2 SYNOPSIS

Name of Sponsor: Blueprint Medicines Corporation

Name of Finished Product: BLU-945

Name of Active Ingredient: BLU-945

Title of Study: A Phase 1/2 Study Targeting Acquired Resistance Mechanisms in Patients With EGFR Mutant Non-Small Cell Lung Cancer

Investigators: PPD

Study Sites: A total of 25 sites enrolled patients: 9 sites in the United States of America, 5 sites in South Korea, 3 sites in Japan, 2 sites in France, and 1 site in Canada, Singapore, Taiwan, Spain, the United Kingdom, and the Netherlands.

Publication (reference): None

Study Period: Approximately 172 weeks

Initiation Date: 22 June 2021

Completion Date: 07 October 2024

Phase of Development: 1/2

Study Objectives:

The primary and secondary objectives and endpoints of Phase 1 are listed in Table S1. For the exploratory objectives and endpoints of Phase 1, see Protocol Amendment 3 (Appendix 16.1.1).

Table S1. Phase 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the MTD and RP2D of BLU-945 as monotherapy and in combination with osimertinib.	• MTD determination: DLT rate; and • RP2D determination: DLT, PK, PD, and preliminary safety and anticancer activity data.
• To determine the safety and tolerability of BLU-945 as monotherapy and in combination with osimertinib.	• Overall safety profile of BLU-945, as assessed by the type, frequency, severity, timing, and relationship to study drug of treatment-emergent adverse events, and changes in vital signs, electrocardiograms, and safety laboratory tests.

Table S1. Phase 1 Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
• To assess anticancer activity of BLU-945 as monotherapy and in combination with osimertinib.	• Overall response rate, defined as the proportion of patients who experienced a best response of confirmed CR or PR according to RECIST 1.1; and • Duration of response, defined as the time from first documented response of CR or PR to the date of first documented progressive disease or death due to any cause, whichever occurred first.
• To characterize the PK profile of BLU-945 and correlate drug exposure with safety assessments.	• PK parameters of BLU-945: PK parameters of interest included, as appropriate, maximum plasma drug concentration, time to maximum plasma drug concentration, time of last quantifiable plasma drug concentration, area under the plasma concentration versus time curve from time 0 to the end of the dosing interval (area under the plasma concentration time curve from 0 to 24 hours for QD and area under the plasma concentration time curve from 0 to 12 hours for BID), trough concentration, apparent volume of distribution, terminal elimination half-life, apparent oral clearance, and accumulation ratio. BLU-945 metabolites may also have been measured.
• Assess treatment-induced modulation of EGFR pathway biomarkers.	• Profile PD changes in expression levels of the EGFR pathway biomarkers DUSP6 and SPRY4.

BID = twice daily; CR = complete response; DLT = dose-limiting toxicity; DUSP6 = dual specificity phosphatase 6; EGFR = epidermal growth factor receptor; MTD = maximum tolerated dose; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PR = partial response; QD = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RP2D = recommended Phase 2 dose; SPRY4 = sprouty receptor tyrosine kinase signaling antagonist 4.
Sources: Protocol Amendment 3 (Appendix 16.1.1) and Statistical Analysis Plan (available within the Trial Master File)

The study was terminated prior to completion of Phase 1 dose escalation. Part 1A (BLU-945 as monotherapy) was completed, and the study was terminated during Part 1B (BLU-945 in combination with osimertinib) due to Sponsor decision and not due to safety concerns or a lack of efficacy. Therefore, no patients were enrolled in Phase 2. For the planned primary, secondary, and exploratory objectives and endpoints for Phase 2, refer to Protocol Amendment 3 (Appendix 16.1.1).

Methodology:

This was planned to be a Phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anticancer activity of BLU-945, an orally available, highly potent, and selective inhibitor of epidermal growth factor receptor (EGFR) resistance mutations, administered orally as monotherapy or in combination with osimertinib in patients with EGFR-mutated non-small cell lung cancer (NSCLC) who had previously received at least 1 prior EGFR-targeted tyrosine kinase inhibitor. The study included an initial Phase 1 portion to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BLU-945 as monotherapy (initially in a once daily [QD] regimen with the

option to evaluate twice daily [BID] dosing, if supported by emerging PK and safety data), as well as an additional dose escalation portion to determine the RP2D of BLU-945 in combination with osimertinib.

Prior to study enrollment, the tumor mutation profile was determined locally for each patient via a Sponsor-approved local testing methodology, using tumor tissue and/or circulating tumor deoxyribonucleic acid in plasma. Each potential patient was reviewed and approved for enrollment by the Sponsor.

On-treatment biopsies were obtained for patients enrolled in Phase 1 Part 1A at doses expected to result in efficacious exposure levels. It was anticipated, based on the half maximal inhibitory concentration observed in preclinical models, that biopsies would be required at starting doses ≥100 mg QD, but this requirement could have been modified by the Sponsor as necessary based on emerging PK and clinical data. However, following approval from the Sponsor, biopsies could have been omitted for patients for whom the Investigator did not feel that biopsy would have been safe and/or feasible. Paired pretreatment and on-treatment tumor samples were utilized to assess treatment-induced modulation of key EGFR pathway biomarkers including, but not limited to, dual specificity phosphatase 6 (DUSP6) and sprouty receptor tyrosine kinase signaling antagonist 4 (SPRY4) expression levels. Post-progression tumor biopsies and plasma were tested for potential mechanisms of resistance, as well as reassessment of EGFR mutational status.

Informed consent could have been obtained up to 56 days (8 weeks) before study enrollment and initiation of study treatment. BLU-945 was given by daily oral administration. Dose modifications were according to specific criteria based on observed toxicities as described in Section 7.2.4 of Protocol Amendment 3 (Appendix 16.1.1). Patients may have received BLU-945 until precluded by disease progression, unacceptable toxicity, or other criteria for treatment discontinuation as described in Section 7.3.1 of Protocol Amendment 3 (Appendix 16.1.1). Patients who experienced Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)-defined progression of disease but continued to experience clinical benefit in the opinion of the treating Investigator may have continued study treatment with approval from the Sponsor. Study visits for assessments of safety (including adverse events [AEs], vital signs, laboratory tests, and electrocardiograms), PK, and biomarkers were conducted periodically throughout study treatment. Patients enrolled in the expansion groups additionally completed health-related quality of life assessments, and at least 25 patients in the expansion groups underwent continuous Holter monitoring for thorough assessment of cardiac intervals, including QT and rhythm. Study visits were intended to be conducted on an outpatient basis, but may have been conducted on an inpatient basis, as needed. At any point in between study visits, patients should have contacted the study center as necessary for AE reporting, evaluation, and medical intervention. Tumor response was assessed in accordance with RECIST 1.1, and disease assessments were performed every 4 weeks for the first 2 assessments (ie, Day 1 of the second and third cycles), every 8 weeks for the remainder of the first year, and then every 12 weeks thereafter.

Patients should have been contacted 30 (+7) days after discontinuation of study treatment for an assessment of safety. Patients without documented progressive disease at the end of study treatment continued to undergo disease assessments for progression-free survival until documentation of progressive disease, initiation of another antitumor therapy, death, or closure of the study by the Sponsor. In addition, all patients continued overall survival follow-up until death, withdrawal from study, or closure of study.

Phase 1 Dose Escalation

Part 1A: BLU-945 as Monotherapy

The Phase 1 BLU-945 monotherapy dose escalation (Part 1A) employed the Bayesian optimal interval (BOIN) design with a target toxicity rate of 30% to identify the MTD of BLU-945 when administered in a QD dosing regimen. During dose escalation, enrollment of patients with NSCLC harboring both EGFR T790M and C797S mutations was encouraged. At each dose level, slots may have been reserved for patients with the mutations of interest.

The first cohort of patients received BLU-945 at a starting dose of 25 mg QD. To limit the number of patients treated at potentially subtherapeutic dose levels, the study initially used a cohort size of 1 to 3 patients, and the incremental dose increase between cohorts was up to 100%. If a patient, at any dose level with fewer than 3 patients, experienced a Grade 2 or higher AE during the first 28 days of treatment that was not clearly attributable to disease progression or another cause clearly unrelated to BLU-945, the cohort and all subsequent cohorts were to contain at least 3 evaluable patients. In addition, all cohorts at dose levels greater than 100 mg QD consisted of at least 3 evaluable patients. Once 1 patient in any dose level experienced a dose-limiting toxicity (DLT) or any 2 patients in any dose level experienced a Grade ≥2 AE considered related to BLU-945 during the first 28 days of treatment, all subsequent dose escalation increments were to be no more than approximately 50%. Each dose level was rounded down or up to the closest multiple of 25 mg, to accommodate the available dosage strengths (25 and 100 mg). Patients who experienced a DLT, or who received at least 75% (ie, ≥21 days) of the prescribed BLU-945 dose and completed the 28-day DLT evaluation period, were evaluable for DLT assessment. Enrollment to each cohort, dose escalation, de-escalation, and dose elimination followed the rules for the BOIN design as described in Section 7.2.1 of Protocol Amendment 3 (Appendix 16.1.1), and according to the plan outlined in Figure 2 of Protocol Amendment 3 (Appendix 16.1.1). A Safety Review Committee (SRC) consisting of the Sponsor's clinical study team and study Investigators met to review accumulated safety data and reach agreement on the decision to open each cohort and the specific dose that was chosen for each cohort. The total number of patients evaluable for DLT for any given dose level should not have exceeded 12, and dose escalation was considered complete when 12 patients were evaluable for DLT at 1 dose level.

The MTD was to be determined based on isotonic regression as specified by Liu and Yuan,[1] while the RP2D, which was not to exceed the monotherapy MTD, may have been selected with consideration to all clinical data, including safety, PK, PD, and antitumor activity.

Intra-patient dose escalation was permitted for patients enrolled at previously tested dose levels in accordance with the criteria in Section 7.2.2 of Protocol Amendment 3 (Appendix 16.1.1).

During the conduct of dose escalation, in order to allow for more robust characterization of safety, PK, PD, and preliminary clinical activity, additional patients may have been enrolled at a previously tested lower dose level, if that dose-level cohort included less than 12 patients evaluable for DLT and had been approved for further escalation by the SRC. These patients were monitored for DLT, and data was considered in the conduct of the BOIN dose escalation. In addition, in order to further inform dose selection for specific groups of patients defined by mutational profile (eg, patients with EGFR L858R sensitizing mutation), up to 12 additional patients with mutations of interest could have been treated at one or more previously-evaluated dose level(s), provided that 1) at least 9 evaluable patients had previously been treated at that dose level; 2) escalation to the next dose level had been cleared by the SRC; 3) at least 1 response (partial response or

complete response) had been observed at that dose level; and 4) the SRC approved the expansion based on emergent safety, efficacy, and PK data. Data from these additional 12 patients were not considered in the conduct of the BOIN dose escalation but were considered in the monitoring for study stopping rules, as described in Section 7.2.3 of Protocol Amendment 3 (Appendix 16.1.1).

In addition, if supported by emerging PK data from the QD dose escalation, a BID dosing schedule could have also been explored using the same BOIN dose escalation design described above. The starting total daily dose level for the BID dose escalation was determined by the SRC, and the total daily dose was not to exceed the highest dose level for the QD schedule that had been approved for further dose escalation by the SRC. For example, if BID dosing began after a QD dose of 100 mg had been deemed safe for further escalation, the maximum BID dose would have been 50 mg BID (equivalent to a total daily dose of 100 mg).

Part 1B: BLU-945 in Combination with Osimertinib

The dose escalation for the combination of BLU-945 and osimertinib included patients who had experienced disease progression while receiving osimertinib. During Part 1B, enrollment of patients with NSCLC harboring EGFR T790M/C797S resistance mutations was encouraged, and slots could have been reserved for patients with EGFR T790M/C797S resistance mutations or other clinically relevant mutation profiles as determined by the Sponsor in discussion with the study Investigators.

Dose level 1 evaluated BLU-945 at 50% of the monotherapy RP2D (or 50% of the highest dose deemed safe in Part 1A, if the monotherapy RP2D was not yet determined) in combination with full-dose osimertinib (80 mg QD). Dose escalation or de-escalation was conducted as per the rules of the BOIN design based on observation of DLT and PK during the first 28-day treatment cycle (Section 7.2.1.2 of the Protocol [Appendix 16.1.1]), with a proposed escalation plan outlined in Figure 3 of Protocol Amendment 3 (Appendix 16.1.1). The dose level increase should have been <100% of BLU-945 in the cohort(s) subsequent to cohort 1 and the next dose of BLU-945 was selected such that the projected area under the plasma concentration time curve (AUC) of BLU-945 in combination with osimertinib was not more than the AUC of BLU-945 as monotherapy at MTD or the highest dose deemed safe in Part 1A in the combination dose escalation. Dose escalation was not to proceed beyond the BLU-945 monotherapy RP2D nor an osimertinib dose of 80 mg.

Patients who experienced a DLT, or who received at least 75% (ie, ≥21 days) of the prescribed BLU-945 and osimertinib doses and completed the 28-day DLT evaluation period, were evaluable for DLT assessment. The total number of patients evaluable for DLT for any given dose level should not have exceeded 12, and dose escalation was to be considered complete when 12 patients were evaluable for DLT at 1 dose level. The MTD was to be determined based on isotonic regression, while the RP2D, which was not to exceed the MTD, may have been selected with consideration to all clinical data, including safety, PK, PD, and antitumor activity.

The study was terminated prior to completion of Phase 1 dose escalation. Part 1A (BLU-945 as monotherapy) was completed, and the study was terminated during Part 1B (BLU-945 in combination with osimertinib) due to Sponsor decision and not due to safety concerns or a lack of efficacy. Therefore, no patients were enrolled in Phase 2. For details regarding the study design for Phase 2, see Protocol Amendment 3 (Appendix 16.1.1).

The efficacy and safety variables, including laboratory tests, and the timing for measurements are described in Tables 1 to 4 of Protocol Amendment 3 (Appendix 16.1.1).

Duration of Treatment:

No maximum treatment duration had been set; however, it was anticipated that patients would receive 12 months treatment on average. Patients received the assigned study treatment until precluded by progression of disease, unacceptable toxicity, or other discontinuation criteria (see Section 7.3.1 of the Protocol [Appendix 16.1.1]). Patients who experienced RECIST 1.1-defined progression of disease but continued to experience clinical benefit in the opinion of the treating Investigator may have continued study treatment with approval from the Sponsor. Following discontinuation of study treatment, patients should have continued to be followed for safety (approximately 30 days post-treatment), progression-free survival (if no prior disease progression and no new anticancer therapy), and overall survival (until death, study closure, or withdrawal from study).

Number of Patients:

Screened: 200 patients screened

Enrolled: 177 patients (Part 1A: 117 patients and Part 1B: 60 patients)

Discontinued: All 177 patients discontinued from the study

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study population consisted of patients ≥18 years of age at the time of signing of the informed consent who had pathologically confirmed, definitively diagnosed, metastatic NSCLC harboring an activating EGFR mutation; previously received at least 1 prior EGFR-targeted tyrosine kinase inhibitor with activity against the T790M mutation; had tumor mutation profile determined locally via a Sponsor-approved testing methodology, using tumor tissue and/or circulating tumor deoxyribonucleic acid in plasma; had pretreatment tumor sample (either an archival sample or a sample obtained by pretreatment biopsy) submitted for central analysis; and had an Eastern Cooperative Oncology Group performance status of 0-1.

Patients with a tumor that harbored any additional known driver alterations; NSCLC with mixed cell histology or a tumor with histologic transformation; central nervous system metastases or spinal cord compression that was associated with progressive neurological symptoms or required increasing doses of corticosteroids to control the central nervous system disease; known intracranial hemorrhage and/or bleeding diatheses; or clinically active ongoing interstitial lung disease were excluded from the study.

The full Inclusion and Exclusion Criteria are described in Protocol Amendment 3 (Appendix 16.1.1).

Investigational Product and Comparator Information:

BLU-945, an orally available, highly potent, and selective inhibitor of EGFR resistance mutations, was administered orally as monotherapy or in combination with osimertinib in patients with EGFR-mutated NSCLC who had previously received at least 1 prior EGFR-targeted tyrosine kinase inhibitor. (Lot/Batch/packaging numbers [available in the Trial Master File]): BLU-945 25 mg (G-21-031A, G-21-163A, and 025665); BLU-945 100 mg (G-21-032A, G-21-164A, G-21-173A, G-21-089A, and 024882 [Packaging Coordinators, Inc. packaging numbers: 025471 and 025125]); and BLU167368 (21600T0001).

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor with high potency for the T790M mutation in addition to the primary exon 19 deletion or L858R sensitizing mutations. (Lot/Batch numbers [available in the Trial Master File]): osimertinib mesylate 80 mg (ABAC); and Tagrisso 80 mg (FKMB).

Criteria for Evaluation:

Efficacy:

See Table S1 for efficacy endpoints for Phase 1.

Safety:

See Table S1 for safety endpoints for Phase 1.

Statistical Methods:

The statistical methodology is described in detail in the Statistical Analysis Plan (available within the Trial Master File).

Summary of Results:

Safety

Of the 177 patients in the study, 166 (93.8%) patients experienced AEs, 60 (33.9%) patients experienced serious AEs (SAEs), 15 (8.5%) patients experienced DLTs, and 8 (4.5%) patients experienced death due to AEs and 3 of these deaths were considered possibly related to BLU-945.

The 5 most common AEs overall by preferred term (PT) were nausea (75 [42.4%] patients), headache (72 [40.7%] patients), alanine aminotransferase (ALT) increased (48 [27.1%] patients), aspartate aminotransferase (AST) increased, and vomiting (47 [26.6%] patients each).

Overall, 69 (39.0%) patients experienced Grade 3 AEs. The most common Grade 3 AEs by PT were ALT increased (24 [13.6%] patients), AST increased (13 [7.3%] patients), anaemia (10 [5.6%] patients), and lymphocyte count decreased (9 [5.1%] patients).

Overall, 12 (6.8%) patients experienced Grade 4 AEs. The most common Grade 4 AEs by PT were hyponatraemia (4 [2.3%] patients) and ALT increased (3 [1.7%] patients). All other Grade 4 AEs were experienced by 1 (<1%) patient each and included the following PTs: neutropenia, pneumonia, blood creatine phosphokinase increased, adjustment disorder, pneumonitis, and acute respiratory failure.

Overall, 8 (4.5%) patients experienced Grade 5 AEs. All Grade 5 AEs were experienced by 1 (<1%) patient each and included the following PTs: febrile neutropenia, cardio-respiratory arrest, pneumonia viral, septic shock, haemorrhage intracranial, hydrocephalus, cerebellar stroke, pneumonitis, acute respiratory failure, and pulmonary embolism.

Three patients experienced AEs leading to death that were considered possibly related to BLU-945 and included the following PTs: haemorrhage intracranial, febrile neutropenia, septic shock, and pneumonitis.

Five patients experienced AEs leading to death that were not related to BLU-945 and included the following PTs: hydrocephalus, acute respiratory failure, cardio-respiratory arrest, pulmonary embolism, cerebellar stroke, and pneumonia viral.

Overall, 38 (21.5%) patients experienced Grade 3 SAEs. The most common Grade 3 SAEs by PT were pneumonia (6 [3.4%] patients), nausea (4 [2.3%] patients), pleural effusion, vomiting, and AST increased (3 [1.7%] patients each).

Overall, 6 (3.4%) patients experienced Grade 4 SAEs. The most common Grade 4 SAE by PT was ALT increased (2 [1.1%] patients). All other Grade 4 SAEs were experienced by 1 (<1%) patient each and included the following PTs: pneumonia, blood creatine phosphokinase increased, adjustment disorder, acute respiratory failure, and pneumonitis.

Overall, 8 (4.5%) patients experienced Grade 5 SAEs. All Grade 5 SAEs were experienced by 1 (<1%) patient and included the following PTs: febrile neutropenia, cardio-respiratory arrest, pneumonia viral, septic shock, cerebellar stroke, haemorrhage intracranial, hydrocephalus, acute respiratory failure, pulmonary embolism, and pneumonitis.

Overall, 15 (8.5%) patients experienced AEs leading to treatment discontinuation. AEs leading to treatment discontinuation for the following PTs were considered possibly related to BLU-945 including rhabdomyolysis (Grade 3), nausea (Grade 3), vomiting (Grade 3), haemorrhage intracranial (Grade 3 and Grade 5), febrile neutropenia (Grade 5), septic shock (Grade 5), pneumonitis (Grade 2 and Grade 5), and acute respiratory failure (Grade 3). Overall, 15 (8.5%) patients experienced DLTs.

The safety and tolerability of BLU-945 as a monotherapy and as a combination therapy with osimertinib was acceptable, and the study was not terminated due to safety concerns.

Conclusions

Overall, BLU-945 was well tolerated at the doses tested for the indication of late-stage lung cancer as a monotherapy and as a combination therapy with osimertinib. The study was terminated during Part 1B (BLU-945 in combination with osimertinib) due to Sponsor decision and not due to safety concerns or a lack of efficacy. Therefore, no patients were enrolled in Phase 2.

Date of the Report: 04 February 2025