patients with histologically- or cytologically-confirmed Stage IIIb or Stage IV NSCLC.

It is anticipated that up to six patients will be enrolled in the Run-in Cohort, 18 patients in Arm A, up to 25 patients in Arm B, and up to 14 patients in Arm C. Recruitment into Arm C may be stopped if Arm B completes recruitment or is stopped before the 14 patient target is reached. Patients already enrolled into Arm C at that time will be allowed to continue in the study in accordance with the protocol.

Prior to starting dosing of BGB324 in combination with erlotinib, the safety and tolerability of single agent BGB324 will be assessed in the Run-in Cohort (Phase 1) in patients who have either exhausted existing licensed therapies or are unsuitable for existing licensed therapies

for NSCLC. A minimum of 6 patients must each receive at least 1 continuous 21-day cycle of BGB324 before enrolment into Arm A can commence.

Arm A (Phase 1) incorporates a standard 3+3 design to determine the dose of BGB324 that can be safety administered in combination with erlotinib in patients who have received prior treatment with erlotinib. To confirm the RP2D for Arms B and C, loading dose schedules, loading doses and daily dose levels will be explored in Arm A. Dosing schedules will be revised in response to reported toxicities, DLT experience and SMC recommendations (Table 4 of the protocol).

When the RP2D dose of BGB324 is identified and the dose of erlotinib to be administered in combination with BGB324 is confirmed, the Phase 2 part of the study will start and Arms B and C will open simultaneously to enrolment.

Arm B will incorporate a two-stage design to evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics and clinical activity of BGB324 in combination with erlotinib in patients with an activating EGFR mutation (including exon 19 deletion or exon 21 [L858R] substitution or other rearrangement of the EGFR gene) who are T790M negative and who have progressed after receiving treatment with an approved EGFR inhibitor (i.e. erlotinib, afatinib or gefitinib). Patients who have previously been treated with a T790M inhibitor (i.e. osimertinib) and who subsequently progressed will not require T790M testing.

Arm C will evaluate the safety and tolerability, PD and clinical activity (time to progression) of BGB324 when administered in combination with erlotinib in patients with an activating EGFR mutation (including exon 19 deletion or exon 21 [L858R] substitution or rearrangement of the EGFR gene mutation) who have received ≥12 weeks treatment with erlotinib without disease progression.

In all parts of the study, BGB324 will be self-administered orally according to a daily schedule during continuous 21-day treatment cycles.

Erlotinib will be self-administered orally according to a daily schedule during continuous 21-day treatment cycles (Arms A, B and C only).

Both drugs will be taken with water in the morning. BGB324 should be administered in the hour following erlotinib administration and at least 2 hours before breakfast.

Patients will be allowed to continue BGB324 treatment (as a single agent or in combination with erlotinib) if, in the opinion of the Investigator, they continue to derive clinical benefit or until unacceptable toxicity, disease progression, death or withdrawal of consent. Patients who stop BGB324 treatment will be withdrawn from the study.

An outline of the study design is provided in Figure 1.

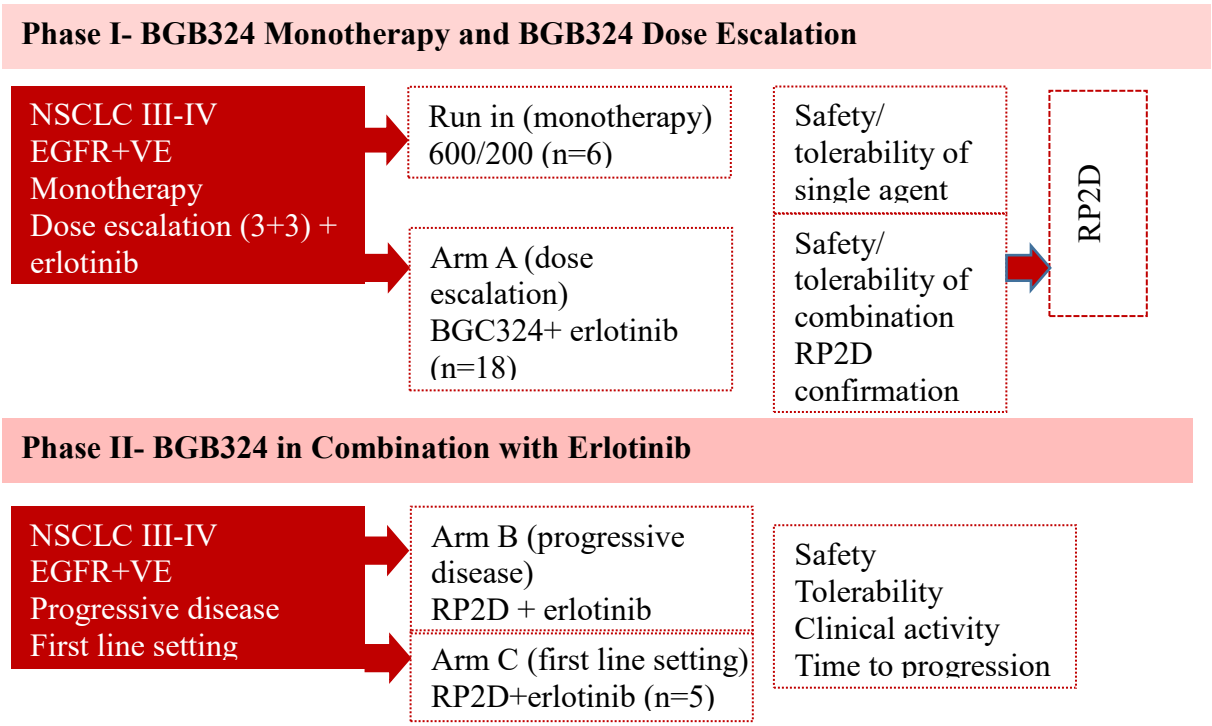

Figure 1: BGB004 study Design Outline

4.2 Study Treatment

BerGenBio ASA will provide BGB324 to each study site.

Erlotinib will be obtained and administered following institutional practices.

4.2.1 Treatment Schedule and Administration of BGB324

BGB324 will be self-administered orally on an empty stomach according to a daily schedule during continuous 21-day treatment cycles.

The BGB324 dose will be based on the cohort and study arm to which the patient is enrolled. BGB324 should be administered with water in the morning at least 2 hours before breakfast and best efforts should be made to administer BGB324 at the same time each day, other than study visit days when BGB324 should be administered during the visit.

Patients will record their dosing at home in a dosing diary that will be reviewed at each study visit by the site staff. Patients will be instructed as to the importance of following the dosing instructions they have been provided with and for maintaining an accurate and up-to-date dosing record. Patients will also be instructed to bring their dosing diary and all BGB324 bottles, including unused and empty bottles, with them to each study visit. The site staff will record the amount of used and unused BGB324 capsules at study visits.

4.2.2 Treatment Schedule and Administration of Erlotinib

Erlotinib will be self-administered orally with BGB324 on an empty stomach according to a daily schedule during continuous 21-day treatment cycles. Best efforts should be made to administer erlotinib in the morning at the same time each day, other than on the morning of study visit days when erlotinib should be administered during the visit. Erlotinib should be administered with water. Patients will be instructed to take their erlotinib dose first followed by BGB324 within the next hour.

Patients will record their dosing at home in a dosing diary that will be reviewed at each study visit by the site staff. Patients will be instructed as to the importance of following the dosing instructions they have been provided with and for maintaining an accurate and up-to-date dosing record. Patients will also be instructed to bring their dosing diary and all boxes of erlotinib, including unused and empty boxes, with them to each study visit. The site staff will record the amount of used and unused erlotinib at study visits.

The details for management of dose modification are specified in the protocol section 11.3.

4.3 Study Schedule

The study period will consist of screening, treatment and an end-of-study visit. The end-of-study visit will occur 28 days after the patient has discontinued BGB324 treatment.

A detailed Schedule of Events can be found in the study protocol, Section 10.

Table 2 provide the study schedule.

4.3.1 Screening

Patient eligibility for the study will be determined within 28 days prior to the first dose of BGB324 (Cycle 1 Day 1). Screening assessments will be conducted according to the study protocol Section 10.1.1 and Table 5.

In Arm B, the screening period may be extended to accommodate T790M confirmation from tumor biopsy Patients who have previously been treated with a T790M inhibitor (i.e., osimertinib) and who subsequently progressed will not require T790M testing. All other assessments including scans should be conducted in the 28-day screening period.

4.3.2 Treatment

Eligible patients will visit the study site to receive study drug and protocol-specified procedures according to Section 10.1.2 to Section 10.1.4 and Table 5 of the protocol. The treatment period will consist of continuous 21-day treatment cycles.

All patients will be carefully monitored throughout Day 1 to Day 4 in Cycle 1 and will attend the clinic on Cycle 1, Day 8, Cycle 1, Day 9 and Cycle 1, Day 15 (and Day -1 in Arms A).

Patients will attend the clinic once per week (on Cycle 2, Day 1, Cycle 2, Day 8 and Cycle 2 Day 15) during Cycle 2 and then once per cycle (on Day 1) thereafter up to 12 months of treatment (Cycle 17). Patients who remain on study after 12 months will attend the clinic every 2 Cycles (6 weekly).

Patients who do not receive loading doses as assigned but are considered suitable for daily dose treatment should attend the clinic for additional ECG assessments. Twice weekly triplicate ECGs should be conducted during Cycle 1, Day 8 – Day 15 and Cycle 1, Day 15 – Day 21.

Additional visits will be scheduled for disease assessment at the end of every two cycles (6 weeks) cycles. The frequency of scans may be extended to the end of every 3 cycles after 12 weeks (4 cycles) and every 4 cycles after 24 weeks (8 cycles). Patients who remain on study for 12 months or longer may have their scans extended to a frequency of 6 months unless disease progression is suspected in which case a scan should be conducted at an earlier time point.

Patients will continue to receive BGB324 (in combination with erlotinib or as a single agent) for as long as, in the opinion of the Investigator, they continue to derive clinical benefit or until disease progression, unacceptable toxicity, death or withdrawal of consent.

In the event of erlotinib-related toxicities in Arms A, B and C, patients may be allowed to continue receiving BGB324 as a single agent until disease progression unless unacceptable toxicity, death or withdrawal of consent). Patients who stop BGB234 treatment will be withdrawn from the study.

4.3.3 End of Study Visit

Patients will return to the study site for an end-of-study visit 28 days after the last dose of study drug (or at study withdrawal) according to Section 10.1.5 and table 5 of the protocol.

If BGB324-related toxicities continue beyond this follow-up period, patients will be followed until all BGB324-related toxicities have resolved to ≤Grade 1, stabilized or returned to baseline. If necessary, follow-up monitoring for AEs may be conducted over the telephone.

Table 2 Schedule of Events

Cycle		1											2							W ≥ 3			End-of-
Week		1(x)						2(x)			3(x)		4(x)		5(x)		6(x)			>7			28 days after last dose
Cycle Day	28 to 0 Screening	-1 Arm A	1	2	3	4	5-7	8	9	10-14	15	16-21	1	2-7	8	9-14	15	16-20	21	1	2-20	21	
Visit window (+/-) days		0	0	0	0	0	0	0	0	0	0	0	+2	0	+1	0	+1	0	+-5	+2	0	+5	+7
Clinic visit	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		**X**		**X**		**X**		**X**			**X**		**X**	**X**
Informed consent	X																						
Demographics	X																						
Medical history	X																						
Cancer history and treatments	X																						
Inclusion/Exclusion	X																						
ECOG performance status	X												X							X			X
Physical examination[a]	X[a]	X	X					X			X		X		X		X			X			X[a]
Vital signs[b]	X	X	X	X	X	X		X	X		X		X		X		X			X			X
12-Lead triplicate ECG[c, v]	X	X	X	X	X	X		X	X		X		X		X		X			X			X
Pregnancy test[d]	X	X[e]	X																	X			X
Clinical chemistry[f]	X	X[e]	X	X	X	X		X			X		X		X		X			X			X
Hematology[g]	X	X[e]	X	X	X	X		X			X		X		X		X			X			X
Coagulation[h]	X	X[e]	X					X			X		X							X			X
Urinalysis[i]	X	X[e]	X					X			X		X		X		X			X			X
echocardiogram or MUGA scan[t]	X																			X			X
PK blood sampling[j]		X	X	X	X	X		X	X		X		X		X		X			X			X
Tissue collection for PD[l, m,k,q]	X										X												X[r]
Blood collection for PD[m, l,k]	X										X												X[s]
EGFR T70M status (Arm B)	X[u]																						

Disease assessment[p,n]	X																		X			X	X

Abbreviations:; ECOG=Eastern Co-operative Oncology Group; MUGA=multi-gated acquisition; PD=pharmacodynamics; PK=pharmacokinetics

a. Physical examination conducted at the screening and end-of-study (EOS) visits. A symptom-directed examination will be conducted at other visits.
b. Blood pressure, pulse, respiratory rate, temperature. In addition, at screening, weight and height to be recorded.
c. Triplicate 12-lead ECG, at least 5 minutes apart, after resting for ≥10 minutes in supine position during screening and during each visit (pre-dose). Patients who re-start BGB324 following interruption for QTc prolongation should also have ECGs performed according to this schedule.
d. For women of child-bearing potential to be repeated every 3 months, or if possibility of pregnancy is identified. A serum test must be performed at screening and the EOS visits; interim tests may be performed on urine samples.
e. Unless conducted as part of the screening procedures within 3 days prior to Day 1.
f. Clinical chemistry laboratory parameters: potassium, calcium, uric acid, electrolytes, blood urea nitrogen, total protein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, creatinine, creatine phosphokinase, alkaline phosphatase, albumin, phosphorus, glucose, magnesium (plus amylase and lipase during screening ONLY).
g. Hematology laboratory parameters: full blood count including differential white cell count, hemoglobin, hematocrit and platelets.
h. Coagulation parameters: prothrombin time and/or international normalized ratio, activated partial thromboplastin time.
i. Dipstick measurement of blood, nitrite, glucose, ketones, leukocytes, protein and pH. (Microscopic analysis is not required unless clinically indicated).
j. Blood sampling for the determination of BGB324 / erlotinib in plasma will be collected in accordance with Table 6.
k. In consenting patients (Arms A, B and C), tissue specimens may be collected for analysis of pharmacodynamics endpoints of Axl inhibition. The baseline tissue specimen should be collected after enrollment within 28 days before the first dose of BGB324. The on-study tissue collection may be performed any time after 14 days of continuous exposure to BGB324 in Cycle 1 or in Cycle 2. The EOS tissue collection should be made at the time of disease progression and prior to the end-of-study visit (derived from the lesion exhibiting disease progression). Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the laboratory manual.
l. Blood will be collected for analysis of pharmacodynamic endpoints of Axl inhibition. The baseline sample should be collected after enrollment within 28 days before the first dose of BGB324. The on-study sample collection may be performed any time after 14 days of continuous exposure to BGB324 in Cycle 1 or in Cycle 2. The EOSEOS sample should be taken at the time of disease progression and prior to the EOS-visit.
m. If a tissue specimen is being collected, the PD blood sample should be collected at the same visit.
n. Disease assessment via RECIST Version 1.1.
o. BGB324 and erlotinib (not Run-in Cohort) will be administered on an empty stomach. Both drugs will be taken with water in the morning. BGB324 should be administered in the hour following erlotinib administration and at least 2 hours before breakfast (except on those days when the patient attends the clinic). Patients should record dosing in the dosing diary provided.
p. Disease assessment will be performed at the end of every 2 cycles (6 weeks) beginning with Cycle 2 (Day 21); the assessment may be performed up to 5 days before Day 21 (Day 17-Day 21) but attempts should be made to conduct the assessment as close to Day 21 as possible. Disease assessment may be performed prior to initiation of the next cycle, but results must be available prior to initiation of treatment and must confirm continued eligibility for next cycle. The frequency of scans may be extended to the end of every three cycles after 12 weeks (4 cycles) and every 4 cycles after 24 weeks (8 cycles). Patients who remain on study for 12months may have their scan frequency reduced to 6 monthly.
q. For consenting patients´ only (Arms A, B and C); performed any time after documentation of disease progression and prior to EOS visit. The tissue specimen should be derived from a lesion exhibiting progression.
r. If not performed within previous 28 days.
s. To be performed at the time of disease progression and prior to the EOS visit.
t. Cycle 4 Day 1 and then at 6 monthly intervals and at EOS.
u. Patients in Arm B must have EFGR T790M status confirmed during screening – Patients who have progressed on osimertinib and have previously progressed on an approved EGFR inhibitor i.e. afatinib, gefitinib) will not require additional T790M testing. T790M testing may be confirmed by blood test or biopsy. Samples collected and analyzed according to local procedures. The screening window of 28 days may be extended to allow for confirmation of T790M status.

v. Patients who do not receive their assigned loading doses and continue to receive daily dose BGB324 should attend the clinic for additional ECG assessments between C1 D8 and D15 and between C1 D15 and the end of Cycle 1.
w. Patients who remain on study post C17 will have a reduced visit schedule and will return to clinic every 2 cycles (+/-7 days)
x. Patients receiving BGB324 who require daily steroids at doses of 10mg to 40mg (prednisolone equivalent) should be monitored at weekly intervals until the steroid dose level is less than 10mg: Assessment should include physical exam, vital signs, hematology, chemistry.

4.4 Concomitant Medication

4.4.1 Prior and Concomitant Therapies

No additional treatment for NSCLC may be taken during the study period.

Previous adjuvant therapy is permitted provided it has been completed for ≥6 months.

Previous radiotherapy for cerebral metastases is permitted providing this is complete for ≥2 weeks before the first dose of study drug (BGB324 or Erlotinib whichever comes first) provided the patient is neurological stable and does not require corticosteroids.

4.4.2 Concomitant Medication and Procedures

All prescription, non-prescription, or over-the-counter medications, including herbal remedies, taken by the patient at entry and during the study must be clearly documented in the eCRF.

The patients must be instructed that no additional medication will be allowed without the prior consent of the Investigator. Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator.

Hematopoietic growth factors may be administered for the treatment of AEs such as neutropenic infections but should not be used to maintain the dose intensity of BGB324 in the Run-in Cohort or Arm A.

Patients who have evidence of treatment benefit after ≥1 cycle (21 days) of treatment in Arms B or C may receive hematopoietic growth factors to maintain BGB324 dosing.

Concurrent treatment with any agent known to cause Torsade de Points is an exclusion criterion for the study. A comprehensive list of these prohibited medications is provided in Appendix 3 of the protocol.

Anti-diarrheal medications (e.g. loperamide) may be administered according to standard practice for the management of diarrhea. Patients must be provided with anti-diarrheal medications to take home, which may be used if required.

Patients being treated with antacid histamine receptor 2 inhibitors or proton pump inhibitors on study entry will be excluded. The Investigator may initiate rescue treatment with these medications during the study, providing they are taken in the evening.

Patients receiving BGB324 who require the support of prednisolone (or equivalent) at 10mg to 40mg daily should be monitored at weekly intervals whilst receiving treatment. If a patient requires prednisolone (or equivalent) at daily doses above 40mg then BGB324 should be interrupted until the steroid dose is equivalent or less than 40mg daily, at which time weekly monitoring will be undertaken until the steroid dose is equivalent or less than 10mg.

Steroid restrictions do not apply to topical/ inhaled/ eye or nasal drops. If required, additional advice on the concomitant use of steroids with BGB324 should be obtained from the BerGenBio Medical Monitor.

4.5 Study Analysis Populations

There will be 3 analysis populations defined for the study analyses:

4.5.1 Enrolled Population

The Enrolled Population will include all patients who have signed the ICF and enrolled into the study (Enrolment date being defined as the date of the first protocol-defined screening procedure).

4.5.2 Safety Population

The Safety Population will be defined as all enrolled patients who receive at least one dose of BGB324 or Erlotinib.

4.5.3 Efficacy Population

The Efficacy Population will include all patients who receive ≥1 cycle of BGB324 and undergo an assessment of response post-baseline.

Patients who on review do not meet the protocol inclusion/exclusion criteria or have a major protocol deviation may be excluded from the efficacy analysis. This will be reviewed (and documented) on a per patient basis at the pre-database lock meeting.

4.6 Withdrawn Subjects

Patients may withdraw informed consent and discontinue from the study at any time, or for any reason, without prejudice to their future treatment.

The reason for the patient's withdrawal from the study must be recorded in the eCRF.

A patient must be discontinued from the study if any of the following criteria are met:

- Patient non-compliance with the protocol, as agreed by the Investigator and the Sponsor.
- Patient lost to follow-up.
- Termination of the study by the Sponsor.
- Subject experiences an unacceptable toxicity that precludes continuation in the study, as agreed by the Investigator and the Sponsor.
- Lack of recovery from a DLT to Grade 0 or 1 within 14 days of occurrence.
- Female patient becomes pregnant.
- Disease progression.

4.7 Randomisation

This is a non-randomized study.

4.8 Blinding

This is an open-label study and consequently there are no blinding procedures in operation.

4.9 Sample Size

Run-in prior to commencing dosing of BGB324 in combination with erlotinib, the safety and tolerability of single agent BGB324 will be assessed in a minimum of 6 patients. The safety data from the first cycle in these 6 patients will be reviewed by the safety monitoring committee (SMC) before enrolment into Arm A can commence.

Arm A will utilize a conventional algorithm 3+3 dose escalation algorithm for phase I cancer trials (3+3 patients per dose level) to identify the dose of BGB324 that can be safely given in

combination with erlotinib. Escalation between dose levels will occur if 0/3 or 1/6 patients experiences a DLT. Under this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20% and <50% chance of escalation if the true but unknown rate of DLT is >30%. The operating characteristics of this 3+3 design are outlined in.

Table 3: Operating Characteristics of the 3+3 Study Design

True but Unknown Rate of DLT (%)	Probability of Escalation (%)
20	71
30	49
40	31
50	17
60	8

It is anticipated that a maximum of three BGB324 dose levels will be evaluated, with up to approximately 18 patients enrolled. The total sample size in Arm A will depend upon whether DLT(s) is experienced at a given dose level (i.e., whether 3 or 6 patients have been treated) and how many dose levels are tested in order to reach the dose that can be safely administered in combination with erlotinib.

Arm B will follow a Simon-like two-stage design with relaxed stopping for futility to evaluate the safety and tolerability, pharmacodynamics and clinical efficacy of BGB324 in combination with erlotinib in patients with an activating EGFR mutation(s) (including exon 19 deletion or exon 21 [L858R] substitution or rearrangement of EGFR gene mutations) who have progressed after or gefitinib). The null hypothesis (H0) that the true response rate is 0.05 receiving a prior EGFR inhibitor (i.e. erlotinib, afatinib, will be tested against a 1-sided alternative. In the first stage, 9 patients will be accrued. If the number of patients with response (complete response or partial response) after 2 cycles or stable disease after 4 cycles is equal to zero in these 9 patients, the study will be stopped. Otherwise, 16 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 4 or more responses are observed in 25 patients. Assuming that the stable disease rate has a uniform distribution under H0, this design yields a type I error rate of at most 0.73 and power of at least 0.0367 when the true response rate is 0.2.

Arm C will evaluate the safety, pharmacodynamics and clinical efficacy (time to progression) of BGB324 when administered in combination with erlotinib in patients with activating EGFR mutation(s) (including exon 19 deletion or exon 21 [L858R] substitution or other rearrangement of the EGFR gene mutations) who have received ≥12 weeks of erlotinib without disease progression. Up to 5 patients will be enrolled. Arm C will recruit up to a maximum of 14 patients. Recruitment into Arm C may be stopped if Arm B completes recruitment or is stopped before the 14 patient target is reached. Patients already enrolled into Arm C will be allowed to continue in the study in accordance with the protocol. A statistical analysis is not planned and it is anticipated that an assessment of general activity will be derived from the enrolled patients; further assessment will require protocol amendment.

5 Statistical Methodology

5.1 Planned Analyses

Disposition analyses will be carried out using the Enrolled Population. Demographic and baseline characteristics analyses will be carried out using the Safety Population. Safety analyses will be carried out using the Safety Analysis Population. Efficacy analyses will be carried out using the Efficacy Population.

Summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum (Min) and maximum (Max) and by way of group frequencies and percentages for categories of categorical variables. No statistical comparison of dose levels will be performed. Percentages will be calculated using the total subjects per dose cohort in the given population unless otherwise noted.

All data from this study will be presented in data listings. Unless otherwise noted, listings will be sorted by cohort dose level and subject.
Baseline is the most recent assessment prior to the first dose of a study drug (BGB324 or erlotinib)administration, i.e within 28 days before the first dose of study drug and after patient eligibility has been confirmed. Typically, this will be Cycle 1 Day 1 or screening. Where calculated, absolute change from baseline will be presented using the following formula for each parameter: Value at the visit/timepoint – value at baseline.

Data will be presented by dose/cohort and overall.

5.2 Interim Analysis

No formal statistical interim analyses are planned, however, data will be monitored by the Safety Monitoring Committee (SMC) to assess patient safety for Run-in cohort before enrolment into Arm A can start and for dose escalation within Arm A.

5.3 Disposition of Subjects

The number of subjects receiving study treatment in each analysis population and the reasons for any discontinuation from the study will be summarized by treatment arm.

5.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarized. This will include age, age group, sex, ethnicity, race, height, weight, and Eastern Cooperative Oncology Group (ECOG) performance status at screening. Cancer history (Histologic Diagnosis, Stage at initial diagnosis, Stage at screening and sites), medical history by system organ class and preferred term, Mutation status and prior cancer therapies (chemotherapy, hormonal therapy, immunotherapy, monoclonal therapy, radiotherapy, other therapy, surgery) will also be summarized.

Notes:

- Age (years) will be calculated as (Date Informed Consent - Date of Birth + 1)/365.25.
- Age groups are defined as: <65 years and ≥65 years of age.
- Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 or above.
- Prior cancer therapies will be coded using World Health Organization (WHO) Drug Dictionary, Mar 2014 or above.

5.5 Concomitant Medication

Medications taken on or after date of informed consent are collected. Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose.

Incidence of concomitant medication will be presented therapeutic area and preferred drug name. Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant. Medications will be coded using WHO Drug Dictionary, Mar 2014 or above.

5.6 Exposure and Compliance

BGB324 exposure will be summarized by the number of cycles started on BGB324/Erlotinib and duration of administration by dose cohort. Duration (days) of BGB324/Erlotinib administration will be defined as:

Date of Last Study Drug Administration – Date of First study Drug Administration + 1 day

Total treatment exposure to BGB324/Erlotinib will also be characterized by total cumulative dose (mg) over the whole study and summarized by dose cohort.

Study drug percent compliance for BGB324/Erlotinib will be calculated as:

((Expected number of doses – Missed number of doses) / Expected number of doses) * 100,

where Expected Number of Doses is defined as duration of study drug administration in days at each cycle, i.e 21 days;

Missed number of doses will be calculated as Last date of missed - First Date Missed;

Overall percent compliance will be summarized by frequency count and percentage of subjects with compliance <80%, 80 to 120% and >120%. Overall percent compliance will also be summarized as a continuous variable using descriptive statistics.

5.7 Efficacy Analysis

Although all efficacy analysis for this study is to be regarded as essentially exploratory, there will be formal hypothesis tests (Arm B only).

For Arm B, the data relating to efficacy response will be listed and summarized by time point, as appropriate.

For Arm C, the data relating to time to progression will be summarized/analyzed and listed by time point, as appropriate.

5.7.1 Normality assumption checking

Not Applicable (NA).

5.7.2 Closed testing procedure for primary analysis

As the analyses of the efficacy endpoints are essentially exploratory in nature no adjustments for multiple comparisons will be made.

5.7.3 Method of analysis for efficacy outcome

5.7.3.1 Objective Response Rate (ORR)

Response criteria for target lesions and non-target lesions (see Section 3.2) will be evaluated at each disease assessment and will be presented in a data listing by subject.

In addition, the presence/absence of new lesions will be collected at each disease assessment and will be presented in a data listing by subject.

The investigator will evaluate the target/non-target lesion response criteria and status (presence/absence) of new lesions against the RECIST Version 1.1 criteria to determine overall response for the appropriate disease assessment time point.

Although all efficacy analysis for this study is to be regarded as essentially exploratory, there will be a formal hypothesis test for the objective response rate here (Arm B only). Specifically, for a given disease assessment time point we denote subjects who achieve a CR or a PR Best overall response. The null hypothesis is that the proportion of objective responders (i.e., the ORR) is less than or equal to 5%. The alternative hypothesis is that the proportion of objective responders is greater than 5%. The binomial test will be used to conduct the hypothesis test at the one-sided significance level of 0.2.

Overall response and the ORR will be presented within a data listing by subject and time point.

Best overall Response (BOR) will also be listed.

The number and percentage of each BOR class will be described by cohort.

Moreover, the Sum of Target Lesion Measurements (STLM) will be analyzed from relative changes from baseline and graphically displayed with waterfall plot in order to visualize changes in sum of lesion without differentiating best response categories.

Best response to therapy will be defined as the Best Changes from Baseline in Sum of Target lesions measurement for a patient during the study.

The Best Percentage change in STLM will be calculated as, STLM =100*(Value of STLM – Baseline value STLM)/Baseline value STLM;

In case of several post baseline assessments of STLM the one with the lowest change (i.e., showing the best diminution of sum of lesions relative to baseline) will be considered.

5.7.3.2 Time to progression (TTP)

For Arm C only, the TTP will be calculated as the time from first administration of BGB324 or Erlotinib to either progressive disease as follows:

TTP (in months) = [(Date of event – date of first administration) + 1]/30.4375

For censored participants, the TTP will be calculated as follows:

TTP (in months) = [(Censored date – date of first administration) + 1]/30.4375

TTP will be analyzed descriptively for Arm C patients.

The Kaplan-Meier approach will be used to estimate TTP. The number and percent of subjects with progression, number and percent of subject censored, and median time to progression – along with its corresponding 95% confidential Interval – will be presented.

Kaplan-Meier Survival curves will be presented for TTP.

5.8 Safety Analysis

No formal statistical analysis will be performed on safety data. Summary statistics by treatment groups and timepoint will be produced.

The safety endpoints will consist of treatment-emergent adverse events, serious adverse events, physical examinations, vital signs, ECOG, ECG, Echocardiograms, and laboratory tests (clinical chemistry, hematology and urinalysis).

5.8.1 Adverse events

The AE reporting period will begin following the first dose of BGB324 (Run-in Cohort) or erlotinib (Arms A, B and C) and will end 28 days after the last dose of BGB324.

The number and percentage of patients reporting TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and summarized by CTCAE grade and relationship to study drug. All AEs commencing prior to dosing with study medication will be excluded from the tabulation but will be fully listed.

A subject with more than one occurrence of the same adverse event in a particular system organ class will be counted only once in the total of those experiencing adverse events in that particular system organ class. If a subject experiences the same adverse event at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. For example, if the event of multiple occurrences of the same adverse events being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related> not related) will be chosen.

Any missing severity, causality, or outcome will not be imputed and classed as unknown.

An overall summary classifying subjects with events according to seriousness, severity, maximum relationship to BGB324, and maximum CTCAE grade will also be presented.

Related events are defined as events that are ticked as suspected by investigator in eCRF .

Treatment-Emergent AEs are any AEs that start or worsen after first dose of study drug regardless of causality. AEs with partial onset dates will be assumed to have the latest possible onset date (while accounting for stop date) for determining treatment emergence, but no formal imputation will be done. AEs that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of study drug (BGB324 or Erlotinib whichever comes first).

5.8.1.1 Subsets

- Related (BGB324) adverse events will be presented by treatment, system organ class and preferred term.
- Related (Erlotinib) adverse events will be presented by treatment, system organ class and preferred term. (Arm A, Arm B and Arm C).
- Serious adverse events will be presented by treatment, system organ class and preferred term as:
    - Related (BGB324) serious adverse events will be presented by treatment, system organ class and preferred term.
    - Related (Erlotinib) serious adverse events will be presented by treatment, system organ class and preferred term.
    - Serious adverse events will be presented by treatment group, system organ class, preferred term, and maximum CTCAE grade.
- Adverse events leading to discontinuation will be presented by treatment group, system organ class and preferred term.

- Adverse events ≥ Grade 3 will be presented by treatment group, system organ class and preferred term.
- The most frequent MedDRA preferred terms (≥10% subjects in the overall safety population) and system organ class will be presented by treatment group.
- Separate listings will be produced for DLTs, SAEs, related AEs, discontinuations due to AEs, and events of ≥ Grade 3 severity.

All other information collected (e.g. action taken) will be listed as appropriate.

Notes:

- AEs coded using MedDRA version17.0 or above.

5.8.2 Physical Examination

Any post-baseline new or worsened physical examination findings during the safety evaluation period will be recorded as AEs and summarized in terms of AEs as described in Section 5.8.1. Both the complete physical examination performed at screening and the symptom directed physical examination results will be presented in data listings.

5.8.3 Vital Signs

Results for systolic and diastolic blood pressure (mmHg), pulse rate (bpm), respiration rate (BREATHS/MIN), and temperature (°C) will be summarized by dose cohort and scheduled visit, as well as the corresponding change from Baseline.

Weight (kg) and Height (cm) at screening will be summarized and listed with other vital signs data.

5.8.4 Eastern Cooperative Oncology Group

ECOG performance status will be summarized categorically at each scheduled visit with frequencies and percentage.

5.8.5 Electrocardiograms

Twelve-lead ECG triplicate will be collected the mean of the values will be analysed. In case, only one assessment is collected this value will be considered, if 2 or 3 assessments are performed the mean of available should be calculated.

The quantitative ECG assessments (PR interval (ms), RR interval (ms), QRS Duration (ms), QT interval (ms), and QTcF interval (ms)) will be summarized for actual values and change from Baseline to each visit/timepoint will be also presented.

ECG overall interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be presented as a categorical summary by treatment groups and scheduled visit.

Any post-baseline new or worsened echocardiogram findings during the safety evaluation period will be recorded as AEs and summarized in terms of AEs as described in Section 5.8.1.

All echocardiogram data, including MUGA scan results will be presented in a data listing.

5.8.6 Laboratory findings

Results from the following laboratory parameters, recorded at scheduled visits, will be presented in listings:

Hematology:

Hemoglobin, Hematocrit, Red Blood Cells (RBC), White Blood Cells (WBC), Absolute Neutrophil Count, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes and Platelets.

Coagulation:

Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR), and Quick Test.

Chemistry:

Sodium, Potassium, calcium, chloride, magnesium, phosphorus, creatine phosphokinase (CPK), creatinine, total protein, total bilirubin, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, uric acid, blood urea nitrogen (BUN), Bicarbonate (CO2), electrolytes, amylase and lipase (during screening ONLY).

Urinalysis:

pH, semi-quantitative "dipstick" evaluation of Proteins, Glucose, Ketones, Blood, Nitrite, Leukocytes, Bilirubin, Bacteria, Casts, Crystals, RBC, and WBC.

Numeric Hematology and Chemistry parameters will be summarized along with each corresponding Change from Baseline for all scheduled visit by dose cohort. The incidence of laboratory test results outside the normal range will be listed by dose cohort and time point.

Clinically significant treatment-emergent laboratory findings will be summarized as adverse events.

Notes:

- All results outside predefined normal ranges will be flagged in the data listings.
- Repeat laboratory results within a visit will not be used in any summary calculations. Unscheduled and repeat results will be listed only
- Serum Pregnancy Test results will be listed.
- All other laboratory results will be listed only.

5.9 Pharmacokinetic Analysis

The Pharmacokinetic (PK) Analysis will be conducted separate by BergenBio from this analysis. Details will be found in a specific analysis plan. Subjects included in PK population can be identified in the clinical datasets.

5.10 Pharmacodynamic Analysis

The Pharmacodynamic Analysis will be conducted separate from this analysis. Details will be found in a specific analysis plan.

5.11 Protocol Deviations

Deviations from the protocol will be documented on an ongoing basis by the study monitors and project manager throughout the study period.

At the time of database lock, prior to unblinding and while the protocol deviations are being reviewed, the project manager will forward all relevant documentation highlighting protocol deviations to the study statistician. These deviations will be included in the protocol violation document for agreement and will be listed with the protocol violations in the CSR.

5.12 Missing Values – Missing Visits

Missing, unused and spurious data will be considered missing at random and dealt with as such. There is no intention to implement any procedure for replacing missing data.

5.13 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report, whether written post interim or final analysis.

5.14 Changes in Conduct or Planned Analyses from the Protocol

There have been no other changes in analyses from those defined in the protocol.

5.15 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 …varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std *Q1=q1 Q3=q3;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need life table with estimates of survival, with CIs:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
    BY treatment;
    TIME duration*censor (0 or 1);
RUN;
```

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1/binomial (p=.05) alpha=0.05;
    EXACT BINOMIAL;
RUN;

PROC FREQ data=dset order=freq;
  TABLES var / binomial(ac wilson exact) alpha=.05;
  WEIGHT Count;
run;
```

6 Tables and Listings

6.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

6.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in parenthesis to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, subject and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

6.1 Tables

6.1.1 Section 14.1: Demographic and baseline

Table 14.1.1.1	Subject Disposition (Enrolled Population)
Table 14.1.1.2	Important Protocol Violations (Enrolled Population)
Table 14.1.2	Demographics (Safety Population)
Table 14.1.3	Cancer History (Safety Population)
Table 14.1.4	Medical History (Safety Population)
Table 14.1.5	Prior Cancer Therapies (Safety Population)
Table 14.1.6.1	Prior Medications (excluding anti-cancer therapies)
Table 14.1.6.2	Concomitant Medications (Safety Population)
Table 14.1.7.1	Summary of Exposure to BGB324 (Safety Population)
Table 14.1.7.2	Summary of Exposure to Erlotinib (Safety Population)
Table 14.1.7.3	Summary of Exposure : Number of participants by cycle (Safety Population)
Table 14.1.7.4	Summary of dose modification during the study (Safety Population)
Table 14.1.7.5	Summary of Erlotinib dose modification during the study (Safety Population)
Table 14.1.8	Compliance (Safety Population)

6.1.2 Section 14.2: Primary and secondary

Table 14.2.1	Assessment of anti-tumour activity – Best Overall Response (Confirmation not Required) (Efficacy Population)
Table 14.2.2	Assessment of anti-tumour activity – Sum of Target Lesions Measurement (Efficacy Population)
Table 14.2.3	Time to progression (TTP) – Kaplan-Meier Analysis (Efficacy Population)

6.1.3 Section 14.3: Safety

6.1.3.1 Adverse events

Table 14.3.1.1	Summary of Adverse Events (Safety Population)
Table 14.3.1.2.1	Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2.2	Adverse Events by System Organ Class, Preferred Term, and CTCAE Grade (Safety Population)
Table 14.3.1.2.3	Adverse Events Related to BGB324 by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2.4	Adverse Events Related to Erlotinib by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2.5	Adverse Events by System Organ Class, Preferred Term and Severity of CTCAE Grade (Safety Population)
Table 14.3.1.3.1	Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3.2	Serious Adverse Events by System Organ Class, Preferred Term, and Severity of CTCAE Grade (Safety Population)
Table 14.3.1.3.3	Serious Adverse Events Related to BGB324 by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3.4	Serious Adverse Events Related to Erlotinib by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.4.1	Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.5.1	Adverse Events with CTCAE Grade >= 3 by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.5.2	Adverse Events >= Grade 3 Related to BGB324 by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.5.3	Adverse Events >= Grade 3 Related to Erlotinib by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.6.1	Adverse Events Occurring >= 10% by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.7.1	Adverse Events leading to death by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.8.1.1	Summary of DLTs occurring during the study (Safety Population)

6.1.3.2 Laboratory results

Table 14.3.5.1.1	Laboratory Results – Hematology - Summary and Change from Baseline (Safety Population)
Table 14.3.5.2.1	Laboratory Results – Coagulation - Summary and Change from Baseline (Safety Population)
Table 14.3.5.3.1	Laboratory Results –Chemistry - Summary and Change from Baseline (Safety Population)
Table 14.3.5.4.1	Laboratory Results for subjects with CTCAE >= Grade 3 (Safety Population)
Table 14.3.5.4.2	Laboratory Results CTCAE Grade >= 3 (Safety Population)

6.1.3.3 Vital signs

Table 14.3.6.1.1	Vital Signs - Summary and Change from Baseline (Safety Population)

6.1.3.4 ECG

Table 14.3.6.2.1	ECG Results - Summary and Change from Baseline (Safety Population)
Table 14.3.6.2.2	ECG Results - Overall Interpretation (Safety Population)
Table 14.3.6.2.3	QTcF (ms) by CTCAE Grade and Dose (Safety Population)
Table 14.3.6.2.4	Maximum QTcF Increase from Baseline (Safety Population)

6.1.3.5 ECOG Performance Status

Table 14.3.6.3.1	Eastern Cooperative Oncology Group (ECOG) Performance Status (Safety Population)

6.2 Listings

Listing 16.1.7.1	Dose Escalation Cohort Assignment (Safety Population)
Listing 16.1.7.2	Drug Accountability (Safety Population)
Listing 16.2.1.1	Subject Disposition (Enrolled Population)
Listing 16.2.1.2	Inclusion/Exclusion Descriptions (Enrolled Population)
Listing 16.2.1.3	Inclusion/Exclusion Criteria Not Met (Enrolled Population)
Listing 16.2.2.1	Important Protocol Deviations (Enrolled Population)
Listing 16.2.3	Subjects Excluded from the Analysis Sets (Enrolled Population)
Listing 16.2.4.1	Demographics (Safety Population)
Listing 16.2.4.2	Cancer History (Safety Population)
Listing 16.2.4.3	Medical History (Safety Population)
Listing 16.2.4.4	Mutation Status (Safety Population)
Listing 16.2.4.5.1	Prior Cancer Therapy (Safety Population)
Listing 16.2.4.5.2	Prior Erlotinib Administration at Screening (Safety Population)
Listing 16.2.4.6	Prior Cancer-related Surgery (Safety Population)
Listing 16.2.4.7	Prior and Concomitant Medications (Safety Population)
Listing 16.2.4.8.1	Physical Examination - Complete (Safety Population)
Listing 16.2.4.8.2	Physical Examination – Symptom Directed (Safety Population)
Listing 16.2.4.9	ECOG Performance Status (Safety Population)
Listing 16.2.5.1	BGB324 Exposure (Safety Population)
Listing 16.2.5.2	Erlotinib Exposure (Safety Population)
Listing 16.2.5.3	BGB324 Administration (In-Clinic) (Safety Population)
Listing 16.2.5.4	BGB324 Administration (By Cycle) (Safety Population)
Listing 16.2.5.5	Erlotinib Administration (Safety Population)
Listing 16.2.6.1	Tumour Assessment – Target Lesions (Safety Population)
Listing 16.2.6.2	Tumour Assessment – Non-Target Lesions (Safety Population)
Listing 16.2.6.3	Tumour Assessment – New Lesions (Safety Population)
Listing 16.2.6.4	Assessment of anti-tumour activity (Safety Population)
Listing 16.2.6.5	Time to progression details
Listing 16.2.7.1	Adverse Events (Safety Population)
Listing 16.2.7.2	Serious Adverse Events (Safety Population)
Listing 16.2.7.3	Adverse Events Related to BGB325 (Safety Population)
Listing 16.2.7.4	Adverse Events Related to Erlotinib (Safety Population)
Listing 16.2.7.5	Adverse Events Leading to Discontinuation (Safety Population)
Listing 16.2.7.6	Adverse Events – Dose Limiting Toxicities (Safety Population)
Listing 16.2.7.7	Adverse Events >= Grade 3 (Safety Population)
Listing 16.2.7.8	List of DLTs (Safety Population)
Listing 16.2.8.1.1	Laboratory Results: Hematology (Safety Population)
Listing 16.2.8.1.2	Laboratory Results: Coagulation (Safety Population)
Listing 16.2.8.1.3	Laboratory Results: Chemistry (Safety Population)
Listing 16.2.8.1.4	Laboratory Results: Urinalysis (Safety Population)
Listing 16.2.8.1.5	Laboratory Results: Urine/Serum Pregnancy Test
Listing 16.2.8.1.6	Clinically Significant Laboratory Results (Safety Population)
Listing 16.2.8.1.7	Laboratory Results for patients with CTCAE Grade >= 3 (Safety population)

6.3 Figures

6.4 References

1. Eisenhauer EA1, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verwei J. **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).** Eur J Cancer. 2009 Jan; 45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.