BerGenBio ASA
Jonas Lies vei 91
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CLINICAL STUDY PROTOCOL

Investigational Product:	BGB324
Protocol Number:	BGBC004
Phase:	Phase 1/2
Protocol Title:	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
Version and Date:	5.0 (16th May 2017)
IND Number:	124645

[redacted]

This study will be conducted in compliance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements

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SUMMARY OF CHANGES SINCE THE PREVIOUS VERSION

Administrative

- Version and date updated.
- Update of sponsor name to BerGenBio ASA
- Table of Contents updated.
- Confirmation that at the time of this Amendment the Run-in Cohort and Arm A have completed recruitment.
- Additional preclinical data added on BGB324 and high dose steroids in mice (New Section 6.1.5)
- Section referencing updated in **Table 9**.
- SAE reporting fax and email address has been updated (previous contacts are still operational).
- Renumbering of inclusion criteria.
- Formatting and typographical errors updated.
- **Table 5** Schedule of Assessments updated to reflect changes.
- **Table 6** updated to reflect the revised pharmacokinetic (PK) schedule.
- Synopsis text has been updated to reflect changes in the body of the protocol.

Study Design and Methodology

Arm B and C, General

- Clarification that the erlotinib dose for Arms B and C may be reduced from 150mg in accordance with the prescribing information (**Sections 11.3.2; 8.3.1**).
- Epidermal Growth Factor Receptor (EGFR) mutation status expanded to include “other rearrangements of the EGFR gene” (**Section 9.1.4 Arm B Incl. 12, and Arm C Section 9.1.5 Incl.20**).
- CTs scan frequency: Patients who remain on treatment for 12 months or longer will require scans at a frequency of 6 months, or earlier if progression of disease is suspected (**Section 10.2.10**).
- Patients who remain on BGB324 for 12 months or more will be able to reduce the frequency and number of assessments required at each visit. Patients will return to clinic every 6 weeks (every 2 cycles) (**New Section 10.1.7**).
- The End of Study (EOS) is defined as when all patients have completed or withdrawn and the EOS visit has been completed (**Section 8.11**).
- Inclusion of 15% boundary from the prescribed dose (**Section 13.4.8**).
- Post dose 30-hour ECG collection time point has been removed (**Section 10 and Table 5**).
- **New Section 10.1.8** Visit schedule while on corticosteroids

  Additional weekly monitoring (physical exam, vital signs, hematology / chemistry analysis) while patients are receiving prednisolone (or equivalent) at 10mg to 40 mg daily

- **New Section 11.3.1.4**

BGB324 dose modification for steroids doses over 40mg daily (prednisolone equivalent)

If a patient requires prednisolone (or equivalent) at daily doses above 40mg then BGB324 should be interrupted until the steroid dose is equivalent to or less than 40mg prednisolone daily, at which time weekly monitoring will be undertaken until the steroid dose is equivalent or less than 10mg (Section 10.1.8)

For those patients who experience a BGB324 dose delay of ≥7 days, the BGB324 loading dose assigned should be repeated. If the patient was unable to tolerate the loading dose in Cycle 1 the repeat loading dose can be omitted. The requirement to reintroduce the loading dose should be discussed with the Medical Monitor.

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.

- **Section 11.5** – Concomitant Medications and Procedures **(New Text)**
  Patients receiving BGB324 who require the support of prednisolone (or equivalent) at 10mg daily or above 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 to or less than 40mg daily, at which time weekly monitoring will be undertaken until the steroid dose is equivalent to 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

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Arm B

- The requirement for collection of and analysis of circulating tumor cell (CTC) samples in has been removed. Pharmacodynamic (PD) endpoints associated with analysis of CTC have been removed (**Sections 10.2.9.1. 7.8**).
- As a 3-day loading dose has been confirmed in Arm A, reference to pharmacokinetic (PK) schedules associated with a 2-day loading dose have been removed (**Table 6 updated**).
- Requirement for starting erlotinib 1 week prior to the first dose of BG324 has been removed (**Section 9; Arm B**).
- PK sampling will be limited to BGB324 and pre-dose PK sampling will stop at Cycle 3 (**Table 6 updated**).
- Cycle 1 –Day 1 assessments have been removed (**Section 10.1.2.**).
- Clarification that only BGB324 PK samples will be required in Arm B (**Section 10**).
- Clarification on the requirements for T790M testing - patients who have progressed on osimertinib will not require retesting (**New Section 10.2.11**).
- The 28-day screening window may be extended to allow for T790M testing, all other assessments are to be conducted in the 28-day window (**Section 9.1.4; Arm B Incl.12**).
- Expansion of the inclusion criteria to allow patients who have progressed on an approved EGFR inhibitor to be considered for inclusion into the study (**Section 9.1.4; Arm B Incl.14**).
- Clarification that toxicities associated with other EGFR inhibitors must be <Grade 2 in severity at the time of first dose of BGB324 (**Section 9.1.4; Arm B Incl.15**).
- Confirmation that afatinib or gefitinib treatment must complete 1 week before the first dose of BGB324 (**Section 9.1.4; Arm B Incl.16**).
- Expansion to allow up to 4 previous treatments in the advanced setting (**Section 9.1.4; Arm B Incl 18**).
- Secondary objectives looking at BGB324 and erlotinib PK have been revised to reflect that only BGB324 PK samples will be collected (**Section 7.3.2**).

- PK population revised to reflect that no erlotinib PK will be collected in Arm B (**Section 14.4.1**).

Arm C
- This arm may be closed if Arm B stops or completes recruitment before Arm C reaches the 14patient target. Patients already enrolled into Arm C will be able to continue in accordance with the protocol (**Section 8.5**).
- Clarification of the exclusion criteria to facilitate those patients who may have received alternative treatment while awaiting confirmation of EGFR status (**Section 9.1.5; Arm C Incl.24**).

Safety Justifications

The protocol has been changed to include patients who experienced disease progression whilst receiving an approved EGFR inhibitor such as afatinib or gefitinib as an alternative to erlotinib. This has been done as the biological mechanisms of resistance to all 3 agents are similar and may be reversed following exposure to BGB324.

Pharmacokinetic data collected and analyzed to date supports that there is no interaction between erlotinib and BGB324, therefore no requirement to collect additional erlotinib PK or long term pre-dose BGB324 PK. BGB324 PK will be collected as per schedule up to Cycle 3 and EOS.

30hr ECG removed. ECGs are already being collected pre-dose on Days 1,2, and 3. The change is not considered to have any impact on safety.

Arm B: Inclusion 18 - revised in response to Investigator eligibility request. The change is not considered to have any impact on patient safety or study integrity.

Arm B: Inclusion.14/15- The Sponsor has seen an increase in the use of EGFR inhibitors other than erlotinib as standard of care. Additional criteria have been implemented that restricts use to 1 week before the first dose of BGB324 and requires the patient to have Grade 2 or less toxicities at the time of BGB324 dosing.

Only erlotinib will be administered in combination with BGB324 thus the change is not anticipated to have any effect on the safety of the patients.

Revised visit schedule after 12 month: This has been expanded from a visit each cycle to a visit to every 2 cycles. This change in frequency is not anticipated to have any effect on patient safety as it only applies to patients who have received treatment with BGB324 for one year, and reduces the visit burden for the patient.

Oral Corticosteroid use with BGB324
Following advice from the FDA on preclinical data in mice with high dose steroids and BGB324, additional weekly monitoring has been introduced for those patients who require treatment with 10mg or above daily prednisolone (or equivalent) and guidance that at doses above 40mg daily BGB324 should be interrupted until the steroid dose is 40mg or less daily.

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1 PROTOCOL SIGNATURES

Protocol BGBC004 Version 5, 16 May 2017

Sponsor's Approval

This protocol has been approved by BerGenBio ASA.

Signature _____ **Date** _____

[redacted] M.D., Ph.D.
[redacted]

Investigator's Acknowledgment

I, the undersigned, have reviewed the protocol and appendices and I will conduct the BGBC004 clinical study as described and in accordance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the BGB324 Investigator's Brochure.

Signature _____ **Date** _____

Printed Name _____

2 STUDY PERSONNEL

Sponsor's Representative	M.D., Ph.D.
Sponsor's Medical Contact	M.D., Ph.D.
Sponsor Site	BerGenBio ASA Jonas Lies vei 91 5009 Bergen Norway
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Note: Laboratory details and contact information are provided in the laboratory manual.

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3-D	Three-dimensional
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity
AUC_{0-t}	Area under the curve within a dosing interval
BID	Twice daily
C_{max}	Maximum concentration achieved
CNS	Central nervous system
CRO	Clinical Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Circulating tumor cell
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H_0	Null hypothesis
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
PD	Progressive disease
QA	Quality assurance
QD	Once daily
QTcF	QT interval utilizing Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SMC	Safety Monitoring Committee

SUSAR	Suspected unexpected serious adverse reaction
t_{max}	Time to maximum concentration
ULN	Upper limit of normal range
US	United States of America

5 PROTOCOL SYNOPSIS

PROTOCOL TITLE	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.
PROTOCOL NUMBER	BGBC004
SPONSOR	BerGenBio ASA Jonas Lies vei 91 5009 Bergen Norway
INVESTIGATIONAL PRODUCT	BGB324
PHASE OF DEVELOPMENT	Phase 1/2
RATIONALE	In patients with non-small cell lung cancer (NSCLC), there is a progressive decline in response to repeated lines of therapy, primarily due to development of biologic resistance within the underlying tumor and a progressive decline in patient performance status resulting from treatment- and disease-related morbidities. There is a significant need for development of strategies that can prolong response and prevent development of resistance to earlier-stage treatment regimens. BGB324 is a potent selective small molecule inhibitor of Axl, a surface membrane protein kinase receptor that is over-expressed in many metastatic solid tumors and has been identified as a marker of a poor prognosis in patients with NSCLC. *In vitro* studies indicate that signaling through Axl stimulates several pro-survival pathways, some of which are mediated by AKT phosphorylation and up-regulation of the epithelial receptor kinase pathway. Recent non-clinical data implicate Axl in development of resistance to several agents used in the treatment of NSCLC, especially epidermal growth factor receptors (EGFR) inhibitors including erlotinib. This study is designed primarily to evaluate the safety and tolerability of BGB324 when administered in combination with erlotinib, 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.
STUDY DESIGN	This is a multi-center, multi-arm open-label Phase 1/2 study that will be conducted at approximately 10 clinical sites; the number of sites may be revised to reflect changes in recruitment rates. Up to 60 patients with histologically- or cytologically-confirmed Stage IIIb or Stage IV NSCLC will receive BGB324 as a single agent (Run-in Cohort) or in combination with erlotinib (Arms A, B and C). At the time of Amendment 5, patient recruitment into the Run-In Arm (BGB324 monotherapy) and Arm A (BGB324 dose escalation in combination with erlotinib) was complete and the RP2D has been confirmed. Patients that remain on treatment in the Run-in Cohort or Arm A should be followed up in accordance with the protocol schedule.

	Run-in Cohort (Phase 1) 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 (Phase 1)** Arm A is designed to determine the daily dose and loading schedule of BGB324 that can be safely administered in combination with erlotinib in patients who have received prior treatment with erlotinib. The starting dose of erlotinib will be 150mg daily. Lower doses of erlotinib may be explored at the request of the SMC. In addition to safety and tolerability, the pharmacokinetics (PK) and pharmacodynamics (PD) of BGB324 and erlotinib will be evaluated. In Arm A, dose and dosing schedules will be explored to assess tolerability of the loading and daily doses and to select the RP2D for expansion into Phase 2 (Arms B and C). The dose of BGB324 will be escalated in a standard 3+3 design. The starting dose level of BGB324 will be 600 mg loading dose (2 days) and 200 mg daily dose. It is anticipated that a maximum of 3 BGB324 Dose Levels will be evaluated with up to 18 patients enrolled. Alternative loading dose schedules may be explored in combination with daily dosing schedules (see Table 4). Dose escalation may be stopped prior to achieving the maximum tolerated dose (MTD) if it is considered that a clinically acceptable recommended Phase 2 dose (RP2D) has been achieved. Safety will be reviewed by the Safety Monitoring Committee (SMC). When the RP2D 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 commence and Arms B and C will open simultaneously to enrolment. **Arm B (Phase 2)** Arm B will follow a Simon-like 2-stage design with relaxed stopping for futility to evaluate the PK of BGB324 and the safety and tolerability, PD, and clinical efficacy of BGB324 in combination with erlotinib in patients with an activating EGFR mutation who have progressed after receiving an approved EGFR inhibitor (i.e., erlotinib, afatinib, or gefitinib) For patients to be eligible for Arm B, their EGFR T790M status should be confirmed during the screening period prior to receiving the first BGB324 dose. This can be done either via blood test (circulating tumor DNA [ctDNA]; serum or plasma;) or tumor biopsy. Patients who test negative for T790M in ctDNA testing will require a confirmatory result from

	a tumour biopsy. Both the blood test/biopsy should be undertaken in accordance with local procedures and do not require central analysis. For patients to be eligible for Arm B, a negative EGFR T790M result must be documented. Patients who have previously been treated with a T790M inhibitor (i.e., osimertinib) and who subsequently progressed will not require T790M testing. If clinical response (complete response or partial response) or disease control (stable disease) is not evident after 4 cycles of treatment in at least 1 patient among the first 9 patients, no further patients will be enrolled. If at least 1 patient in the first 9 patients demonstrates evidence of clinical response or disease control, an additional 16 patients will be enrolled. Recruitment will continue whilst data from the first 9 patients are being analyzed. Thus, up to 25 patients are anticipated to be enrolled in Arm B. **Arm C (Phase 2)** Arm C will evaluate the safety and tolerability, PD, and clinical efficacy (time to progression) of BGB324 when administered in combination with erlotinib in patients with an activating EGFR mutation who have received ≥12 weeks of erlotinib without disease progression. Up to 14 patients will be enrolled. 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 this time will be allowed to continue in the study in accordance with the protocol. In all parts of the study, patients will be allowed to continue BGB324 treatment (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 unacceptable toxicity, disease progression, death or withdrawal of consent. In the event of erlotinib-related toxicities in Arms A, B, or C, patients who stop treatment with erlotinib will be allowed to continue receiving BGB324 as a single agent until disease progression (unless unacceptable toxicity, disease progression, death or withdrawal of consent). Patients who stop BGB234 treatment will be withdrawn from the study.
OBJECTIVES	**Run-In Cohort (Phase 1)** <u>Primary Objective</u> To explore the safety and tolerability of single agent BGB324 in patients with NSCLC. **Arm A (Phase 1)** <u>Primary Objective</u> To identify RP2D of BGB324 administered in combination with erlotinib in patients with NSCLC. <u>Secondary Objectives</u>

	• 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 PK of BGB324 and erlotinib and the potential effect of BGB324 on erlotinib. Exploratory Objective • To evaluate the PD effects of BGB324 administered in combination with erlotinib. **Arm B (Phase 2)** Primary Objective To explore the safety and tolerability of the combination of BGB324 and erlotinib in patients with NSCLC with an activating EGFR mutation who have progressed after receiving an approved EGFR inhibitor (i.e., erlotinib, afatinib, or gefitinib) and who are T790M negative. Secondary Objectives • To assess the PK of BGB324 • To explore the clinical efficacy of the combination of BGB324 and erlotinib in this setting. Exploratory Objectives • 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. **Arm C (Phase 2)** 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. Secondary Objectives • To explore the time to progression of the combination of BGB324 and erlotinib in this setting. Exploratory Objectives • 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.
DOSE LIMITING TOXICITY	In Arm A DLTs will be evaluated 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.
INCLUSION CRITERIA	**General Criteria** 1. Provision of written informed consent to participate in this investigational study. 2. Histological or cytological confirmation of Stage IIIb or Stage IV (unresectable) NSCLC. 3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 4. Age 18 years or older at the time of consent. 5. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to taking their first dose of BGB324. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, total sexual abstinence, vasectomy) throughout the study and for ≥3 months after the last dose of BGB324. Female patients are considered NOT to be of childbearing potential if they have a history of surgical sterility, including tubal ligation, or evidence of post--menopausal status defined as any of the following: • Natural menopause with last menses >1 year ago. • Radiation induced oophorectomy with last menses >1 year ago. • Chemotherapy induced menopause with last menses >1 year ago. **Additional Inclusion Criteria for Run-in Cohort** 6. Has received previous systemic therapy for unresectable NSCLC. 7. Has exhausted existing licensed therapies, or is unsuitable for treatment with existing licensed therapies for NSCLC. **Additional Inclusion Criteria for Arm A** 8. Known EGFR mutation status. 9. Either: a) Has received ≥6 weeks historical treatment with erlotinib. Erlotinib treatment must be re-started ≥1 week before the first dose of BGB324 (Cycle 1, Day 1). Or:

	b) Is currently receiving erlotinib treatment for NSCLC and will have received ≥6 weeks treatment at the time of the first dose of BGB324 (Cycle 1, Day 1). 10. Erlotinib-related toxicities being well-controlled and <Grade 3 in severity at the time of the first dose of BGB324 (Cycle 1, Day 1). 11. Toxicity from other prior therapy has resolved to ≤Grade 1 (previous treatment with bevacizumab and other licensed antibody therapies is permitted). **Additional Inclusion Criteria for Arm B** 12. Patients must have documented EGFR mutation (including exon 19 deletion or exon 21 L85R substitution or other rearrangement of the EGFR gene. EGFR mutation may be confirmed historically prior to study entry) and during the 28 day[1] screening period confirmation of negative T790M status (confirmed with blood test or biopsy from a progressing tumor). Patients who have previously been treated with a T790M inhibitor and have progressed (i.e., osimertinib) will not require T790M testing 13. Disease that is measurable according to the response evaluation criteria in solid tumors (RECIST) Version 1.1 14. Has progressed after receiving an approved EGFR inhibitor (i.e., erlotinib, afatinib, or gefitinib) at any time during therapy for advanced disease. 15. Erlotinib-related toxicities being well-controlled and <Grade 3 in severity at the time of the first dose of BGB324 (Cycle 1, Day 1). Toxicities associated with other EGFR inhibitors to be <Grade 2 in severity at the time of first dose of BGB324. 16. Patients must have completed afatinib and/or gefitinib treatment at least 1 week before the first dose of BGB324. There is no requirement to discontinue ongoing treatment with erlotinib. 17. Toxicity from other prior therapy has resolved to ≤Grade 1 (previous treatment with bevacizumab and other licensed antibody therapies is permitted). 18. Patients who have an activating EGFR mutation may have up to 4 lines of previous treatment in the advanced setting. Additional chemotherapy may also have been given for treatment of limited stage disease in the adjuvant setting provided this was completed at least 6 months prior to study treatment **Additional Inclusion Criteria for Arm C** 19. Known EGFR mutation status:

[1] The screening window may be extended to allow for confirmation of T790M status through tumor biopsy. Other assessments including CT should be conducted in the 28-day screening period.

	20. Presence of an activating EGFR mutation (including exon 19 deletion or exon 21 [L858R] substitution mutation or other rearrangement of the EGFR gene). 21. Disease that is measurable or evaluable according to RECIST Version 1.1. 22. Is currently receiving erlotinib for NSCLC and will have received ≥12 weeks' treatment at the time of the first dose of BGB324 (Cycle 1, Day 1). 23. Have erlotinib-related toxicities that are well-controlled and <Grade 3 in severity the time of the first dose of BGB324 (Cycle 1, Day 1). 24. No prior treatment for advanced NSCLC except erlotinib and/or previous surgery (patients who have received treatment for their NSCLC while awaiting confirmation of EGFR status, may be eligible to participate and the inclusion of such patients should be discussed with the Medical Monitor).
EXCLUSION CRITERIA	1. Pregnant or lactating. 2. Abnormal left ventricular ejection fraction (less than the lower limit of normal for a patient of that age at the treating institution or <45%). 3. Treatment with any of the following; histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 3 days or 5 half-lives of administration of BGB234, whichever is longer. The Investigator may initiate rescue treatment with these medications during the study, providing they are taken in the evening. 4. History of an ischemic cardiac event, including myocardial infarction, within 3 months of consent. 5. Pulmonary hemorrhage or hemoptysis >2.5 mL blood within 6 weeks of consent unless cause has been addressed and is medically resolved. 6. Congestive cardiac failure of >Class II severity according to the New York Heart Association (NYHA) defined as symptomatic at less than ordinary levels of activity. 7. Unstable cardiac disease, including unstable angina or unstable hypertension, as defined by the need for change in medication for lack of disease control within 3 months of consent. 8. History or presence of sustained bradycardia (≤60 bpm) or history of symptomatic bradycardia, left bundle branch block, cardiac pacemaker or significant atrial tachyarrythmias, as defined by the need for treatment. 9. Current treatment with agents that may prolong QT interval and may cause Torsade de Points which cannot be discontinued at least 2 weeks prior to treatment. 10. Known family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy. 11. Previous history of ≥Grade 3 drug-induced QTc prolongation. 12. Screening 12-lead triplicate electrocardiogram (ECG) with an average measurable QTc interval utilizing Fridericia's correction (QTcF) >450 ms. 13. Inadequate liver function as demonstrated by:

	Serum bilirubin ≥1.5 times the upper limit of normal range (ULN); or Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the ULN (up to 5 times the ULN in the presence of liver metastases). 14. Inability to tolerate oral medication. 15. Impaired coagulation as evidenced by: a) International normalized ratio (INR) >1.5 times ULN (or equivalent); or b) Activated partial thromboplastin time (aPTT) >1.5 times ULN. 16. Existing gastrointestinal disease affecting drug absorption, such as celiac disease or Crohn's disease. 17. Previous bowel resection that may impair study drug absorption. 18. Impaired renal function as demonstrated by creatinine clearance of ≤50 mL/min determined by Cockcroft-Gault formula. 19. Absolute neutrophil count <1.5 x 10^9/L, hemoglobin <9.0 g/dL, platelet count <100 x 10^9/L in the absence of blood product support. 20. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol. 21. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index. 22. Active, uncontrolled central nervous system (CNS) disease; (previously-treated CNS metastases that are asymptomatic and do not require steroid treatment are allowed). Note: Patients with known CNS metastases who have completed radiotherapy at least 2 weeks prior to BGB324 treatment are eligible. 23. Known active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses (screening not required): • Patients who have a history of hepatitis B infection are eligible provided they are hepatitis B surface antigen negative. • Patients who have a history of hepatitis C infection are eligible provided they have no evidence of hepatitis C ribonucleic acid using a quantitative polymerase chain reaction assay at least 6 months after completing treatment for hepatitis C infection. 24. Major surgery requiring general anesthesia within 28 days prior to the start of BGB324, excluding biopsies and procedures for insertion of central venous access devices. 25. Treatment with cytotoxic chemotherapy, within the 3 weeks prior to the first dose of BGB324 (Cycle 1, Day 1) with the exception of treatment with other EGFR

	inhibitors which must be completed 1 week prior to commencing treatment with BGB324. There is no requirement to discontinue ongoing treatment with erlotinib. 26. Treatment with other non-cytotoxic agents for NSCLC in the 10 days or 4 half-lives, prior to the first dose of BGB324 (Cycle 1, Day 1) whichever is shorter. 27. Prior biological therapies in the 4 weeks (or 5 half-lives, whichever is shorter) before the first dose of BGB324 (Cycle 1, Day 1). Note prior treatment with an alternative EGFR inhibitor and/or PD-1 blockade is permitted.
TREATMENTS AND INTERVENTIONS	Patient eligibility for the study, including assessment of EGFR mutation/T790M status in Arm B, and disease status according RECIST Version 1.1 will be performed within 28 days prior to the first dose of BGB324. The 28-day screening window may be extended to confirm T790M status, however all other assessments including scans will be conducted in the 28-day screening window. Patients who have previously been treated with a T790M inhibitor (i.e., osimertinib) and who subsequently progressed and fulfil all other eligibility criteria will not require T790M testing. The treatment period will consist of continuous 21-day treatment cycles. Patients will be monitored through daily clinic visits on Day 1 to Day 4, Days 8, 9, and 15 in Cycle 1 (and Day -1 in Arms A and B) and weekly during Cycle 2. Beginning with Cycle 3, patients will have a clinic visit on Day 1 of each cycle. Patients who remain on treatment for 12 months will need to return for a clinic visit every 2 cycles (i.e. 6 weekly). Patients receiving BGB324 who require the support of prednisolone (or equivalent) at 10mg to 40 mg daily should be monitored at weekly intervals whilst receiving treatment. Disease assessment will be performed at the end of every 2 cycles or to confirm disease progression. 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 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. The end of study (EOS) visit will occur 28 days after the last dose of study drug (including study withdrawal).
STUDY DRUG DOSE, SCHEDULE, ROUTE of ADMINISTRATION	In the Run-in Cohort, BGB324 will be administered as a single agent. In Arms A, B, and C, BGB324 will be administered in combination with erlotinib. At the time of

	Amendment 5 the Run in Cohort and Arm A have completed recruitment. **BGB324** BGB324 is prepared in size zero capsules each containing 100 mg of drug substance for oral administration. BGB324 will be self-administered orally on an empty stomach according to a daily schedule during continuous 21-day treatment cycles. In Cycle 1, a loading dose of BGB324 may be administered followed by smaller daily dose (see Table 4). Dose escalation can only occur in Arm A. If unacceptable toxicity is reported, the Sponsor and Investigators may agree to implement a lower dose for investigation or other dosing schedules. In Arms B and C, BGB324 will be administered at the RP2D (the dose identified in Arm A that can be safely administered in combination with erlotinib).
	Erlotinib Erlotinib will be self-administered orally on an empty stomach according to a daily schedule during continuous 21-day treatment cycles in Arms A, B, and C. The starting erlotinib dose in Arm A will be 150 mg daily. Patients requiring a dose reduction before the end of Cycle 1 will not be evaluable for toxicity and may be replaced. The prescribing information for erlotinib recommends a 150mg dose for NSCLC patients**,** however if local clinical judgement/standards require, a patient in Arm B or C may be treated at a lower erlotinib dose (i.e., 100 mg). If a patient presents with erlotinib toxicities that warrant dose reduction, the dose may be reduced in accordance with the current prescribing information. If the patient is required to cease treatment with erlotinib due to toxicity, they should either be withdrawn from the study or allowed to continue receiving BGB324 as a single agent until disease progression (unless unacceptable toxicity, death or withdrawal of consent). Both drugs will be taken with water in the morning on a fasted stomach. 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).
DURATION OF PARTICIPATION	Patients may remain on study until disease progression, development of unacceptable toxicity or withdrawal of consent. Patients in Arms A, B, or C who discontinue treatment with erlotinib may remain on BGB324 as a single agent.

	A patient who discontinues treatment with BGB324 but remains on erlotinib therapy will be considered to have withdrawn from the study. With the exception of erlotinib, no other anti-cancer agent may be given while participating in the study.
CRITERIA FOR EVALUATION	**Safety** Safety will be assessed through the monitoring of adverse events (AEs), including serious adverse events (SAEs), clinical laboratory parameters (hematology, clinical chemistry, coagulation, urinalysis) vital sign measurements, ECG monitoring, ECOG performance status and physical examinations. **Clinical Efficacy** Clinical efficacy will be estimated based on imaging assessments of disease status performed after every 2 cycles (6 weeks) of treatment. 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 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. Identification of target and non-target lesions and assessment of treatment response and progression will be conducted according to RECIST Version 1.1. Endpoints will include time to progression. **Pharmacokinetics** (Run-in Cohort, Arm A and Arm B only) Blood samples for assessment of PK for BGB324 and erlotinib (Arm A) will be collected at specified time points before and after beginning treatment with BGB324: • Cycle 1 Day -1: 0 (pre-dose), 2, 4, 6, and 8 hours[2]. • Cycle 1 Day 1: 0 (pre-dose). • Cycle 1 Day 2: 0 (pre-dose). • Cycle 1 Day 3: 0 (pre-dose), 2, 4, 6, and 8 hours. • Cycle 1 Day 4: 0 (pre-dose). • Cycle 1 Day 8: 0 (pre-dose), 2, 4, 6, and 8 hours. • Cycle 1 Day 9: 0 (pre-dose. • Cycle 1 Day 15:0 (pre-dose). • Cycle 2 Day 1, Day 8, Day 15: 0 (pre-dose). • Cycle 3 Day 1: 0 (pre-dose). • End-of-study visit. **Pharmacodynamics** Blood and tissue samples for the evaluation of PD endpoints will be collected at baseline (within 28 days before the first dose of study drug after patient eligibility has been

[2] Sampling for erlotinib and BGB324. In Arm B PK sampling for BGB324 only. In Arm B there is no requirement for Day -1 PK sampling.

	confirmed), after 14 consecutive days of treatment with BGB324 and at the time of disease progression. The tissue samples for PD testing are optional and require additional consent. The tissue specimen collected at the time of disease progression should be derived from a lesion exhibiting progression. Pharmacodynamic samples will be analyzed to determine endpoints associated with Axl.
STATISTICAL METHODS	The primary objectives of this Phase 1/2 study are to determine the safety and tolerability of BGB324 administered in combination with erlotinib and to establish a RP2D. Arm B will incorporate a 2-stage design that is intended to minimize patient exposure if preliminary evaluation of activity suggests the combination may not be active. The statistical analysis will be primarily descriptive in nature and will account for all dose levels studied. Although all clinical efficacy analysis for this study is to be regarded as essentially exploratory, there will be a formal hypothesis test for the objective response rate in Arm B. This will consist of 1-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. The PK of erlotinib in combination with BGB324 will be compared to that when erlotinib is administered alone.

6 INTRODUCTION

In patients with non-small cell lung cancer (NSCLC), there is a progressive decline in response to repeated lines of therapy, primarily due to development of biologic resistance within the underlying tumor and a progressive decline in patient performance status resulting from treatment- and disease-related morbidities (NCCN Treatment Guidelines Version 4.2014). There is a significant need for development of strategies that can prolong response and prevent development of resistance to earlier-stage treatment regimens.

BGB324 is a potent selective small molecule inhibitor of Axl, a surface membrane protein kinase receptor that is over-expressed in many metastatic solid tumors (Linger, 2008) and has been identified as a marker of a poor prognosis in patients with NSCLC (Ishikawa, 2013; Zhang, 2012). *In vitro* studies indicate that signaling through Axl stimulates a number of pro-survival pathways, some of which are mediated by AKT phosphorylation and up-regulation of the epithelial receptor kinase pathway (Korshunov, 2012). Recent non-clinical data implicate Axl in development of resistance to a number of agents used in the treatment of NSCLC, especially epidermal growth factor receptor (EGFR) inhibitors including erlotinib (Brand, 2014; Byers, 2013; Zhang, 2012). The current study is designed primarily to evaluate the safety of the Axl inhibitor BGB324 when administered in combination with erlotinib, 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.

6.1 Non-clinical Studies with BGB324

6.1.1 Specificity of inhibition of Axl kinase activity

BGB324 demonstrates potent inhibition of Axl in biochemical and cell-based kinase inhibition assays. The selectivity of BGB324 for Axl is illustrated in Table 1.

Table 1 BGB324 Kinase Selectivity Profile

	Kinome Scan binding assay (K_d)		**KinaseProfiler kinase activity assay (IC_{50})**		**BaF3 cell-based kinase activity assay (IC_{50})**	
Kinase	**nM**	**Fold**	**nM**	**fold**	**nM**	**Fold**
Axl	0.4	1	4.6	1	63	1
Ysk4	1.6	4	n/a		n/a	
Stk10	9.2	23	22	4.7	n/a	
Tie2	270	680	30	6.4	355	5.5
Wee1	17	42	32	6.9	n/a	
Ret	73	180	38	8.1	>316	>5
Flt1	400	>1000	40	8.7	>1000	>15
Flt4	460	>1000	41	8.8	>1000	>15
Yes	810	>1000	43	9.2	n/a	n/a
Abbreviations: IC_{50}=half maximal inhibitory concentration; n/a=not applicable						

6.1.2 Inhibition of proliferation of NSCLC cells

The anti-proliferative activity of BGB324 was demonstrated in a panel of human NSCLC cell lines by either resazurin cell viability assay or colony formation assay. As summarized in Table 2, BGB324 inhibited proliferation of several human lung cancer cell lines with half maximal inhibitory concentration (IC_{50}) values of 0.4 - 0.8 µM; the anti-proliferative effect was dose--responsive (not shown).

Table 2 Effect of BGB324 on Proliferation of Human NSCLC Cell Lines

Tumor Type	Cell Line	IC_{50} (μM)
NSCLC	A549	0.56
	NCI-H1299	0.67
	HCC827	0.76
	H358	0.43
Abbreviations: IC_{50}=half maximal inhibitory concentration		

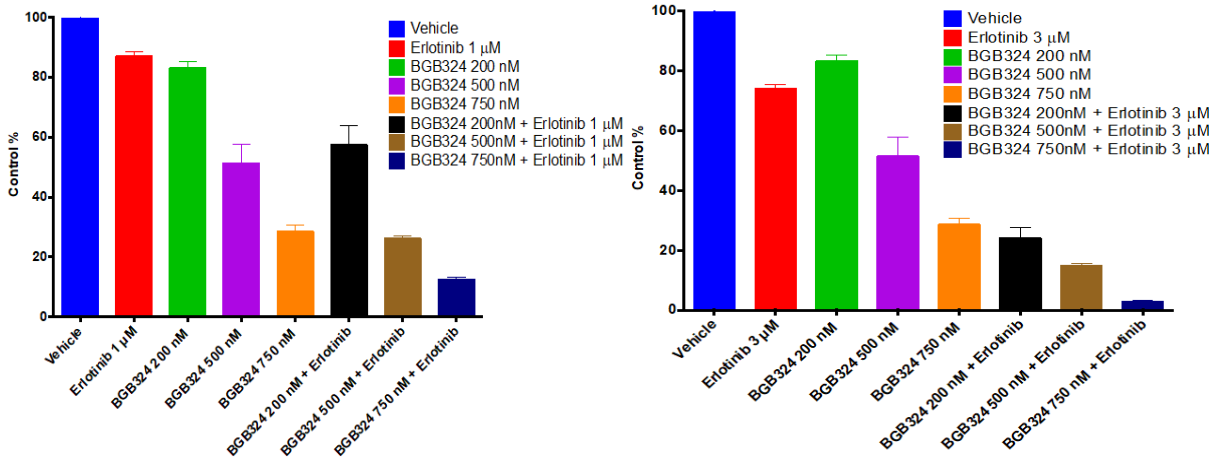
The ability of BGB324 to inhibit cell proliferation was investigated in a panel of 654 human tumor cell lines. When administered at a concentration of 1 μM, BGB324 inhibited proliferation by >50% in 48 of the cell lines tested, including 10/101 NSCLC.

6.1.3 Re-sensitization to erlotinib in a NSCLC cell line by BGB324

It has been reported that Axl mediates chemoresistance in a variety of cancer types, including NSCLC (Zhang, 2012), breast cancer (Liu, 2009), and esophageal adenocarcinoma (Alvarez, 2010). *In vitro* and *in vivo* models also suggest that Axl activation is one of the main mechanisms of acquired resistance to EGFR targeted therapies in NSCLC (Zhang, 2012) and inhibition of Axl may restore drug sensitivity.

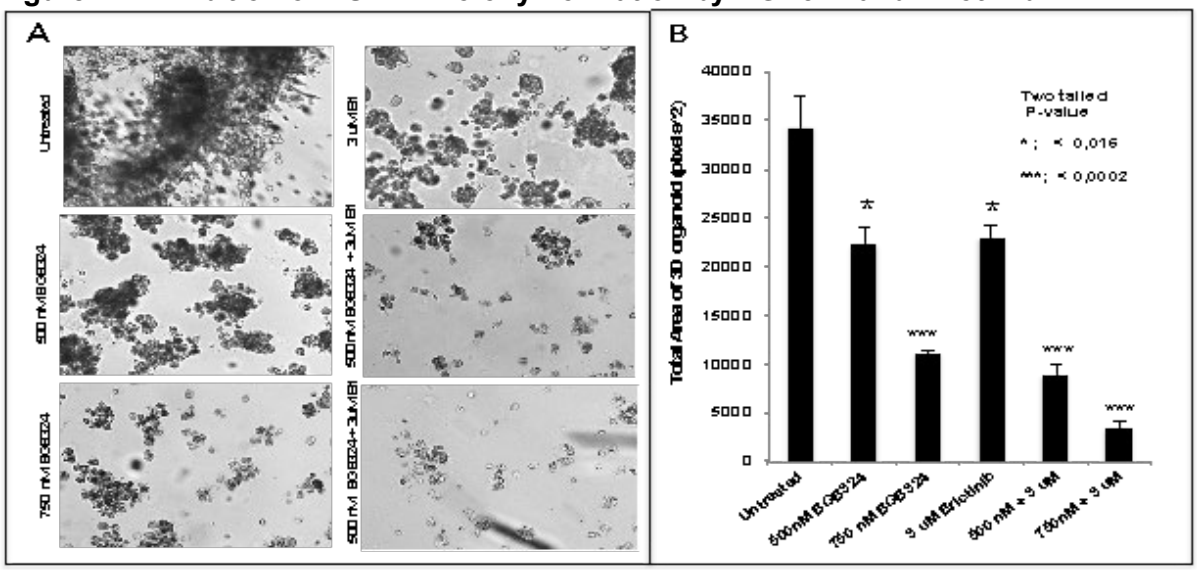
To evaluate whether BGB324 can restore sensitivity to the EGFR inhibitor erlotinib, the erlotinib-resistant human NSCLC cell line NCI-H1299 was treated with BGB324 (concentrations of 200, 500 and 750 nM) and erlotinib (concentrations of 1 and 3 μM) and evaluated in a colony formation assay. As can be seen in Figure 1, the combination of BGB324 and erlotinib restored erlotinib-sensitivity, in an additive or synergistic manner, as demonstrated by the substantial inhibition of proliferation.

Figure 1 Restoration of Erlotinib Sensitivity in NSCLC Cells



To confirm these results, a 3-dimensional (3-D) tumorsphere assay was performed in NCI-H1299 NSCLC cells treated with BGB324 ± erlotinib. This study showed that BGB324 in combination with erlotinib demonstrates an additive or synergistic effect ($p < 0.05$) in inhibiting the growth and establishment of NCI-H1299 lung cancer cells in Matrigel (Figure 2).

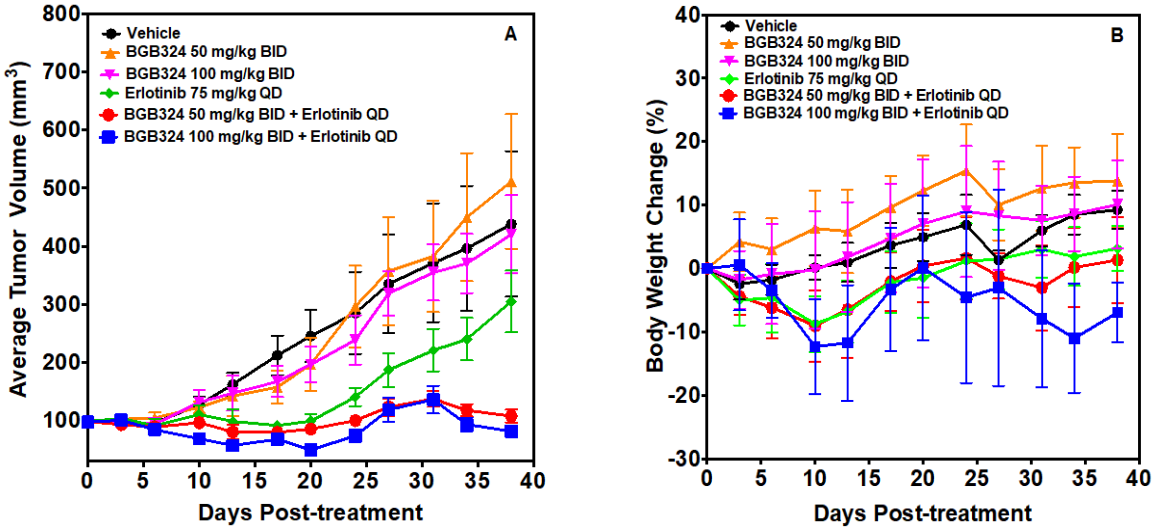
Figure 2 Inhibition of NSCLC Colony Formation by BGB324 and Erlotinib



6.1.4 In vivo anti-tumor activity of BGB324 and erlotinib

The anti-tumor activity of BGB324 in combination with erlotinib was evaluated in the human A549 NSCLC xenograft model. Treatment was initiated when tumors reached 100 mm^3. BGB324 alone at doses of 50, 75, and 100 mg/kg orally twice daily (BID) were evaluated, as well as BGB324 at 50 and 100 mg/kg orally BID with erlotinib at 75 mg/kg orally once daily. Single agent BGB324 showed minimal anti-tumor activity, while the combination of BGB324 and erlotinib resulted in significant ($p < 0.005$) anti-tumor activity (, left panel). BGB324 alone and in combination with erlotinib was well-tolerated, as evidenced by evaluation of body weight (Figure 3, right panel), and there was no drug-related mortality.

Figure 3 Anti-Tumor Effect (left panel) and Tolerability (right panel) of BGB324 and Erlotinib in the A549 Human NSCLC Xenograft Model

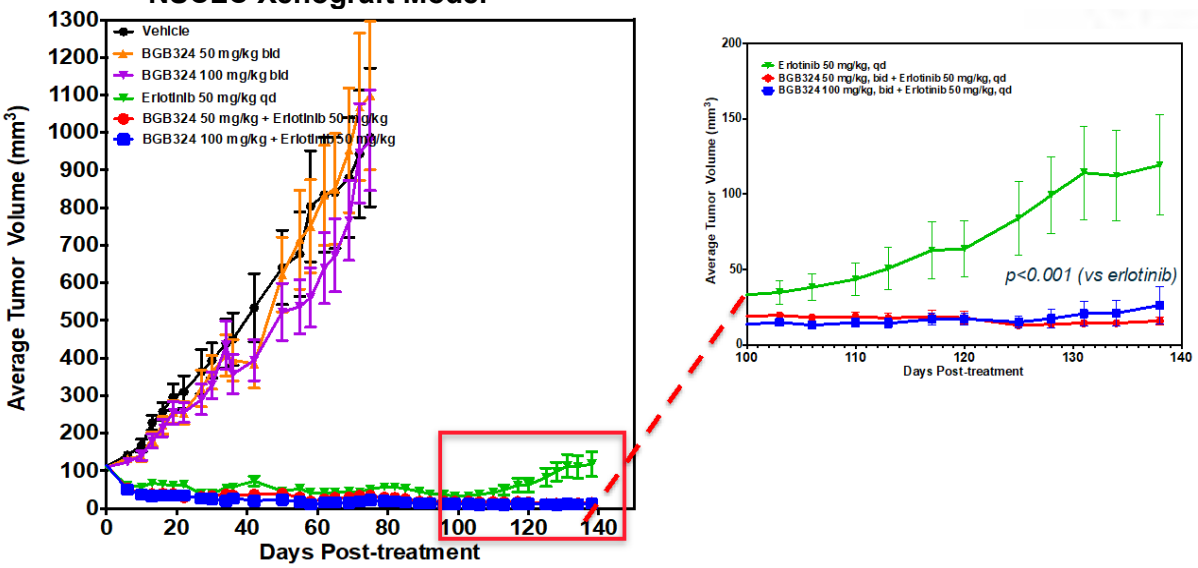


Abbreviations: BID=twice daily; QD=once daily

The anti-tumor activity of BGB324 in combination with erlotinib was further evaluated in a xenograft model of the human HCC827 NSCLC, which bears an EGFR exon 19 deletion. Mice were treated with vehicle alone, BGB324 at 50 and 100 mg/kg orally BID, erlotinib at 50 mg/kg orally once daily (QD) or a combination of both drugs, using a 5-day on and 2-day off dosing schedule. As shown in Figure 4, animals receiving single agent erlotinib began to develop acquired drug resistance at approximately Day 100. However, combination dosing with

BGB324 significantly delayed the onset of acquired resistance to erlotinib by at least 40 days (n=7-8, p <0.001).

Figure 4 BGB324 Blocks Acquired Resistance to Erlotinib in the HCC827 Human NSCLC Xenograft Model



Abbreviations: BIDBID=twice daily; QDQD=once daily

6.1.5 High Dose Steroids and Mouse Model

In an academic model of osteoporosis, BGB324 was administered in combination with high dose corticosteroids (12.5 mg/kg per day of prednisolone). In this research study, 6 out of 7 mice experienced severe toxicity after five continuous days of combination therapy. Four out of 7 animals died and the other 2 were euthanized for humane reasons. The exact mechanism of this effect is currently under investigation. The mice received very high levels of corticosteroids to induce rapid onset of osteoporosis – on a mg/kg basis, the corticosteroid dose was 20 fold higher than a typical high dose commonly used in clinical practice. Additionally, the dose of BGB324 used in this model was 50mg/kg which is 6 fold higher than the maximum exposure observed in human clinical studies.

6.2 Clinical Studies with BGB324

There has been1 previous clinical study conducted with BGB324 (Protocol BGBC001). This study explored the effect of a single administration of BGB324 in healthy male subjects. Eight dose levels (50 mg, 100 mg, 150 mg, 200 mg, 400 mg, 600 mg, 1000 mg and 1500 mg) were evaluated under fasted conditions in cohorts of 4 subjects (32 subjects in total). Seven of these subjects went on to receive a single administration of the same dose of BGB324 under fed conditions.

The current Investigator's Brochure (IB) contains a description of ongoing studies and preliminary safety data and should be used as a reference in conjunction with the protocol.

6.2.1 Summary of clinical safety to date

In general, exposure to BGB324 in healthy subjects was well tolerated with all toxicities being spontaneously reversible and predominantly gastrointestinal in nature. No serious adverse events (SAE) were reported. Adverse events (AE) judged as related to BGB324 are summarized in Table 3.

Table 3 BGB324-Related AEs Reported Following a Single Oral Administration of BGB324 to Healthy Male Subjects

BGB324 Dose (mg)	Number of Subjects Treated	Adverse Event	Maximum Grade
50	4 fasted; 1 fed	Non-cardiac chest pain	1
100	4 fasted; 2 fed	Orthostatic hypotension	1
150	4 fasted; 1 fed	Abdominal distension (2 subjects)	1
400	4 fasted; 2 fed	Diarrhea	1
600	4 fasted	Diarrhea Flatulence Nausea (2 subjects)	1 1 1
1000	4 fasted	Nausea	1
1500	4 fasted	Diarrhea Nausea Vomiting Headache Dizziness	1 2 2 1 1

In addition to this study there is one other clinical study of BGB324 recruiting patients with either relapsed/refractory Acute Myeloid Leukemia or high-risk Myelodysplastic Syndrome. Treatment with BGB324 has been generally well tolerated with most AEs being mild or moderate in severity and reversible. Approximately one half of patients who receive treatment with BGB324 experience gastrointestinal AEs including diarrhea and nausea. Further details can be found in the current version of the IB.

ECG findings

In light of the recoverable, non-adverse decreases in heart rate and corresponding increases in the RR interval durations observed in the cardiovascular study in monkeys, each subject in Study BGBC001 underwent serial electrocardiogram (ECG) assessment after administration of BGB324. At the 1500 mg dose level, 3 subjects had increases from baseline in QT interval utilizing Fridericia's correction (QTcF) of >30 ms, with subject exceeding 60 ms. Three subjects (1 in the 400 mg group and 2 in the 1000 mg group) had noticeable, mild changes in T-wave morphology from baseline (flattening and, in one case, broadening).

6.2.2 BGB324 pharmacokinetics

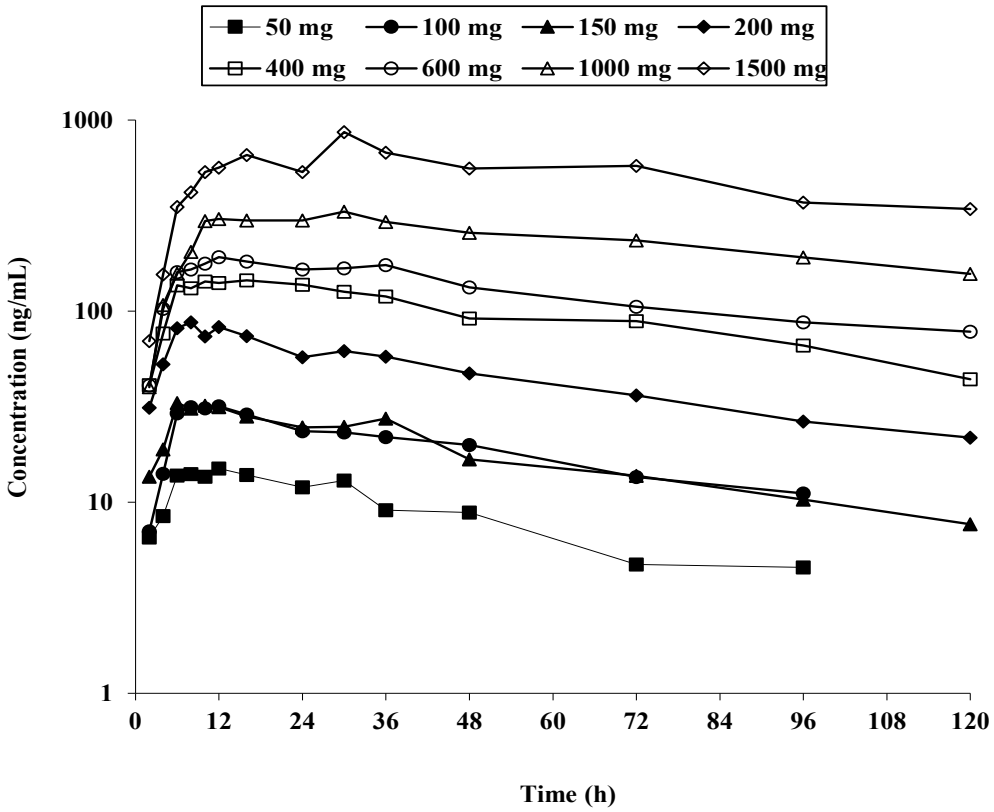
Concentrations of BGB324 were quantified in plasma samples from subjects enrolled in Study BGBC001 using a fully-validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with a lower limit of quantitation of 2.0 ng/mL. Pharmacokinetic parameters were derived by non-compartmental analysis using WinNonlin Phoenix Version 6.3 (Pharsight Corporation Inc., Mountain View, CA).

Following a single oral administration of BGB324 at doses of 50 - 1500 mg, mean maximum plasma concentrations achieved (C_{max}) of 7.6 to 388 ng/mL were reached 8-23 hours post-dose.

The mean apparent terminal half-life of BGB324 was 45.6 to 88.7 hours. Between-subject variability in systemic exposure (area under the curve extrapolated to infinity [$AUC_{0-\infty}$] and C_{max}) to BGB324 at 50 mg to 1500 mg was generally high (coefficient of variation of 25.8% to 96.7% for area under the curve within a dosing interval [AUC_{0-t}] and C_{max}), most probably reflecting variable absorption. Across this dose range, C_{max} of BGB324 increased approximately dose

proportionately, although the $AUC_{0-\infty}$ of BGB324 increased slightly greater than dose proportionately

Figure 5 Mean Plasma Concentrations of BGB324 Following a Single Oral Administration of BGB324 at 50, 100, 150, 200, 400, 600, 1000, and 1500 mg to Healthy Male Subjects



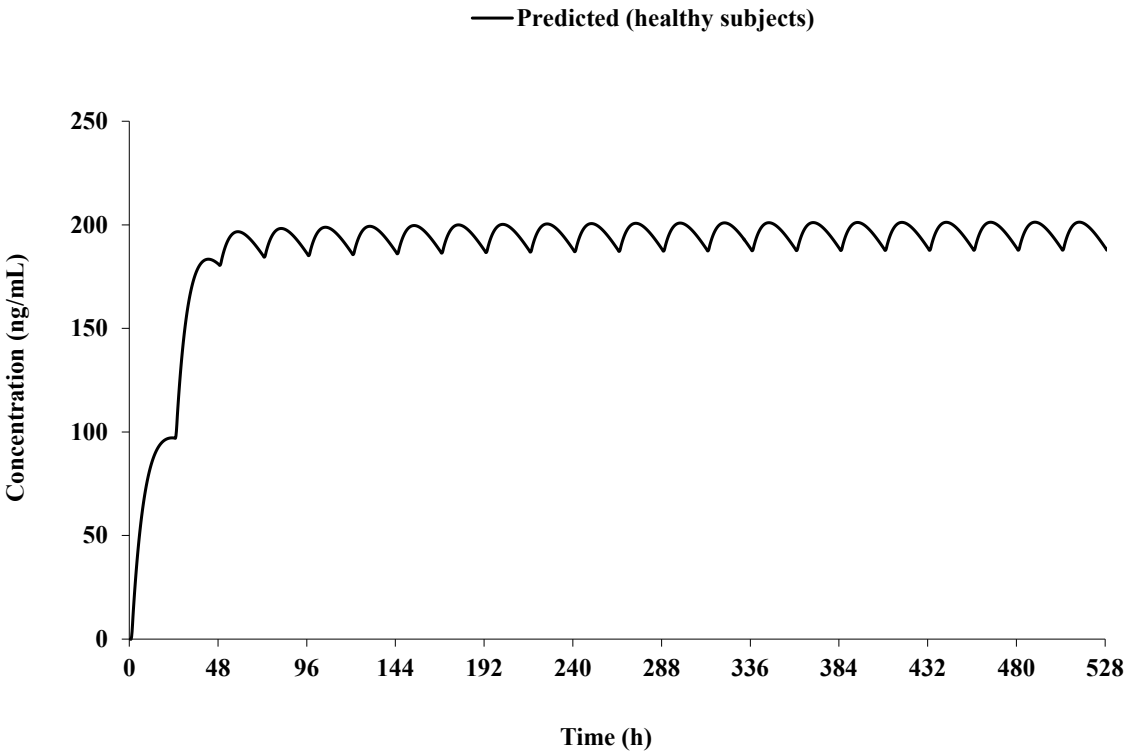
Following administration of BGB324 with food (whole milk and buttered toast) to 7 subjects who had previously received BGB324, there was an overall reduction in the between-subject variability with an increase in systemic exposure to BGB324 in 3 subjects, no appreciable change in 3 subjects and an apparent reduction in 1 subject. It was estimated that administration with food would achieve an increase in exposure in some subjects of up to 2-fold.

6.2.3 Rationale for BGB324 starting dose

In healthy subjects who received a single oral dose of BGB324, the elimination of BGB324 was slow, with mean apparent terminal half-life >24 hours. The administration schedule and starting dose of BGB324 proposed for Study BGBC004 is based on fitting a 1e-compartment model, incorporating a lag time and no weighting, to the available clinical PK data. It is anticipated that administration of a loading dose of BGB324 on Days 1 and 2 of Cycle 1, followed by daily dosing at a lower level, will deliver the optimum exposure of BGB324. The application of a loading dose will facilitate achievement of therapeutic levels, while daily dosing will prevent wide changes in systemic concentration during therapy. The simulated mean plasma concentration-time profile of BGB324, based on the PK model, following dosing of BGB324 at 600 mg on Days 1 and 2 and 200 mg daily thereafter is presented in Figure 6.

In Arm A, dose and dosing schedules have been explored to assess tolerability of the loading and daily doses and to select the RP2D for expansion into Phase 2 (Arms B and C).

Figure 6 Simulated Plasma Concentrations of BGB324 Following Repeat Once Daily Oral Administration of 200 mg BGB324 to Healthy Male Subjects Under Fasted Conditions (Loading Dose of 600 mg on Day 1 and Day 2)



On the basis of the PK profile identified in healthy subjects, it is anticipated that a loading dose of 600 mg on Days 1 and 2 of Cycle 1, followed by 200 mg daily thereafter will maintain mean systemic concentrations of approximately 400 ng/mL. PK-ECG modeling performed on the data collected in healthy subjects showed that a plasma concentration of 400 ng/mL would be expected to result in a mean increase in QTcF of 54.3 ms (90% CI of mean increase of 47.7 and 58.2 ms) from baseline.

7 OBJECTIVES AND ENDPOINTS

7.1 Run-In Cohort (Phase 1)

7.1.1 Primary objective

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

7.2 Arm A (Phase 1)

7.2.1 Primary objective

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

7.2.2 Secondary objective

- 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 PK of BGB324 and erlotinib and the potential effect of BGB324 on erlotinib.

7.2.3 Exploratory objective

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

7.3 Arm B (Phase 2)

7.3.1 Primary objective

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

7.3.2 Secondary objective

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

7.3.3 Exploratory objective

- 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.

7.4 Arm C (Phase 2)

7.4.1 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.

7.4.2 Secondary objective

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

7.4.3 Exploratory objective

- 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.

7.5 Safety Endpoints

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

- Treatment-emergent AEs.
- Physical examination.
- Vital signs including blood pressure and heart rate.
- Echocardiogram 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 performance status.

7.6 Clinical Efficacy Endpoints

Disease assessment will be performed after every 2 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 3 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.

7.7 Pharmacokinetic Endpoints

Pharmacokinetics of BGB324 and erlotinib will include $AUC_{0\text{-}t}$, C_{max} and time to maximum concentration (t_{max}) measured in plasma. Additional parameters may also be reported as deemed appropriate once data are reviewed.

7.8 Pharmacodynamic Endpoints

The effects of BGB324 on PD endpoints of Axl inhibition may be determined in blood samples and tissue specimens:

- Evaluation of changes in the phosphorylation status or levels of signaling proteins.
- Evaluation of circulating markers in the blood including sAxl, Gas6, cytokines and cell-free nucleic acids.
- Evaluation of changes in gene expression profile of tumor tissue or circulating nucleic acids.
- Evaluation of the spectrum of mutations present within the cancer cell population or in circulating nucleic acids, including EGFR mutations.
- Evaluation of the epithelial-mesenchymal transition gene signature.
- The Sponsor may evaluate other biomarkers associates with Axl as part of ongoing development plans.

8 STUDY DESIGN

8.1 Overview

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 the 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 approximately 60 patients with histologically- or cytologically-confirmed Stage IIIb or Stage IV NSCLC.

It is anticipated that up to 6 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).

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 2-stage design to evaluate the safety and tolerability, PK, PD 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 other 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 on an empty stomach according to a daily schedule during continuous 21-day treatment cycles.

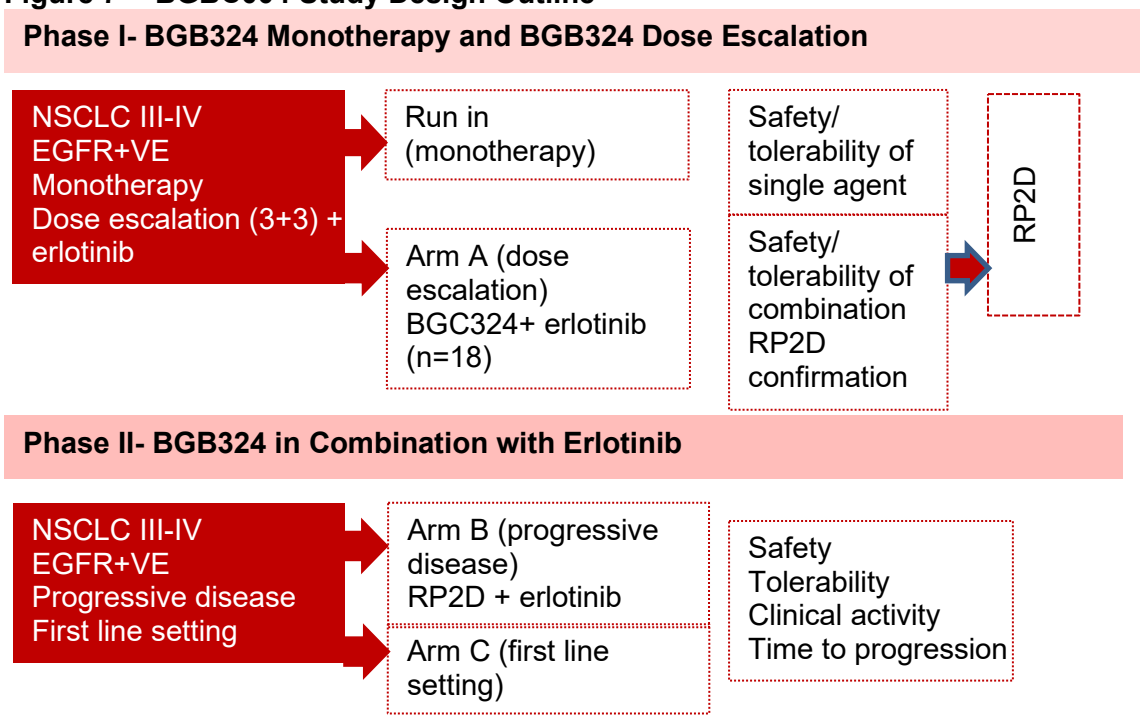
Erlotinib will be self-administered orally on an empty stomach as specified by a daily schedule during continuous 21-day treatment cycles (Arms A, B, and C only).

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 7.

Figure 7 BGBC004 Study Design Outline



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.

8.2 Run-in Cohort (Phase 1)

The primary goal of the Run-in Cohort is to establish the safety and tolerability of BGB324 administered as a single agent. Eligible patients will have either exhausted existing licensed therapies or be unsuitable for treatment with existing licensed therapies for NSCLC. BGB324 will be administered at a loading dose of 600 mg on Day 1 and Day 2 of Cycle 1, followed by 200 mg daily thereafter.

The safety data from a minimum of 6 patients who have each received at least 1 cycle of treatment with BGB324 will be reviewed by the Safety Monitoring Committee (SMC) before enrolment into Arm A can commence. The SMC will be comprised of a representative from each actively-recruiting investigational site and a representative of the Sponsor study team.

8.3 Arm A (Phase 1)

The primary goal of Arm A is to establish the dose of BGB324 administered in combination with erlotinib to be used in Arms B and C.

Patients in Arm A will have received ≥6 weeks treatment with erlotinib. This may either be historical treatment in which case there may have been an interval prior to the study and erlotinib treatment must be re-started ≥1 week immediately before the first dose of BGB324 or the treatment may be current and ongoing at the time of the first dose of BGB324 (Cycle 1, Day 1).

All erlotinib toxicities must be well controlled and <Grade 3 at the time of the first dose of BGB324 (Cycle 1, Day 1).

Erlotinib is typically administered in patients with activating EGFR mutations and it is anticipated that the majority of patients enrolled in Arm A will have activating mutations in EGFR; however, patients with wild-type EGFR who are receiving erlotinib for treatment of their NSCLC are eligible to participate in Arm A.

In addition to safety and tolerability, the PK of BGB324/erlotinib and the PD of BGB324 and erlotinib will be evaluated.

When the RP2D of BGB324 is identified the Phase 2 part of the study will start and Arms B and C will open simultaneously to enrolment.

8.3.1 BGB324 and erlotinib dose levels

The dose of BGB324 will be escalated following a standard 3+3 design in combination with erlotinib. The starting dose level of Arm A (600 mg loading dose administered over 2 days with a 200 mg daily) was selected based on the results of PK modelling.

The total loading dose may be given over 2 days (Days 1 and 2) or 3 days (Days 1, 2, and 3)*. Possible dosing levels are illustrated in Table 4 also describes the maximum dose escalation step for any increase in loading or daily dose. Note that although the half-life of BGB324 has resulted in the recommendation to give a BGB324 loading dose over 2 days to achieve steady state by Day 4, the use of the loading dose will depend on tolerability and DLT evaluation, and the SMC may recommend the dose is reduced. This may be achieved by giving the total loading dose over 3 days, giving a lower (including intermediate) loading dose, or not giving a loading dose at all.

** At the time of Amendment 5 a 3 day loading dose schedule has been confirmed*

In Arm A, at least 3 evaluable patients will be entered per dose cohort according to the 3+3 study design as described below. A dose cohort will include at least 3 patients on the same loading dose schedule and daily dose level.

The SMC may consider that data from 3 patients at any dose level is sufficient to confirm the RP2D. In addition, the SMC may recommend that alternative dose levels or dosing schedules are explored as part of the study. At the time of patient registration, the loading dose schedule, loading dose and daily dose will be confirmed.

Table 4 Possible BGB324 Dosing Levels Involving A Loading Dose and Daily Dose

Total Loading Dose (mg)	Day 1 and 2 Loading Dose (mg)	Days 1, 2 and 3 Loading Dose (mg)	Daily Dose (mg)
600	--	200	100
800	400	--	100
1200	600	400	200

If 2 DLTs occur in the combination treatment at the Arm A BGB324 starting dose, a lower dose level may be investigated (see Section 8.3.2)

If a patient withdraws or is withdrawn for reasons other than DLT prior to completing Cycle 1, the patient will be replaced for the purposes of toxicity evaluation. Patients who experience a DLT during Cycle 1 may continue on BGB324 treatment (at their assigned daily dose or lower).

In Arm A the starting erlotinib dose will be 150 mg daily during the first continuous 21-day treatment cycle. Patients who require an erlotinib dose reduction prior to completing 1 cycle of treatment will not be evaluable for toxicity and may be replaced. After completion of Cycle 1 the daily dose of erlotinib may be reduced in accordance with the patient prescribing information. In response to potential toxicity the SMC may recommended evaluating lower doses of erlotinib.

The prescribing information for erlotinib recommends a 150mg dose for NSCLC patients, however if local clinical judgement/standards require, a patient in Arm B or C may be treated at a lower erlotinib dose (i.e.,100 mg).

8.3.2 Dose escalation scheme

In Arm A, initially 3 patients will be recruited at a starting dose of 600 mg on Days 1 and 2 followed by 200 mg daily, and must complete 1 21-day cycle of treatment before a dose evaluation is made. A patient must receive all loading doses and miss no more than 3 daily doses in Cycle 1 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. If2 of 3 or 2 of6 patients in a cohort experience DLT, no further dose-escalation will take place and the prior dose level will be nominated as the RP2D.

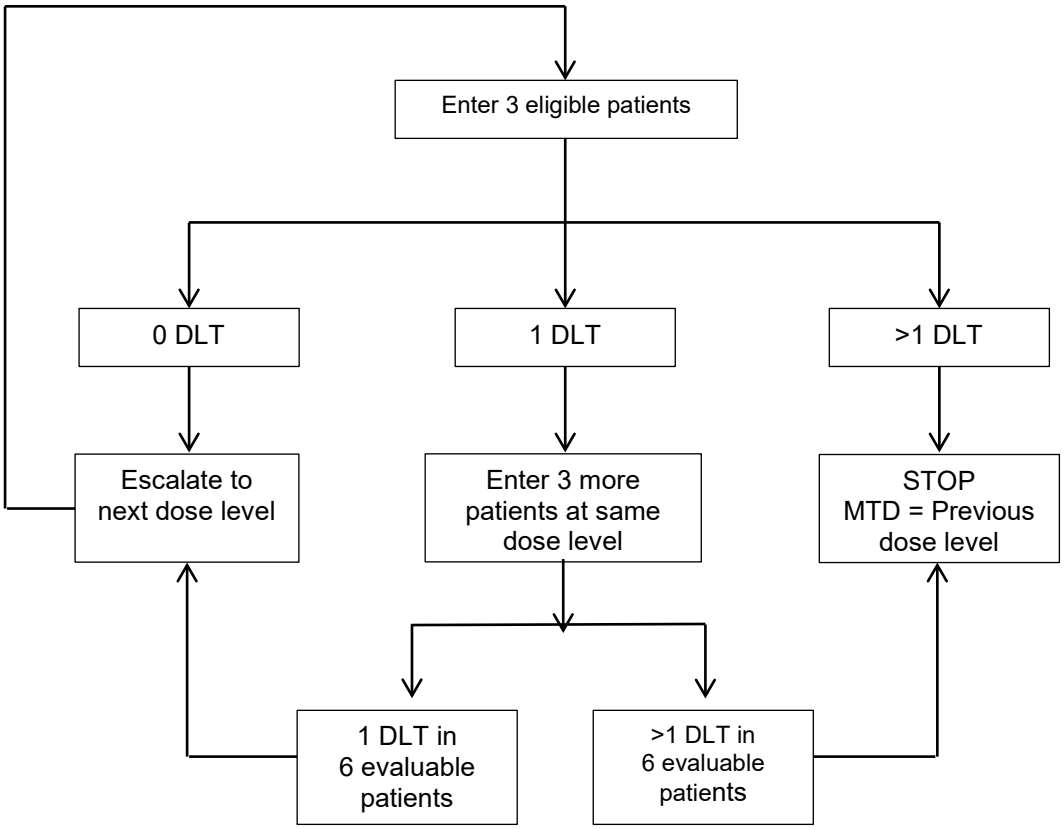
Safety reviews and recommendations for dose escalation or reduction will be made by the SMC. Minutes of the SMC meetings will be placed in the Trial Master File. The decision to dose escalate will be based on the safety and tolerability of BGB324 in combination with erlotinib observed in the first cycle of treatment.

If dose escalation occurs, 3 patients will be recruited at Dose Level 2 and will complete 1 cycle of treatment before a dose escalation evaluation is made, as outlined above.

Dose escalation may be stopped prior to achieving the MTD if it is considered by the Sponsor and SMC that a clinically acceptable RP2D has been achieved. If the starting dose exceeds the MTD, a lower dose, or dosing schedule (including an extended loading dose schedule) may be explored if recommended by the SMC.

If a patient withdraws or is withdrawn for reasons other than DLT prior to completing Cycle 1, the patient will be replaced for the purposes of evaluation of BGB324 dose. The operating characteristics of the 3+3 dose escalation process are summarized in Figure 8.

Figure 8 Operating Characteristics of the 3+3 Dose Escalation Process



Abbreviations: DLT=dose limiting toxicity; MTD=maximum tolerated dose

8.3.3 Assessment of DLTs

AEs will be assessed using the National Cancer Institute (NCI) CTCAE Version 4.03 (See Appendix 4) during the first cycle (21 days) of treatment in Arm A for the purposes of establishing the dose of BGB324 that can be safely 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.

8.4 Arm B (Phase 2)

Arm B will follow a Simon-like 2-stage design with relaxed stopping for futility to evaluate the safety and tolerability, PK, PD 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 other rearrangement of the EGFR gene mutations) who during screening have been confirmed as T790M negative, who have progressed after receiving an approved EGFR inhibitor (i.e., prior erlotinib, afatinib, or gefitinib) and who have radiological confirmation of progressive disease. Patients who have progressed on osimertinib and fulfill all other Arm B criteria will not require testing of T790M status.

If clinical response (complete response or partial response) or disease control (stable disease) is not evident after 4 cycles of treatment in at least 1 patient among the first 9 patients enrolled, no further patients will be enrolled in Arm B. If at least 1 patient in the first 9 patients demonstrates evidence of clinical response or disease control, an additional 16 patients will be enrolled. Recruitment will continue whilst data from the first 9 patients are being analyzed. Thus, up to 25 patients are anticipated to be enrolled in Arm B.

The daily dose of erlotinib may be reduced in accordance with the erlotinib prescribing information and in line with standard practice. If a patient presents with erlotinib toxicities that warrant that they stop treatment with erlotinib, then they should be either withdrawn from the study or they may continue receiving BGB324 as a single agent until disease progression (unless unacceptable toxicity, death or withdrawal of consent).

8.5 Arm C (Phase 2)

Arm C will evaluate the safety and tolerability, PD and clinical efficacy (time to progression) of BGB324 in combination with erlotinib in the first-line setting. Eligible patients will have activating EGFR mutation(s) (including exon 19 deletion or exon 21 [L858R] substitution or other rearrangement of the EGFR gene mutations) ≥12weeks of erlotinib without disease progression at the time of the first dose of BGB324 (Cycle 1, Day 1), with erlotinib-related toxicities well-controlled and <Grade 3.

The daily dose of erlotinib may be reduced in accordance with the erlotinib prescribing information. If a patient presents with erlotinib toxicities that warrant that they stop treatment with erlotinib, then they should be either withdrawn from the study or may continue receiving BGB324 as a single agent until disease progression (unless unacceptable toxicity, death or withdrawal of consent).

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.

8.6 Overall Study Duration and Follow-Up

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

8.7 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 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.

8.8 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. 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 Arm A).

Patients will attend the clinic once per week (on Cycle 2, Day1, 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 2 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 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.

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.

8.9 End-of-Study Visit

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

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.

8.10 Study Stopping Rules

The Sponsor may close a site or terminate the study or arm of the study at any time. The Investigator may also terminate the study at his/her clinical site at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Advance notice is not required by either party if the study is stopped due to safety concerns.

The reason for closure of an investigational site or termination of a study or arm of the study by the Sponsor may include but is not limited to:

- The discovery of an unexpected, serious or unacceptable risk to patients enrolled in the study.
- Failure of the Investigator to comply with the protocol and Good Clinical Practice (GCP) guidelines.
- Inadequate recruitment of patients.
- Attainment of the study objectives.
- As a result of commercial considerations, including discontinuation of further clinical development of BGB324 in NSCLC.

8.11 End of Study

The EOS is defined as when all patients have completed or withdrawn and the EOS visit has been completed. Patients who continue to receive clinical benefit while receiving BGB324 may remain on treatment until such time of unacceptable toxicity or disease progression. Patients

who remain on treatment after 12 months of treatment (Cycle 17) will have a revised visit and assessment schedule.

9 SELECTION OF PATIENTS

9.1 Inclusion Criteria

9.1.1 General inclusion criteria

1. Provision of written informed consent to participate in this investigational study.
2. Histological or cytological confirmation of Stage IIIb or Stage IV (unresectable) NSCLC.
3. ECOG performance status 0 or 1.
4. Age 18 years or older at the time of consent.
5. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to taking their first dose of BGB324. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, total sexual abstinence, vasectomy) throughout the study and for ≥3 months after the last dose of BGB324. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility, including tubal ligation, or evidence of post-menopausal status defined as any of the following:
   - Natural menopause with last menses >1 year ago.
   - Radiation induced oophorectomy with last menses >1 year ago.
   - Chemotherapy induced menopause with last menses >1 year ago.

9.1.2 Additional inclusion criteria for run-in cohort

6. Has received previous systemic therapy for unresectable NSCLC.
7. Has exhausted existing licensed therapies, or is unsuitable for treatment with existing licensed therapies for NSCLC.

9.1.3 Inclusion criteria for Arm A

8. Known EGFR mutation status.
9. Either:
   - Has received ≥6 weeks historical treatment with erlotinib. Erlotinib treatment must be re-started ≥1 week before the first dose of BGB324 (Cycle 1, Day 1);

Or:

   - Is currently receiving erlotinib treatment for NSCLC and will have received ≥6 weeks treatment at the time of the first dose of BGB324 (Cycle 1, Day 1).

10. Erlotinib-related toxicities being well-controlled and <Grade 3 in severity at the time of the first dose of BGB324 (Cycle 1, Day 1)
11. Toxicity from other prior therapy has resolved to ≤Grade 1 (previous treatment with bevacizumab and other licensed antibody therapies is permitted)

9.1.4 Inclusion criteria for Arm B

12. Patients must have documented EGFR mutation (including exon 19 deletion or exon 21 [L858R] substitution or other rearrangement of the EGFR gene). EGFR mutation may be confirmed historically (prior to study entry) and during the 28-day screening period confirmation of negative T790M status (confirmed with blood test or biopsy from

a progressing tumor). Patients who have previously been treated with a T790M inhibitor i.e., osimertinib) and who have progressed will not require T790M testing.[3]

13. Disease that is measurable according to RECIST Version 1.1.
14. Has progressed after receiving erlotinib or any other approved EGFR inhibitor (i.e., afatinib, or gefitinib) at any time during therapy for advanced disease.
15. Erlotinib-related toxicities being well-controlled and <Grade 3 in severity at the time of the first dose of BGB324 (Cycle 1, Day 1. Toxicities associated with other EGFR inhibitors to be <Grade 2 in severity at the time of first dose of BGB324).
16. Patients must have completed afatinib and/or gefitinib treatment at least 1 week before the first dose of BGB324.
17. Toxicity from other prior therapy has resolved to ≤Grade 1 (previous treatment with bevacizumab and other licensed antibody therapies is permitted).
18. Patients who have an activating EGFR mutation may have up to 4 lines of previous treatment in the advanced setting. Additional chemotherapy may also have been given for treatment of limited stage disease in the adjuvant setting provided this was completed at least 6 months prior to study treatment

9.1.5 Inclusion criteria for Arm C

19. Known EGFR mutation status:
20. Presence of an activating EGFR mutation (including exon 19 deletion or exon 21 [L858R] substitution mutation or other rearrangement of the EGFR gene.).
21. Disease that is measurable or evaluable according to RECIST Version 1.1.
22. Is currently receiving erlotinib for NSCLC and will have received ≥12 weeks of treatment at the time of the first dose of BGB324 (Cycle 1, Day 1).
23. Erlotinib-related toxicities well-controlled and <Grade 3 in severity at the time of the first dose of BGB324 (Cycle 1, Day 1).
24. No prior treatment for advanced NSCLC except erlotinib and/or previous surgery (patients who have received treatment for their NSCLC while awaiting confirmation of EGFR status, may be eligible to participate and the inclusion of such patients should be discussed with the Medical Monitor)

9.2 Exclusion Criteria

1. Pregnant or lactating.
2. Abnormal left ventricular ejection fraction (less than the lower limit of normal for a patient of that age at the treating institution or <45%).
3. Treatment with any of the following: histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 3 days or 5 half-lives, whichever is longer. The Investigator may initiate rescue treatment with these medications during the study, providing they are taken in the evening.
4. History of an ischemic cardiac event including myocardial infarction within 3 months of consent.
5. Pulmonary hemorrhage or hemoptysis >2.5 mL blood within 6 weeks of consent unless cause has been addressed and is medically resolved.
6. Congestive cardiac failure of >Class II severity according to the New York Heart Association (NYHA) defined as symptomatic at less than ordinary levels of activity (see Appendix 2).

[3] The 28-day screening period may be extended to allow for confirmation of the T790M status. Other assessments including CT should be conducted in the 28-day screening period. (see Section 10.12.11 for additional information on T790M testing).

7. Unstable cardiac disease, including unstable angina or unstable hypertension, as defined by the need for change in medication for lack of disease control within 3 months of consent.
8. History or presence of sustained bradycardia (≤60 bpm) or history of symptomatic bradycardia, left bundle branch block, cardiac pacemaker or significant atrial tachyarrythmias, as defined by the need for treatment.
9. Current treatment with agents that may prolong QT interval and may cause Torsade de Points which cannot be discontinued at least 2 weeks prior to treatment.
10. Known family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy.
11. Previous history of ≥Grade 3 drug-induced QTc prolongation.
12. Screening triplicate 12-lead ECG with an average measureable QTcF >450 ms.
13. Inadequate liver function as demonstrated by:
    - Serum bilirubin ≥1.5 times the upper limit of normal range (ULN); or
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the ULN (up to 5 times the ULN in the presence of liver metastases.
14. Inability to tolerate oral medication.
15. Impaired coagulation as evidenced by:
    - International normalized ratio (INR) >1.5 times ULN (or equivalent); or
    - Activated partial thromboplastin time (aPTT) >1.5 times ULN.
16. Existing gastrointestinal disease affecting drug absorption, such as celiac disease or Crohn's disease.
17. Previous bowel resection that may impair study drug absorption.
18. Impaired renal function as demonstrated by creatinine clearance of ≤50 mL/min determined by Cockcroft-Gault formula.
19. Absolute neutrophil count <1.5 x 10^9/L, hemoglobin <9.0 g/dL, platelet count <100 x 10^9/L in the absence of blood product support.
20. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol.
21. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index.
22. Active, uncontrolled central nervous system (CNS) disease (previously-treated CNS metastases that are asymptomatic and do not require steroid treatment are allowed). Note: Patients with known CNS metastases who have completed radiotherapy at least 2 weeks prior to BGB324 treatment are eligible
23. Known active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses (screening not required).
    - Patients who have a history of hepatitis B infection are eligible provided they are hepatitis B surface antigen negative.
    - Patients who have a history of hepatitis C infection are eligible provided they have no evidence of hepatitis C ribonucleic acid using a quantitative polymerase chain reaction assay at least 6 months after completing treatment for hepatitis C infection.
24. Major surgery requiring general anesthesia within 28 days prior to the start of BGB324, excluding biopsies and procedures for insertion of central venous access devices.
25. Treatment with cytotoxic chemotherapy, within 3 weeks prior to the first dose of BGB324 (Cycle 1, Day 1) with the exception of treatment with other EGFR inhibitors which must be completed 1 week prior to commencing treatment with BGB324.There is no requirement to discontinue ongoing treatment with erlotinib.
26. Treatment with other non-cytotoxic agents for NSCLC in the 10 days or 4 half-lives prior to the first dose of BGB324 (Cycle 1, Day 1), whichever is shorter.

27. Prior biological therapies in the 4 weeks (or 5 half-lives, whichever is shorter) before the first dose of study BGB324 (Cycle 1, Day 1). Note prior treatment with an alternative EGFR inhibitor and/or PD-1 blockade are permitted

10 STUDY PROCEDURES AND ASSESSMENTS

The schedule of events is summarized in Table 5.

Table 5 Schedule of Events

Cycle		1											2							≥3 w			End-of-Study
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

BGB324 administration[0]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Erlotinib administration[0]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability			X					X			X		X		X		X		X	X		X	X	
Adverse events		X ----------X																						
Concomitant medications		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.

10.1 Procedures at each Visit

10.1.1 Screening and enrollment

Patients must provide written informed consent before any screening procedures are performed. The screening period covers up to 28* days prior to the first dose of BGB324.

During screening, the following procedures will be performed:

- Demographics.
- Medical history.
- Cancer history and treatments (medications and surgeries).
- EGFR mutation recorded
- T790M status confirmed in the screening period (Arm B)[4]
- Performance status assessment (ECOG).
- Physical examination.
- Vital signs (including height and weight)
- Serial 12-lead ECGs, in triplicate.
- Serum pregnancy test, if applicable.
- Clinical chemistry, (including amylase and lipase), hematology, urinalysis, coagulation
- Echocardiogram or MUGA scan.
- Disease assessment.
- Review of inclusion/exclusion criteria.

Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception throughout the study and for ≥3 months after the last dose of BGB324. Highly effective methods of contraception are defined as:

- Hormonal implants, combined oral contraceptives, injectable contraceptives.
- An intrauterine device with hormone spirals.
- Tubal ligation.
- True total sexual abstinence.
- Vasectomy.

If it is not possible to use one of these highly effective methods of contraception, 2 barrier methods used simultaneously are acceptable.

The following baseline samples should be taken in the 28 days before the first dose of BGB324 after the patient has been confirmed as otherwise eligible:

- Blood collection for PD (Arms A, B, and C only).
- Tissue collection for PD (consenting patients only) (Arms A, B, and C).

Patients who meet all inclusion/exclusion criteria will be allocated a study-specific patient number.

10.1.2 Cycle 1

All AEs and concomitant medication use will be recorded throughout the cycle.

[4] The screening period for Arm B may be extended to allow for confirmation of T790M status all other assessments are to be conducted in the 28-day screening period. Patients who have previously been treated with a T790M inhibitor (i.e., osimertinib) and who subsequently progressed will not require T790M testing.

In addition, tissue (in consenting patients) and blood will be collected for pharmacodynamic assessment at one on-study time point after 14 consecutive days of BGB324 administration either in Cycle 1 or Cycle 2 (Arms A, B, and C).

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

10.1.2.1 *Day -1 (Arm A)*

- Symptom-directed physical examination.
- Vital signs.
- Serial 12-lead ECGs, in triplicate.
- Serum pregnancy test (does not have to be repeated on Day -1 if conducted as part of screening procedures within 3 days prior to Day 1).
- Clinical chemistry, hematology, coagulation, urinalysis (does not have to be repeated on Day -1 if conducted as part of screening procedures within 3 days prior to Day 1).
- Blood sampling for erlotinib PK
- Erlotinib administration orally, on an empty stomach.

10.1.2.2 *Day 1, Day 8, Day 15*

- Symptom-directed physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate.
- Clinical chemistry, hematology, coagulation, urinalysis.
- Blood sampling for PK (Run-in Cohort, Arms A and B).
    - PK sampling in Arm B will be for BGB324 only- see Table 6.
- BGB324 administration orally on an empty stomach.
- Erlotinib administration (Arms A, B, and C) orally, on an empty stomach.
- Drug accountability.

10.1.2.3 *Day 2, Day 3, Day 4*

- Vital signs.
- Pre-dose serial 12-lead ECGs, in triplicate.
- Clinical chemistry and hematology.
- Blood sampling for PK (Run-in Cohort, Arms A and B)
    - PK sampling in Arm B will be for BGB324 only- see Table 6.
- BGB324 administration orally on an empty stomach.
- Erlotinib administration (Arms A, B, and C) orally, on an empty stomach.

10.1.2.4 *Day 9*

- Vital signs.
- Serial 12-lead ECGs in triplicate.
- Blood sampling for PK (Run-in Cohort, Arms A and B)
    - PK sampling in Arm B will be for BGB324 only-see Table 6.
- BGB324 administration orally, on an empty stomach.
- Erlotinib administration (Arms A, B, and C) orally, on an empty stomach.

10.1.2.5 *Days 5-7, 10-14, 16-21*

- BGB324 and erlotinib (Arms A, B, and C) will be self-administered orally on an empty stomach by the patient at home.

10.1.3 Cycle 2

10.1.3.1 *Day 1, Day 8, Day 15*

All AEs and concomitant medication use will be recorded throughout the cycle.

In addition, tissue (in consenting patients) and blood will be collected for PD assessment at one on-study time point after 14 consecutive days of BGB324 administration in Cycle 1 or Cycle 2 (Arms A, B, and C).

- Performance status assessment (Day 1 only).
- Symptom-directed physical examination.
- Vital signs.
- Serial 12-lead ECGs, in triplicate.
- Clinical chemistry, hematology, urinalysis
- Coagulation (Day 1 only).
- Blood sampling for PK (Run-in Cohort, Arms A and B).
    - PK sampling in Arm B will be for BGB324 only- see Table 6.
- BGB324 administration orally, on an empty stomach.
- Erlotinib administration (Arms A, B, and C) orally, on an empty stomach.
- Drug accountability.

10.1.3.2 *Days 2-7, 9-14, 16-20*

- BGB324 and erlotinib (Arms A, B, and C) will be self-administered orally on an empty stomach by the patient at home.

10.1.4 Cycles ≥3-C17

All AEs and concomitant medication use will be recorded throughout each cycle.

10.1.4.1 *Day 1*

- Performance status assessment.
- Symptom-directed physical examination.
- Vital signs.
- Serial 12-lead ECGs, in triplicate.
- Urine pregnancy test at 3 month intervals.
- Clinical chemistry, hematology, urinalysis, coagulation (+/- 3 days).
- Blood sampling for PK.
    - PK sampling in Arm B will be for BGB324 only- and will continue to Cycle 3, Day 1 - see Table 6
- Echocardiogram or MUGA scan (Cycle 4 only).
- BGB324 administration orally, on an empty stomach.
- Erlotinib administration (Arms A, B, and C) orally, on an empty stomach.
- Drug accountability.

10.1.4.2 *Days 2-20*

- BGB324 and erlotinib (Arms A, B, and C) will be self-administered orally, on an empty stomach, by the patient at home.

10.1.5 End-of-study visit

The following assessments will then be carried out at the EOS visit (28 days after the last dose of study drug) for every patient enrolled into the study.

- Performance status assessment.
- Physical examination.

- Vital signs.
- Serial 12-lead ECGs, in triplicate
- MUGA/ECHO.
- Serum pregnancy test.
- Clinical chemistry, hematology, coagulation and urinalysis.
- Blood sampling for PK
    - PK sampling in Arm B will be for BGB324 only - see Table 6.
- Disease assessment (if not performed within previous 28 days).
- Drug accountability.
- AEs assessment.
- Concomitant medications assessment.

10.1.6 Assessments at disease progression

The following assessments are required at disease progression

- Tissue collection for PD (in consenting patients) (Arms A, B, and C).
- Blood collection for PD (Arms A, B, and C).
- CT scan and RECIST evaluation (as per local standards).

10.1.7 Visit schedule after 12 months of treatment

Patients who remain on BGB324 for 12 months or more will be able to reduce the frequency and number of assessments required at each visit.

Patients will return to clinic every 6 weeks (every 2 cycles). The following assessments will be undertaken:

- Symptom-directed physical examination (every 3 months).
- Serial 12-lead ECGs, in triplicate.
- Clinical chemistry, hematology, urinalysis (every 3 months).
- Drug accountability.
- AE and concomitant medication reporting.
- Pregnancy test as applicable (every 3 months).

10.1.8 Visit schedule while on corticosteroids

Patients receiving BGB324 who require the support of prednisolone (or equivalent) at 10mg to 40mg daily should be monitored at weekly intervals whilst receiving steroid treatment until the steroid dose is 10mg or less daily or is stopped.

Patients will be requested to return weekly at which time the following assessments will be undertaken:

- Physical examination
- Vital signs
- Clinical chemistry, hematology
- AE reporting/concomitant medication reporting

Patients who require daily steroids of more than 40mg prednisolone (or equivalent) should interrupt BGB324 until the steroid dose is 40mg or less daily.

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

Patients who are already attending weekly visits for C1 and C2 do not require additional visits.

10.2 Details of Study Procedures

10.2.1.1 *Clinical Laboratory Assessments*

The following clinical laboratory parameters will be measured at a local laboratory:

- Clinical chemistry (serum): potassium, calcium, uric acid, electrolytes, blood urea nitrogen, total protein, total bilirubin, ALT, AST, creatinine, creatine phosphokinase, alkaline phosphatase, albumin, phosphorus, glucose, magnesium plus amylase and lipase (during screening only).
- Hematology: full blood count including differential white cell count, hemoglobin, hematocrit and platelets.
- Coagulation parameters: prothrombin time and/or INR, aPPT.
- Urinalysis: Dipstick measurement of blood, nitrite, glucose, ketones, leukocytes, protein, and pH. (microscopic analysis is not required unless clinically indicated).
- EGFR T790M to be undertaken in accordance with local standard practice.

All tests will be performed at screening (and on Cycle 1, Day -1 for patients in Arm A)

Thereafter, clinical chemistry and hematology will be performed at each study visit. Coagulation will be performed on Days 1, 8, and 15 in Cycle 1, Day 1 in all subsequent cycles and the end-of-study visit.

Urinalysis will be performed on Days 1, 8, and 15 in Cycle 1 and Cycle 2, Day 1 in all subsequent cycles and the EOS visit.

10.2.2 Pregnancy test

In women of child bearing potential a serum pregnancy test should be taken at screening and Day 1 (and on Cycle 1, Day -1 for patients in Arm A unless conducted as part of screening procedures within 3 days prior to Cycle 1, Day 1) and at the EOS visit.

During the study, a urine pregnancy test should be repeated every 3 months.

Should a patient suspect that pregnancy may have occurred an unscheduled pregnancy test should be conducted. The patient must have negative tests for eligibility and continuation on the study.

10.2.3 Vital signs

Blood pressure, pulse, respiratory rate and oral temperature will be consistently recorded at all study visits (with the exception of visits performed for disease assessment).

10.2.4 Triplicate 12-lead ECG

Triplicate 12-lead ECGs, at least 5 minutes apart, will be performed after resting for ≥10 minutes in supine position during screening and pre-dose on Day -1 (Arms A and B) then Day 1, 2, 3, 4, 8, 9, and 15 in Cycle 1, pre-dose on Days 1, 8, and 15 in Cycle 2, pre-dose on Day 1 in Cycle 3 onwards, and at the EOS visit.

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 ECGs should be conducted during Cycle 1, Day 8 - Day 15 and Cycle 1, Day 15 – Day 21.

Continuous variables (PR interval, RR interval, QRS duration, QT and QTcF intervals) and an overall assessment will be recorded in the electronic case report form (eCRF).

QTc values recorded should be calculated as the average from the 3 traces taken.

10.2.5 Echocardiogram/MUGA

An ECG or MUGA scan will be performed at screening at 6 monthly intervals and at the EOS visit.

10.2.6 Physical examination

A full physical examination of each body system will be performed at screening and the EOS visit. Note genitalia/pelvic/rectal examinations only need to be performed if clinically indicated.

A symptom-directed examination will be performed pre-dose on Day -1 (Arm A) then Days 1, 8, and 15 in Cycles 1 2 and Day 1 in Cycle 3 onwards.

10.2.7 Performance status

Performance status will be assessed using the ECOG scale (see Appendix 1) at screening, Day 1 of each cycle starting on Cycle 2 and the EOS visit.

10.2.8 Pharmacokinetic assessments

Detailed procedures for the collection, processing, storage and shipment of samples will be provided in the laboratory manual. Approximate blood volumes required for PK analysis will be included in the patient information sheet, actual volumes will depend upon the arm to which the patient has been enrolled and the duration of treatment.

Blood samples will be taken for the determination of BGB324 in plasma in the Run-in Cohort and Arm B and for the determination of BGB324 and erlotinib in Arm A at the time points shown in **Table** 6.

If there is sufficient PK data from the first 9 patients in Arm B, consideration may be given to omitting PK sampling in the second 16 patients. In addition, sampling on Day 1 of each cycle will be discontinued after Cycle 3.

Table 6 Time points for Pharmacokinetic Sample Collection (Run-in Cohort, Arms A and B Only)

		Arm A	Run in Arm B (3-day loading dose)
Study Day	**Time (hours)**	**Erlotinib and BGB324**	**BGB324**
C1-Day1	0 (pre-dose)	X	
	2	X	
	4	X	
	6	X	
	8	X	
C1 Day 1	0 (pre-dose)	X	X
C1 Day 2	0 (pre-dose)	X	X
C1 Day 3	0 (pre-dose)	X	X
	2		X
	4		X
	6		X
	8		X
C1 Day 4	0 (pre-dose)	X	X
C1 Day 8	0 (pre-dose)	X	X
	2	X	X
	4	X	X
	6	X	X
	8	X	X
C1 Day 9	0 (pre-dose)	X	X

C1 Day 15	0 (pre-dose)		X
C2 Day 1	0 (pre-dose)		X
C2 Day 8	0 (pre-dose)		X
C2 Day 15	0 (pre-dose)		X
C3 Day 1	0 (pre-dose)	X	X
End-of-Study Visit	NA	X	X

C = Cycle; NA = Not applicable

Pharmacokinetic schedules should be adhered to where possible. Pre-dose samples should be taken has close to the erlotinib/BGB324 dose as possible (and within a maximum of 20 minutes prior to the erlotinib dose). At each post-dose time point an approximate ±20 minute window is allowed.

Standard procedure should be followed for the collection of blood and the preparation of plasma samples for pharmacokinetic analysis. Sufficient blood (approximately 3 mL) should be collected and processed to support the preparation of **duplicate 1 mL plasma samples** (primary sample for analysis and secondary sample for retention).

10.2.9 Pharmacodynamic assessments (Arms A, B and C)

10.2.9.1 *Pharmacodynamic tissue and blood samples*

Detailed procedures for the collection, processing, storage and shipment of samples will be provided in the laboratory manual. The effects of BGB324 on PD endpoints of Axl inhibition will be determined in blood samples and tissue specimens (see Section 7.8).

A tumor tissue sample for analysis of PD endpoints should be taken using a core needle biopsy at baseline (within 28 days before the first dose of BGB324, after patient eligibility has been confirmed), 1 on-study collection time point performed any time after 14 days of continuous exposure to BGB324 during Cycle 1 or in Cycle 2 and 1 collection time point at the time of disease progression and prior to the EOS visit (derived from the lesion exhibiting disease progression).

Standard clinical site practice should be followed for the collection of core needle tumor tissue samples. These samples are optional and will only be taken from patients providing separate consent in Arms A, B and C.

10 mL (2 x 5 mL) blood samples (for the preparation of plasma and buffy coat fractions) will be collected for all patients enrolled in Arms A, B, and C at baseline (within 28 days before the first dose of BGB324 and after patient eligibility has been confirmed), 1 on-study collection time point performed any time after 14 days of continuous exposure to BGB324 during Cycle 1 or in Cycle 2 and 1 collection time point at the time of disease progression and prior to the EOS visit.

Note: If a patient has consented to **have optional tumor biopsy** samples taken, the PD blood samples should be taken at the same time.

10.2.10 Clinical efficacy

Disease assessment will be performed at screening and 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.

- 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.

Disease assessment and confirmation of response will be performed according to RECIST Version 1.1 guidelines (Eisenhauer, 2009).

10.2.11 T790M confirmation

For patients to be eligible for Arm B, their latest EGFR T790M status should be confirmed during the screening period. This can be done either via blood test (circulating tumour DNA [ctDNA], serum or plasma) or tumour biopsy. Both the blood test/biopsy should be undertaken in accordance with local standard procedures

Patients who have previously been treated with a T790M inhibitor (i.e., osimertinib) will not require T790M testing and will be eligible providing they meet all other inclusion/exclusion criteria.

For those patients who have not been on a T790M inhibitor, blood-based testing using circulating tumor DNA for the presence of the mutation may be utilised, however if a negative T790M blood result is obtained, the result requires confirmation on biopsy material.

11 STUDY TREATMENT

The Sponsor will provide BGB324 to each study site.

Erlotinib will be obtained locally and administered following institutional practices.

11.1 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.

11.2 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.

11.3 Dose Modification

The AE profile for BGB324 suggests that diarrhea and gastrointestinal disturbances are frequently reported (see current IB for further information). As BGB324 and erlotinib have the potential for overlapping toxicities patients should be advised accordingly and provided with antidiarrheals for symptomatic management.

Dose modifications and dose interruptions to manage toxicities should be considered for both BGB324 and erlotinib. Dose modifications for erlotinib should be undertaken in line with the current prescribing information.

Dose modifications and recommendations for the management of toxicities suspected to be related to BGB324 are provided in Table 7 and Table 8.

11.3.1 BGB324 toxicities and dose modification

11.3.1.1 *BGB324 loading dose toxicities*

If the patient is unable to tolerate the loading doses (i.e. for example more than a single CTCAE grade worsening of any adverse event or the appearance of any new Grade 3 toxicities), they may continue with the assigned daily dose, but will be required to attend the clinic for additional ECG assessments between Cycle 1, Days 8 and 15 and between Cycle 1, Day 15 and the end of Cycle 1.

11.3.1.2 *BGB324 daily dose toxicities*

Recommended BGB324 dose modifications are provided in Table 7 and Table 8.
If, after a 14-day delay, treatment-related toxicity has not resolved, the patient may be discussed with the Medical Monitor prior to being withdrawn from the study.

For those patients who experience a BGB324 dose delay of ≥7 days, the BGB324 loading dose assigned should be repeated. If the patient was unable to tolerate the loading dose in Cycle 1 the repeat loading dose can be omitted. The requirement to reintroduce the loading dose should be discussed with the Medical Monitor.

Drug holidays for reasons other than BGB324 or erlotinib toxicity may be permitted on a case--by-case basis and should be discussed with the Medical Monitor.

Table 7 Daily Dose Modification of BGB324 for Toxicity

Grade (CTCAE)	Recommended Dose Modification
Grade 1 and Grade 2 (tolerable)	
Any occurrence	Maintain dose if toxicity is tolerated by the patient
Grade 2 (intolerable)	
1st or 2nd occurrence of same event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2. Resume dosing at same dose
3rd occurrence of same event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2. Dose reduce by 100 mg

Grade (CTCAE)	Recommended Dose Modification
4th occurrence of same event	Discontinue permanently
Grade 3	
1st occurrence	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2. Dose reduce by 100 mg or, Discontinue permanently if dose has already been reduced
2nd occurrence of same event at Grade 3	Discontinue permanently
Grade 4	
1st occurrence	Discontinue permanently
Notes: • Treatment interruption for BGB324-related toxicity should be limited to 14 days, • Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg BGB324), • Patients being considered for dose reduction or permanent discontinuation of BGB324, may be discussed with the Medical Monitor,	

11.3.1.3 *BGB324 dose modification for QTC*

BGB324 demonstrates some potential for QTc prolongation. In order to reduce the risk of QTc prolongation, all efforts should be made to maintain the patient's serum potassium levels at >4 mmol/L during treatment with BGB324 and for 2 weeks following completion of therapy (at an unscheduled visit, if required). If a patient presents with QTcF prolongation of ≥Grade 2, the dose modification / dose interruption recommendations (Table 8) are recommended.

Table 8 Daily Dose Modification of BGB324 for QTc Prolongation

QTcF	Recommended BGB324 Dose Modification
Grade 1 (451-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms)	
1st occurrence	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, dose reduce by 100 mg
≥2nd occurrence (without dose modification)	Repeat procedure for "1st occurrence"
≥2nd occurrence (at reduced dose)	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no further dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, interrupt treatment for ≤14 days - if QTcF reduces to ≤Grade 1, no dose modification is required and dosing can recommence; if treatment interruption is required on more than 2 occasions at reduced dose, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible
≥Grade 3 (≥501 ms)	
1st occurrence	Interrupt treatment for ≤14 days;

QTcF	Recommended BGB324 Dose Modification
	- if QTcF reduces to ≤Grade 1, dose reduce by 100 mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, discontinue treatment
2nd occurrence	Discontinue permanently
Ventricular arrythmia	
1st occurrence	Discontinue permanently

Notes:

- Serum calcium, magnesium and potassium should be measured regularly whilst receiving BGB324; all abnormal results should be corrected.
- The mean QTcF value from triplicate ECG readings should be used when considering dose modification
- Treatment interruption for BGB324-related toxicity should be limited to 14 days.
- Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg BGB324).
- Patients being considered for dose reduction or permanent discontinuation of BGB324 should be discussed with the Medical Monitor.

11.3.1.4 *BGB324 dose modification for steroids doses over 40mg daily (prednisolone equivalent)*

If a patient requires prednisolone (or equivalent) at daily doses above 40mg then BGB324 should be interrupted until the steroid dose is equivalent to or less than 40mg daily, at which time weekly monitoring will be undertaken until the steroid dose is equivalent or less than 10mg (Section 10.1.8)

For those patients who experience a BGB324 dose delay of ≥7 days, the BGB324 loading dose assigned should be repeated. If the patient was unable to tolerate the loading dose in Cycle 1 the repeat loading dose can be omitted. The requirement to reintroduce the loading dose should be discussed with the Medical Monitor.

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.

11.3.2 Erlotinib dose reduction

In Arm A Cycle 1, the erlotinib dose should be maintained at 150mg daily for at least 21 days, after which dose reductions may be made in accordance with the erlotinib prescribing information.

In Arms B and C, erlotinib dose reductions may be made in accordance with the current erlotinib prescribing information. The prescribing information for erlotinib recommends a 150mg dose for NSCLC patients, however if local clinical judgement/standards require, a patient in B and C may be treated at a lower erlotinib dose (i.e., 100mg).

11.4 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 completed ≥2 weeks before the first dose of BGB324 and provided the patient is neurological stable and does not require corticosteroids.

11.5 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.

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.

11.6 Discontinuation of Treatment and Withdrawal

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.

11.7 Patient Replacement

Patients in Arm A who discontinue during the DLT assessment period (Cycle 1 [21 days]) for any reason other than a DLT will be replaced. All other patients who discontinue study treatment will not be replaced.

12 MANAGEMENT OF STUDY MEDICATIONS

Every patient enrolled in the study will receive BGB324 as a single agent (Run-in Cohort) or in combination with erlotinib (Arms A, B, and C).

12.1 BGB324

Accountability for study treatment BGB324 is the responsibility of the Investigator. The Investigator/designee must ensure that BGB324 will be dispensed to patients in accordance with the protocol and that any unused BGB324 will be reconciled in accordance with written instructions from the Sponsor.

Study staff should refer to the pharmacy manual for specific instructions regarding the handling, storage, dispensing of BGB324.

BGB324 has been manufactured in accordance with appropriate Good Manufacturing Practice (GMP) standards. BGB324 will be labelled in compliance with GMP Annex 13 requirements, US Food and Drug Administration (FDA) requirements and local regulatory guidelines.

BGB324 will be supplied in size zero Swedish orange hydroxypropyl methylcellulose (HPMC) capsules at a dose strength of 100 mg for oral dosing.

Please refer to the current version of the IB for additional information on the physical, chemical and pharmaceutical properties of BGB324.

12.1.1 BGB324 storage

BGB324 will be shipped to the site and must be stored at the site in a secure location under ambient temperature conditions (store below 77^0F). The patient dosing diary will provide guidance for storage at home.

12.1.2 BGB324 accountability

The Investigator/designee must maintain complete and accurate accountability records for BGB324, showing the date of receipt and quantity of all supplies of investigational product. These records must include accurate patient-specific dispensing information, including quantity, bottles dispensed, date dispensed and quantity and date returned.

At the end of the study, reconciliation must be made between the amount of BGB324 supplied, dispensed with reconciliation of any discrepancies. The Pharmacy manual will contain additional information on the reconciliation and returns procedures.

12.2 Erlotinib

Erlotinib will be stored and dispensed following institutional guidelines.

The Investigator or his/her designee must maintain complete and accurate erlotinib dispensing logs, including the amount administered and the date.

13 SAFETY MONITORING AND REPORTING

Safety assessments will consist of monitoring and recording AEs, including SAEs; measurement of protocol-specified clinical laboratory assessments; 12-lead ECGs measurement of protocol-specified vital signs; and other protocol-specified tests that are

deemed critical to safety evaluation of each patient. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 13.5.

13.1 Adverse Event Definitions

13.1.1 Adverse event

According to the International Conference on Harmonisation (ICH) guideline for GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency or severity of a known condition); worsening of the patient's underlying cancer is not considered an AE.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive screening procedures, such as biopsy, blood sampling).

13.1.2 Serious adverse event

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death).
- Is life-threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death). This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization, with exception of those events described in Section 13.4.7.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient‘s ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Is a significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms *severe* and *serious* are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, severe or life threatening or according to NCI CTCAE criteria Version 4.03 [Appendix 4]; see Section 13.3.1). The event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 13.5 for reporting guidelines).

The Investigator is responsible for ensuring that all AEs are recorded on the AE eCRF pages and appropriately reported to the Sponsor in accordance with instructions provided.

For each AE recorded on the AE eCRF, the Investigator will make an assessment of seriousness, severity (see Section 13.3.1), and causality.

13.2 Adverse Event Reporting Period

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. If study drug-related toxicities continue beyond this period, patients will be followed until these toxicities have resolved to ≤Grade 1 or less, stabilized or returned to baseline. Any study drug-related SAEs will be collected indefinitely.

Any SAEs occurring between informed consent and the first dose of BGB324 or erlotinib must also be reported to the Sponsor according to the process in Section 13.5 and also recorded on the eCRF if the patient receives study treatment.

Investigators will seek information on AEs at each patient contact.

All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient‘s medical record and in the AE eCRF. A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points. Examples of non-directive questions include the following:

- How have you felt since your last clinic visit?
- Have you had any new or changed health problems since you were last here?

13.3 Assessment of Adverse Events

13.3.1 Assessment of severity of adverse events

The AE severity grading scale for the NCI CTCAE Version 4.03 (Appendix 4) will be used for assessing AE severity.

For AEs not specifically listed in the NCI CTCAE, the guidelines in Table 9 will be used for assessing severity.

Table 9 Guidelines for Assessment of Severity for Adverse Events not Listed in CTCAE

Grade	Guideline
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
Grade 4	Life-threatening consequences or urgent intervention indicated[d]
Grade 5	Death related to adverse event[d]

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event per the definition of serious adverse event in Section 113.1.2.
d. Grade 4 and 5 events must be reported as serious adverse events per the definition of serious adverse event in Section 13.1.2.

13.3.2 Assessment of causality of adverse events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to BGB324 and/or related to erlotinib indicating "suspected" or "not related" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Causality will be assessed individually for each protocol-mandated treatment.

13.4 Recording Adverse Events

Investigators should use correct medical terminology and concepts when recording AEs on the AE eCRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field on the AE eCRF.

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A pre-existing medical condition which is present at the start of the study and described in the Medical History eCRF, should only be recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g. “more frequent headaches”).

13.4.1 Adverse events occurring secondary to other events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the AE eCRF.

For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe hemorrhage leads to renal failure, both events should be reported separately in the eCRF.
- If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.

- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

13.4.2 Persistent and recurrent adverse events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE eCRF. The initial severity of the event should be recorded and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the AE eCRF should be updated to reflect this. A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the AE eCRF.

13.4.3 Abnormal laboratory and ECG values

Not every laboratory abnormality qualifies as an AE.

A laboratory test result should be reported as an AE if it is assessed to be clinically significant. Suggested criteria for the assessment of clinical significance are:

- Is accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Requires more frequent follow-up assessments, further diagnostic investigation, etc.
- Is judged as clinically significant in the Investigator‘s opinion.

Abnormal laboratory results clearly consistent with the pattern of NSCLC disease or progression do not need to be reported as an AE.

It is the Investigator‘s responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the AE eCRF. If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as hyperkalemia.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded and the severity or seriousness should be updated any time the event worsens.

13.4.4 Abnormal vital sign values

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms.

- Results in a change in study treatment (e.g., dosage modification, treatment interruption or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Is judged as clinically significant in the Investigator‘s opinion.

It is the Investigator‘s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE. If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the AE eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

13.4.5 Abnormal liver function tests

An AE meeting the following criteria should be reported to the Sponsor within 24 hours of its initial discovery:

An increase in ALT or AST greater than 3.0 times the ULN accompanied by an increase in serum bilirubin at least 2.0 times the ULN or in the presence of clinical jaundice in the absence of any non-drug related cause such as viral hepatitis.

The event must then be reported to the Regulatory Authority following the process for SAEs (see Section 13.6).

13.4.6 Deaths

Deaths that occur during the AE reporting period that are attributed by the Investigator solely to cancer progression should be recorded only on the End of Treatment eCRF and not as an SAE. All other on-study deaths, regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the Sponsor. Death should be considered an outcome and not a distinct event.

The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only 1 such event should be reported. The term *sudden death* should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, the term *unexplained death* should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), the term *unexplained death* should be replaced by the established cause of death.

13.4.7 Hospitalization or prolonged hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except as outlined below. The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care.
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease;
  - The patient has not suffered an AE.

- Hospitalization due solely to progression of the underlying cancer.

13.4.8 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. An overdose is defined by a boundary of 15% above the prescribed dose of any medicinal product.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

13.5 Reporting of Serious Adverse Events

Any SAE experienced by a patient between the time of consent and 28 days after the last dose of BGB324 is to be recorded on an SAE Report Form within 24 hours of knowledge by the Investigator of its occurrence, regardless of the severity and causality of the event. Study drug-related SAEs should continue to be reported indefinitely.

The SAE Report Form should be faxed or e-mailed to the Chiltern Pharmacovigilance Group.

GlobalSAEInbox@Chiltern.com
Fax: + 888-726-8416

A telephone report may only be made in exceptional circumstances and must be followed by completion of the SAE Report Form within 1 working day. Where applicable, information from relevant hospital case records and post-mortem reports should be obtained.

All SAEs that have not resolved by the EOS, or that have not resolved upon the patient's discontinuation from the study, must be followed until any of the following occur:

- The event resolves.
- The event stabilizes.
- The event returns to baseline status.
- The event can be attributed to agents other than study treatment or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained.

13.6 Immediate Reporting of Serious Adverse Events

Expedited safety reporting within this clinical study complies with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A), investigational new drug (IND) application safety reporting (under 21CFR312.32), and with applicable local regulatory requirements.

The Sponsor assumes responsibility for appropriate reporting of AEs to the Regulatory Authorities and Institutional Review Boards (IRB). Although this responsibility can be delegated to the Sponsor's Clinical Research organization (CRO), the Sponsor retains ultimate responsibility for safety reporting.

All SAEs that are unexpected and associated with the use of the investigational product are classified as suspected, unexpected serious adverse reactions (SUSARs) and will be reported to the IRBs, Regulatory Authorities and to all investigational sites according to local requirements.

Any safety information from other observations that could change the risk-benefit evaluation of BGB324 should be promptly communicated to the Regulatory Authorities and IRBs.

Any other SUSARs associated with BGB324 should be reported as soon as the Sponsor becomes aware of them, including SUSARs which occur in another clinical study conducted by the same Sponsor or which are identified by spontaneous reports, a publication, or which are transmitted to the Sponsor by another Regulatory Authority.

Other safety issues that also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of the BGB324 (sufficient to consider changes in the administration or in the overall conduct of the trial), include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the Investigator to the Sponsor.
- New events relating to the conduct of the trial or the development of BGB324 likely to affect the safety of the patients, such as:
  - An SAE which could be associated with study procedures and which could modify the conduct of the study;
  - A major safety finding which differs from the underlying disease.

Expedited reporting is not usually required for reactions which are serious but expected, and it is inappropriate to report events that are considered unrelated to the investigational product. The cause of death of a patient in a clinical study, unless it is associated with disease progression, is considered a SAE whether the event is expected or associated with the investigational agent.

13.7 Procedures for Handling Special Situations

13.7.1 Pregnancy

In the event of a pregnancy occurring in female patients, or in the partners of male patients during the study, the pregnancy must be reported to:

the Chiltern Pharmacovigilance Group (fax + 888-726-8416 or email GlobalSAEInbox@Chiltern.com

by the investigational staff within **1 working day** of their knowledge of the event using a Pregnancy Notification Form.

The reporting period for pregnancies will start with the first administration of BGB324 and end 28 days after the final administration of BGB324.

Any female patients who become pregnant while taking part in the study will be withdrawn; a male patient whose partner becomes pregnant can remain in the study. Female partners of male patients will be asked to provide details of the pregnancy (may be subject to additional consent).

A patient who completes or withdraws from the trial before the full term of the pregnancy will be asked to consent to provision of follow-up information about the pregnancy and its outcome.

13.7.2 Medical emergency

In a medical emergency requiring immediate attention, study staff will apply appropriate medical intervention according to standard medical practice.

13.8 Investigator's Safety Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to BGB324.
- Determine the seriousness, relationship and severity of each event.
- Determine the onset and resolution of each event.
- Complete an SAE form for each SAE.
- Pursue SAE follow-up information actively and persistently.
- Ensure all AE and SAE reports are supported by documentation in the patient medical records.
- Report SAEs to their local IRB as required by local law.

13.9 Sponsor's Safety Responsibilities

The Sponsor's responsibilities include the following:

- Ongoing safety evaluation of BGB324.
- Reporting of SUSARs to the Regulatory Authorities, main IRB and Investigators according to required timelines.
- Submission of annual updates to the Regulatory Authorities and main IRB.

14 STATISTICAL CONSIDERATIONS

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan. Any deviations to the planned analyses will be justified in writing and presented within the final clinical study report (CSR). The database lock will take place when all data are reconciled. A single CSR will be generated for this study. All study data will be listed.

14.1 Patient Disposition, Demography and Baseline Disease Characteristics

Patient disposition, including reason for withdrawal will be summarized by dose group.

Demographics and baseline characteristics will be performed on the Safety Analysis Population (see Section 14.2.1). Demographics and disease baseline characteristics, pregnancy test results, medical history and prior medications will be tabulated.

14.2 Safety

14.2.1 Safety analysis population

The Safety Analysis Population will be defined as all patients who receive at least 1 dose of BGB324 or erlotinib.

14.2.2 Methods of analysis

No formal statistical analysis will be performed on safety data. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0 or above. The number and percentage of patients reporting treatment-emergent AEs will be tabulated by preferred term, system organ class and dose cohort, and further summarized by both CTCAE grade and relationship to study drug. All AEs commencing prior to dosing with study drug will be excluded from the tabulation but will be fully listed. 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 BGB324.

Separate listings will be produced for DLTs, SAEs, discontinuations due to AEs, and events of ≥Grade 3 severity.

Summary statistics by dose cohort and time point will be produced for vital signs, 12-lead ECG parameters and laboratory safety data, together with changes from baseline. The incidence of laboratory test results showing shifts of more than one CTCAE grade will be summarized

by dose cohort, time point and overall. Laboratory test results outside the normal range will be individually listed for clinical review, including clinical significance and the baseline value. Abnormal ECG results will be summarized by dose cohort. Changes in continuous parameters will be analyzed according to administered dose.

14.3 Efficacy

14.3.1 Efficacy analysis population

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

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 on a per patient basis at the pre-database lock meeting.

14.3.2 Methods of analysis

Data relating to efficacy will be summarized descriptively by dose cohort and time point, as appropriate.

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 in Arm B. This will consist of 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.

14.4 Pharmacokinetics

14.4.1 Pharmacokinetic analysis population

The Pharmacokinetic Analysis Population will include those patients in the Run-in Cohort and Arm B who receive at least 1 dose of BGB324 and have PK data available and those patients in Arm A who receive at least 1 dose of BGB324 and erlotinib and have BGB324 and erlotinib PK data available.

14.4.2 Methods of analysis

Full details of analysis of BGB324 PK will be provided in a Pharmacokinetics Analysis Plan. BGB324 plasma concentration-time data will be summarized descriptively mean, standard deviation and coefficient of variation). Mean plasma profiles will be illustrated in graphical form. An appropriate PK model will be fitted to the individual plasma profiles of BGB324.

Pharmacokinetic parameters of BGB324 that will be estimated are summarized in Table 10. These parameters will be estimated at steady state.

Table 10 BGB324 Pharmacokinetic Parameters to be Evaluated

C_{max}	The observed maximum plasma concentration after single dose administration
t_{max}	The time to reach C_{max}
$AUC_{0-\tau}$	The area under the curve within a dosing interval, calculated by the linear up-log down trapezoidal method.

14.5 Pharmacodynamics

14.5.1 Pharmacodynamic analysis population

The Pharmacodynamic Analysis Population will include all patients who receive at least 1 dose of BGB324 and erlotinib and have at least 1 PD biomarker sample collected for analysis.

14.5.2 Methods of analysis

No formal analysis of PD will be performed. Pharmacodynamic biomarker results will be summarized descriptively by dose cohort and timepoint as appropriate.

14.6 Sample Size Considerations

Arm A will utilize a conventional algorithm (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 11.

Table 11 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 3 BGB324 dose levels will be evaluated, with up to approximately 18 patients enrolled. The total sample size in Arm A will depend upon whether a DLT is experienced at a given dose level (i.e., whether 3 or 6 patients have been treated) and how many dose levels are tested to reach the dose that can be safely administered in combination with erlotinib.

Arm B will follow a Simon-like 2-stage design with relaxed stopping for futility to evaluate the PK of BGB324 ,safety and tolerability,, PD 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 other rearrangement of the EGFR gene mutations) who have progressed after receiving a prior EGFR inhibitor (i.e., erlotinib, afatinib, or gefitinib). The null hypothesis (H_0) that the true response rate is 0.05 will be tested against a 1-sided alternative in the first stage, 9 patients 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 H_0, 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, PD 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.

14.7 Clinical Study Report

The results of the study will be presented in an integrated CSR in accordance with ICH guidelines.

15 ETHICAL CONSIDERATIONS

15.1 Good Clinical Practice Statement

The clinical study will be performed in accordance with the protocol, the Declaration of Helsinki, ICH Guidelines, GCP and all applicable local regulatory requirements.

15.2 Institutional Review Board

The final study protocol and informed consent form (ICF) must be approved, in writing, by the relevant IRB before patient enrollment commences.

The following information should be reported to the IRB (*in accordance with local requirements*) during the study:

- All amendments to the clinical research study.
- Annual progress reports.
- Individual SUSARs.
- Urgent safety measures.

15.3 Patient Information and Consent

Prior to performing any study-related activities, including screening tests and procedures, written informed consent must be obtained from the patient, in accordance with local regulations.

The ICF must be in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements and Sponsor policy and must be approved by the prevailing IRB for each study center.

15.4 Subject Data Protection

Personally identifiable information, i.e., identifiable information from or about an individual subject, will not be collected by the Sponsor. The collection and processing of data from patients enrolled in this study will be limited to those data that are necessary to investigate the clinical activity, safety, tolerability, quality and utility of the study drug used in this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The ICF must explain that identifying information will be kept by the Investigator on file and that portions of the patient's medical records pertinent to the study will be reviewed by Sponsor personnel (or their designees) and possibly by Regulatory Agencies and the IRB for data verification purposes.

16 ADMINISTRATIVE PROCEDURES

16.1 Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor/designee, external Regulatory Agency and/or /IRB may conduct quality assurance (QA) audits at any time during or following completion of the study. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

16.2 Case Report Form and Source Document Verification

Electronic CRFs will be provided for recording clinical data. Designated site personnel will record data in the eCRF for observations, tests and assessments as specified in the protocol. The Sponsor will provide eCRF completion guidelines to assist site personnel.

Data required for the eCRF should be completed in a timely manner so as to aide Sponsor and CRO management.

The Investigator must permit the Sponsor/designee reasonable direct access to designated source documentation (e.g., medical records) for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

16.3 Study Monitoring

Before a patient can be screened for enrollment into the study, the Sponsor/designee will conduct a study initiation visit to:

- Determine that site facilities are adequate.
- Discuss responsibilities with regard to the protocol with the Investigator and the study team.
- Conduct training on completion of the eCRF and other study- related documentation.
- Review study procedures.

During the conduct of the study, the Sponsor/designee will provide ongoing support to the Investigator and study team. The Sponsor/designee will conduct regular site visits, according to applicable ICH and GCP guidelines, to:

- Confirm the facilities remain acceptable.
- Confirm the site study team is adhering to the protocol and regulatory requirements.
- Confirm that the investigational product is being properly maintained and accountability records are accurate and current.
- Confirm data are being accurately recorded in the eCRF by performing source document verification.
- To intervene and stop any serious protocol non-compliance by a site and if required report to IRB and the Regulatory Authority.

16.4 Retention of Study Data

A copy of all records and essential documents must be retained in the study files for a minimum of 2 years following the last approval of the drug in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or a minimum of 2 years have elapsed since the formal discontinuation of the clinical development of the drug. No documents should be destroyed without prior written agreement between the Sponsor and the Investigator and/or clinical site.

Should the Investigator wish to assign the documents to another party or move them to another location, prior approval of the Sponsor must be obtained. The Sponsor will notify the Investigator in writing when any study-related documents are no longer needed.

16.5 Use of Information and Publication Policy

All information regarding BGB324 and the Sponsor's operations (e.g., patent applications, formulas, manufacturing processes, basic scientific data, or formulation information) supplied by the Sponsor to the Investigator and not previously published is considered confidential. This confidential information remains the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes, including publication or presentation without the Sponsor's written consent. The full terms of confidentiality, intellectual property and publication policy are detailed in the current Clinical Trial Agreement between the Sponsor and the site.

16.5.1 Clinical research organizations

Monitoring, data management, statistics and programming, pharmacovigilance, medical writing, auditing and QA services will be outsourced to the Sponsor's CRO.

Pharmacokinetic and pharmacodynamic analyses will be outsourced to the Sponsor's bioanalytical services vendors.

16.5.2 Changes to the final study protocol

All protocol amendments must be submitted to the IRB and Regulatory Authorities.

Protocol amendments that affect patient safety, the scope of the investigation, or the scientific quality of the study should not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to the patients.

16.5.3 Investigator responsibilities

By signing the protocol the Investigator agrees to:

- Conduct the study in accordance with the protocol and make changes only after so directed by the Sponsor, except to protect the safety, rights or welfare of patients.
- Personally conduct or supervise the study.
- Inform any patients enrolled in the study that BGB324 is being used for investigational purposes.
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21CFR50 and 21CFR56.
- Report to the Sponsor any AEs that occur during the course of the study, in accordance with 21CFR312.32, as well as ICH guidelines.
- Have read and understood the Investigator's Brochure for BGB324, including potential risks and side effects of the drug.
- Maintain adequate and accurate records, in accordance with 21CFR312.62 and to make those records available for inspection by the Sponsor, its designated representatives, relevant Regulatory Authorities, the IRB or any agency authorized by law.
- Ensure that an IRB that complies with the requirements of 21CFR56 will be responsible for initial and continuing review of the clinical study.
- Report promptly to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to patients or others (to include protocol amendments and IND safety reports).
- Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subject/subjects.
- Comply with all other requirements regarding the obligations of Clinical Investigators and all other pertinent requirements listed in 21CFR312.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Enter data collected from patients into the eCRF as soon as possible i.e. within 5 working days of the respective visit.

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18 APPENDICES

Appendix 1 ECOG Performance Status Scale

Grade	ECOG Performance Status
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, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* (1982) 5: 649 – 655.

Appendix 2 The NYHA Functional Classification in a Subject with Heart Disease

Overview: The NYHA developed a functional classification for subjects with heart disease.
Subjects: Heart disease must be present.
Parameters:

- Limitations on physical activity

Symptoms (undue fatigue palpitations dyspnea and/or anginal pain) with ordinary physical activity

- Status at rest

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp#.VsXt6ZOLR-U

Appendix 3 Drugs that are Generally Accepted to Have a Risk of Causing Torsades de Pointes

Generic Name	Brand Name
Amiodarone	Coradone/Pacerone
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox
Astemizole	Hismanal
Azithromycin	Zithromax®, Zmax®
Bepridil	Vascor
Chlorquine	Arelan
Chlorpromazine	Thorazine
Cisapride	Propulsid
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Dronedarone	Multaq®
Droperidol	Inapsine
Erythromycin	Erythrocin/E.E.S.
Escitalopram	Cipralex®, Lexapro®
Flecainide	Tambocor®, Almarytm®
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Covert
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Methadose/Dolophine
Moxifloxacin	Avelox
Ondansetron	Zofran®, Anset®
Petamidine	NebuPent/Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl/Procan
Quinidine	Cardioquin/Quinaglute
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace
Sparfloxacin	Zagam
Sulpiride	Dogmatil®, Dolmatil®
Terfenadine	Seldane
Thioridazine	Mellaril
Vandetanib	Zactima

Adapted from “The University of Arizona Center for Education and Research on Therapeutics.” See the following website for an updated list of drugs that cause Torsades de Pointes: www.AZCERT.org

Appendix 4 NCI CTCAE, Version 4.03

NCI CTCAE Version 4.03 of the, dated 14 June 2010, may be found at the following website:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf