APPLICATION NUMBER:

213721Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
MEETING PRELIMINARY COMMENTS

Blueprint Medicines Corporation  
Attention: Megan Sanchez, M.P.H.  
Director, Regulatory Affairs  
45 Sidney Street  
Cambridge, MA 02139

Dear Ms. Sanchez:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pralsetinib.

We also refer to your December 20, 2019, correspondence requesting a pre-New Drug Application (NDA) meeting to discuss outstanding Chemistry, Manufacturing, and Controls (CMC) and clinical items, in addition to presenting top-line efficacy and safety data from Study BLU-667-1101, in support of your planned marketing application for pralsetinib for the treatment of patients with RET-positive non-small cell lung cancer.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
If you have any questions, call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
• Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 10, 2020; 12:00 PM – 1:00 PM, EST
Meeting Location: Teleconference

Application Number: IND 143094
Product Name: Pralsetinib
Indication: Treatment of patients with rearranged during transfection (RET)-positive advanced non-small cell lung cancer (NSCLC)

Sponsor Name: Blueprint Medicines Corporation

FDA ATTENDEES (tentative)
Harpreet Singh, Director, Division of Oncology 2 (DO2)
Erin Larkins, Clinical Team Leader, DO2
Luckson Matthieu, Clinical Reviewer, DO2
Idara Udoh, Project Management Staff, DO2
Xing Wang, CMC Team Leader, Office of Pharmaceutical Quality

SPONSOR ATTENDEES
Chris Murray, Senior Vice President, Technical Operations
Csani Varga, Vice President, Pharmaceutical Sciences
Sara Green, Associate Director, Regulatory Affairs
Sherwin Sattarzadeh, Vice President, Regulatory Affairs
Debra Mazaik, Director, Formulation Sciences
Mark Trone, Director, Analytical Development
Angela Pontrello, Director, Quality Control
Megan Sanchez, Director, Regulatory Affairs
Ben Mohimen, Director, CMC Regulatory Affairs
Muhammad Khan, Senior Manager, CMC Regulatory Affairs

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 10, 2020, at 12:00PM – 1:00PM, EST, between Blueprint Medicines Corporation and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments.
following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Regulatory

FDA received a request for orphan-drug designation, from Blueprint Medicines Corporation (Blueprint), for small molecule rearranged during transfection (RET) inhibitor, BLU-667, for the treatment of RET-rearranged non-small cell lung cancer (NSCLC), on March 13, 2018. On April 11, 2018, FDA granted orphan drug-designation for the following indication: treatment of RET-rearranged NSCLC.

On August 30, 2019, IND 143094 was submitted to the Division of Oncology Products 2 (DOP2) for the evaluation of BLU-667 (pralsetinib) for the treatment of RET-arranged NSCLC. The IND contained study BLU-667-2303 entitled, “A Randomized, Open-Label, Phase 3 Study of Pralsetinib versus Standard of Care for First Line Treatment of RET fusion-positive, Metastatic Non-Small Cell Lung Cancer,” and was allowed to proceed on September 27, 2019. The new IND submission also included a request for Breakthrough Therapy Designation (BTD); and on October 30, 2019, FDA granted BTD for pralsetinib for the following indication:

Blueprint submitted a request for rolling submission of its anticipated New Drug Application (NDA), on October 11, 2019; and an amended request for submitting the nonclinical sections of the NDA, on December 27, 2019. FDA granted their request on January 6, 2020.

Blueprint has submitted the following Type B meeting requests to obtain FDA feedback on development of pralsetinib:

- Pre-IND/End of Phase 2 (EOP2) meeting held May 1, 2019, to discuss the design of a confirmatory trial intended to verify and further describe the clinical benefit of BLU-667 in patients with RET fusion-positive NSCLC, discuss the sourcing of the comparator for the proposed study, and discuss the overall nonclinical package to support a marketing application for BLU-667 in this population. Meeting minutes issued on May 10, 2019.
• Initial Multidisciplinary BTD meeting held October 17, 2019, to discuss the overall development program including the proposed strategy to submit an NDA under the provisions of accelerated approval for the BTD indication granted on October 30, 2019. Meeting minutes issued on October 28, 2019.

• Guidance meeting was scheduled for November 26, 2019, to discuss and seek feedback on the Chemistry, Manufacturing, and Controls (CMC), and Clinical Pharmacology aspects for the planned NDA, specifically, the dissolution and PXRD methods for BLU-667 and the comparability assessment for BLU-667 capsules produced with the current manufacturing process. The meeting was cancelled upon receipt of the Preliminary Meeting Comments, issued on November 25, 2019.

Blueprint submitted a request for review of the proposed proprietary name “Gavreto,” on December 11, 2019. The submission is currently under review.

Chemistry. Manufacturing. Controls
Pralsetinib is an inhibitor of oncogenic rearranged during transfection (RET) alterations. Pralsetinib drug product is supplied as capsules for oral administration in 100 mg strength. The drug substance is (b)(4). The recommended dosing regimen is 400 mg QD.

Nonclinical
Pralsetinib is a kinase inhibitor that preferentially targets the RET surface receptor as well as several RET mutations. Pralsetinib also showed activity against other kinases including JAK1-3, FLT 1-3, FGFR1, and VEGFR2. Nonclinical studies conducted with pralsetinib were submitted to Module 4 of NDA 213721 on January 7, 2020. Blueprint has submitted in vitro and in vivo pharmacology and pharmacokinetic (PK) studies; GLP-compliant repeat-dose toxicity studies of up to 13-weeks duration in Sprague-Dawley rats and cynomolgus monkeys with SEND datasets; a full battery of genotoxicity studies; a GLP-compliant embryo-fetal development study in rats; in vitro phototoxicity studies; and 14-day repeat-dose toxicity studies of impurities in rats with SEND datasets.

Clinical Pharmacology
Blueprint stated that the single dose and steady state PK of BLU-667 have been evaluated in Study BLU-667-1101. BLU-667 exhibited non-linear increase in systemic exposure over the dose range of 30-400 mg. The Tmax, volume of distribution and terminal half-life of BLU-667 after oral administration were approximately 2 to 4 hours, 289L and 14 to 20 hours, respectively. The observed accumulation ratio of BLU-667 was around 2 to 3-fold steady state. A food effect study suggested that high-fat high-calorie food increased the Cmax and AUC0-inf of BLU-667 by 104% and 122%.

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Reference ID: 4557533
respectively. The aqueous solubility of BLU-667 is pH-dependent. A clinical drug interaction study reported that coadministration of esomeprazole 40 mg QD decreased BLU-667 Cmax and AUC0-inf by 25% and 15%, respectively.

A Human ADME study with [14C]BLU-667 in six healthy male subjects reported that, the mean recovery of radioactivity was 78.6 ± 1.6%, of which 6.1 ± 2.1% and 72.54 ± 2.78% was recovered in urine and feces, respectively. Unchanged BLU-667 represented approximately 66% and 4.8% of the total radioactive dose in feces and urine, respectively. In vitro studies suggested that BLU-667 is majorly metabolized by CYP3A4, and has some potential in inhibiting CYP2C8, CYP2C9 & CYP3A4 and inducing CYP3A4 & CYP1A2. Clinical drug interaction studies reported that co-administration of itraconazole 200 mg QD (a strong CYP3A4 inhibitor) increased BLU-667 Cmax and AUC0-inf by approximately 1.8- and 3.6-fold, respectively; co-administration of rifampin 600 mg QD (a strong CYP3A4 inducer) decreased BLU-667 Cmax and AUC0-inf by approximately 31% and 68%, respectively. In vitro studies also indicated that BLU-667 is likely also a P-gp substrate.

Clinical

Proposed NDA
Study BLU-667-1101 (ARROW) is a global, first-in-human (FIH), safety and activity-estimating study of BLU-667 in patients with medullary thyroid cancer, RET fusion-positive NSCLC, and other RET-altered advanced solid tumors. The study consists of two phases, a dose escalation portion and a multi-cohort, dose expansion portion. Based on the results from the dose-escalation part of the ARROW study, Blueprint selected 400 mg once daily (QD) as the recommended phase 2 dose (RP2D) for BLU-667. The dose expansion portion of the ARROW study opened on April 9, 2018 and enrollment is ongoing. The primary objectives of the dose expansion portion are to determine investigator-assessed overall response rate (ORR) by RECIST v1.1 (or Response Assessment in Neuro-oncology [RANO], if appropriate for tumor type) in each cohort (“group”) and to further define the safety and tolerability of BLU-667.
The primary efficacy population for the proposed NDA will include 132 patients with RET-fusion positive NSCLC who were enrolled by July 11, 2019, and received BLU-667 at a starting dose of 400 mg QD (including three patients from the dose escalation portion of the study). Results of confirmed ORR per blinded independent central review (BICR) for all 132 patients in the proposed primary efficacy population and for subgroups based on prior therapy are presented in the table below (data cut-off data November 18, 2019; table abstracted from the meeting package).
Based on Figure 13 in the meeting package, among the 49 responders in the subgroup of patients previously treated with platinum-based chemotherapy, 39 (80%) have a duration of response (DOR) $\geq 6$ months. Of the 19 responders in the subgroup of patients with no prior systemic treatment, six patients (32%) have a DOR $\geq 6$ months, four (21%) had disease progression within 6 months of onset of response, and nine (47%) had ongoing response but were not yet 6 months beyond onset of response.

As of the cutoff date of November 18, 2019, the safety population included 404 patients treated with at least one dose of study drug at any dose level. The most common (>20%) treatment-emergent adverse event (TEAEs), regardless of causality, included aspartate aminotransferase increased (39%), constipation (34%), anemia (33%), diarrhea (29%), alanine aminotransferase increased (28%), hypertension (28%), and fatigue (22%). Approximately 68% of patients had Grade $\geq 3$ TEAEs. Serious AEs (SAEs) were reported in 46% patients and the most frequent SAEs (≥2%), regardless of causality, included pneumonia (8%), pneumonitis (4.0%), sepsis (3.2%), urinary tract infection (3.0%), and pyrexia (2.2%). Two deaths were reported as related to the study drug, but no additional information regarding these deaths is provided in the meeting package.

Blueprint’s target date for the planned NDA submission for BLU-667 for treatment of patients with RET-positive advanced NSCLC is March 31, 2020. Blueprint states the Assessment Aid will be submitted within 30 days of the original NDA submission.

Blueprint proposes a cut-off of date of February 13, 2020 for the 90 Day Update, with submission to the NDA by June 15, 2020. Blueprint proposes to provide updates to the following data for the 132 patients included in the primary efficacy analysis population:
(July 11, 2019 enrollment cutoff): ORR, DOR, progression-free survival (PFS), overall survival, and responses in intracranial lesions among patients with measurable central nervous system (CNS) metastases at baseline (as assessed by BICR).

**Planned Study to Verify Clinical Benefit**

Study BLU-667-2303 is a randomized trial in patients with previously untreated RET fusion-positive NSCLC. Blueprint intends to use the results of Study BLU-667-2303 to verify the clinical benefit of BLU-667 for the treatment of patients with RET fusion-positive NSCLC. Study BLU-667-2303 will investigate BLU-667 compared to platinum-based chemotherapy with or without pembrolizumab in 244 patients with RET fusion-positive NSCLC who have not received prior systemic therapy for metastatic NSCLC. The primary endpoint is PFS. The companion diagnostic (CDx) to be used for central testing in this study is Oncomine™ Dx Target Test. This study was formally submitted to IND 143094 in August 2019 and the anticipated start of enrollment is in Q1 2020.

**Companion Diagnostic Development**

Blueprint is developing a CDx with Thermo Fisher Scientific for detection of relevant RET fusions in NSCLC.

**DISCUSSION**

1) Does the Agency agree with the proposed approach to establishing the drug product shelf life?

**FDA Response:** FDA acknowledges the intended stability package that will be submitted in the initial NDA and augmented within 30 days of the initial submission. This data package will be sufficient to determine a shelf-life, though the shelf-life granted at approval will be determined during review. In addition to the data outlined in the meeting package, if stability data becomes available during the review period, this data will be reviewed as resources allow.

In general, FDA considers the shelf-life to start when...
2) Blueprint Medicines utilizes contract manufacturing organizations (CMOs) for the production of pralsetinib drug substance and drug product; considering the breakthrough therapy designation of pralsetinib and anticipated accelerated review timelines:

a. Can the Agency comment on the timing of potential pre-approval inspection (PAI), if deemed necessary to be conducted during the NDA review-cycle?

FDA Response: Per “Instructions for using Form FDA-356h”, all facilities listed in the 356h form should be ready for inspection at the time of submission. The form also has an option to indicate whether the site is ready for inspection, or if not, when it will be ready.

b. Can the Agency comment if sites involved in research and development need to be listed in form 356h and / or Module 3?

FDA Response: Per “Instructions for using Form FDA-356h”, only sites involved in manufacture and testing of drug substance and drug product for commercial manufacturing should be listed in the form FDA-356h.

Module 3 can list all sites involved and planned for the commercial manufacturing and testing of drug substance and drug product including sites used in research and development. Refer to Field #28 in “Instructions for using Form FDA-356h” for the content of the site information that need to be listed.
3) Does the agency agree with the content of the Module 3 of this application?

FDA Response: The proposed content and organization of Module 3 for this application appears reasonable.

4) Does the Agency agree with the proposed approach for the NDA Day 90 Update?

FDA Response: In general, FDA agrees with the proposed approach for the 90 Day Update. While it would be acceptable for Blueprint to provide updated ORR data, the 90 Day Update should include updated DOR results for patients already documented to have confirmed response at the time of the original data cut-off date for the NDA of November 18, 2019.

5) Does the Agency agree with the proposed approach for a complete NDA Application?

FDA Response: In addition to feedback provided during previous meetings, Blueprint should confirm that the Clinical Summaries included in Module 2.7 of the original NDA submission will include Summary of Clinical Pharmacology, Summary of Clinical Efficacy, and Summary of Clinical Safety.

The FDA would like to offer Blueprint the opportunity to participate in a pilot program for the Assessment Aid. Further information regarding this program can be found in the link below:

https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

In general, the FDA expects that the Assessment Aid will be submitted with the complete dossier, however may be submitted up to 30 days after the submission is complete.

The FDA is able to provide completed examples of the Assessment Aid upon request.

6) All data and analyses related to the Oncomine™ Diagnostic Target Test (ODxTT) NSCLC sub-population and the Companion Diagnostic validation data will be submitted in the Thermo Fisher Scientific (Thermo) sPMA, which is planned to be submitted almost in parallel with the pralsetinib NDA. Does the Agency have any concern with this approach?

FDA Response: The proposal to submit the CDx validation data in the sPMA for the Oncomine Dx Target Test (ODxTT) is acceptable. Please note that the device sponsor, Thermo Fisher Scientific, should submit a letter of authorization
in the NDA to authorize CDER to cross-reference Thermo Fisher’s sPMA for the ODxTT. The sPMA should also include a letter of authorization to allow CDRH to cross-reference the NDA submission. In addition, please be advised that the device sponsor should plan to submit their panel track sPMA within 30 days of the corresponding NDA submission.

ADDITIONAL COMMENTS

Clinical Pharmacology

7. Refer to FDA’s comments on recommendations for the clinical pharmacology studies that will be used to support future NDA submission conveyed in the pre-IND/EOP2 meeting minutes (issued May 1, 2019) under IND 143094 and following granting of breakthrough designation (BTD) meeting minutes (issued October 17, 2019).

8. It is FDA’s expectation that the NDA submission be complete at the time of original NDA submission. The adequacy of the clinical pharmacology package to support an NDA submission will be determined at the time of filing. For clinical pharmacology studies that are not completed prior to NDA submission, adequate information on why these studies are not completed and when completion is expected should be included in the NDA submission. The status of any ongoing clinical pharmacology studies should also be provided.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 11, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the
In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.2

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Because BLU-667 was granted orphan drug designation on April 11, 2018, and you plan to submit prior to August 2020, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information3 and Pregnancy and Lactation Labeling Final Rule4 websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

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2 [https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm](https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm)
human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study
data that use the standards specified in the Data Standards Catalog.\(^5\)

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,\(^6\) as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page\(^7\) that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at

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\(^5\) [http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm](http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm)

\(^6\) [https://www.fda.gov/media/88173/download](https://www.fda.gov/media/88173/download)

\(^7\) [http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)
FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with SAMPLE STANDARDIZED DATASETS on the cover letter of your submission.

Additional information can be found at FDA.gov.

**DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:
- Description of all trials to be included in the ISS. Please provide a tabular listing

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9 [https://www.fda.gov/media/88173/download](https://www.fda.gov/media/88173/download)
10 [https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm](https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)

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of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources\(^\text{12}\) and the CDER/CBER Position on Use of SI Units for Lab Tests website.\(^\text{13}\)

\(^{12}\) [http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)

\(^{13}\) [https://www.fda.gov/media/109533/download](https://www.fda.gov/media/109533/download)

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SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File (except Type III) and Commercial INDs must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.14

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see FDA.gov.15

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
</table>

14 http://www.fda.gov/ectd
15 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Reference ID: 4557533
OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.16

16 https://www.fda.gov/media/85061/download

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov
NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:
   - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
   - Other significant changes
   - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry Collection U.S. Food and Drug Administration Silver Spring, MD 20993 www.fda.gov
of Race and Ethnicity Data in Clinical Trials for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

**ONCOLOGY PILOT PROJECTS**

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA’s assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR\(^{17}\): In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid\(^{18}\)

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\(^{17}\) [https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program](https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program)


U.S. Food and Drug Administration
Silver Spring, MD 20993
[www.fda.gov](http://www.fda.gov)
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IDARA UDOH
02/06/2020 10:13:32 AM
CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA # | IND 143094
Request Receipt Date | August 30, 2019
Product | BLU-667
Indication | RET fusion-positive non-small cell lung cancer (NSCLC)
Drug Class/Mechanism of Action | Kinase inhibitor
Sponsor | Blueprint Medicines
ODE/Division | OHOP/DOP2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt) | October 29, 2019

Note: This document must be uploaded into CDER’s electronic document archival system as a clinical review: REV-Clinical-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.

REVIEWER NOTE: Breakthrough Designation for the above indication was granted on May 3, 2019, under IND H4. BTD was granted under IND H4 because there was not yet an open IND specifically for development of BLU-667 for the treatment of NSCLC and the study supporting the BTDR is being conducted under IND H4. With the opening of IND 143094 for the development of BLU-667 for RET-rearranged NSCLC, a BTDR based upon the same data for which BTD was granted under IND H4 was submitted to IND 143094. The information in this BTDR review is based upon the review previously conducted under IND H4.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

   BLU-667 is indicated for the treatment of patients with RET fusion-positive non-small cell lung cancer (NSCLC)

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?
   □ YES  □ NO

3. Was the BTDR submitted to a PIND?
   □ YES  □ NO
   If “Yes” do not review the BTDR. The sponsor must withdraw the BTDR. BTDR’s cannot be submitted to a PIND.

If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No,” proceed with below:

4. Consideration of Breakthrough Therapy Criteria:
   a. Is the condition serious/life-threatening?
      □ YES  □ NO
If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☐ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
v. No or minimal clinically meaningful improvement as compared to available therapy/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature:  
{See appended electronic signature page}

Team Leader Signature:  
{See appended electronic signature page}

Division Director Signature:  
{See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response:

• Information regarding the disease and intended population for the proposed indication.
• Disease mechanism (if known) and natural history (if the disease is uncommon).

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2 For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”  
**Disease Background:**
BLU-667 is an inhibitor of RET mutant and transfusion proteins. RET mutations occur in approximately 50% of patients with medullary thyroid cancer (MTC) (>90% in hereditary forms of MTC), and RET fusions have been identified in up to 10–20% of patients with papillary thyroid cancer (PTC), 1-2% of non-small cell lung cancers (NSCLC), and less commonly in other tumor types such as colorectal cancer and breast cancer. Oncogenic activation of RET can occur by two primary mechanisms: chromosomal rearrangements that lead to RET fusion proteins or mutations that directly or indirectly activate the kinase (RET mutations). Both mechanisms result in constitutively active RET kinase activity. BLU-667 currently has no FDA-approved indications.

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide and the leading cause of cancer-related deaths in the United States (US). First-line treatment of patients with metastatic NSCLC with standard platinum-doublet chemotherapy is associated with median progression-free survival (PFS) of 5-7 months and median overall survival (OS) of 10-16 months. The clinical activity of second-line FDA-approved therapies for metastatic NSCLC are listed in Table 1 below.

**Regulatory History**
On November 21, 2016, Blueprint submitted IND including Protocol BLU-667-1101, entitled “A Phase 1 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors.”

On May 24, 2018, Blueprint submitted a Preliminary Breakthrough Therapy Designation (BTD) request for BLU-667 for the treatment of NSCLC.

On October 4, 2018, FDA met with Blueprint in a Type B, End-of-Phase 1 meeting to discuss preliminary data and proposed approach to support an NDA for BLU-667 in patients with advanced solid tumors with RET-alterations. Key discussion points from this meeting are as follows:

- The proposed primary endpoint of overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 may be acceptable as a surrogate endpoint reasonably likely to predict clinical benefit provided that: 1) the ORR is clinically meaningful in magnitude and duration and represents a "meaningful therapeutic benefit" (21CFR314.500) over available therapy, and 2) BLU-667 has demonstrated an acceptable safety profile in the intended population.

- FDA stated that an NDA should rely primarily on results in patients who have received a prior platinum-containing regimen (with or without receiving a checkpoint inhibitor).

- FDA stated that it considers patients with RET mutations to be a distinct population compared to that of patients with RET-fusions.
On March 5, 2019, Blueprint submitted their second request for Breakthrough Therapy designation for BLU-667 for the treatment of patients with RET fusion-positive NSCLC. During review of this request, the review team requested updated information on duration of response.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

This request for breakthrough therapy designation is based on preliminary results from Study BLU-667-1101. Study BLU-667-1101 is a multi-center, open-label, multi-cohort, activity-estimating study designed to evaluate the anti-tumor activity and safety of BLU-667 in patients with patients with RET fusion positive metastatic NSCLC, who have disease progression after platinum-based chemotherapy.

Specifically, the clinical evidence in support of this BTDR is derived from Cohort 1, which enrolled patients with metastatic NSCLC harboring RET fusion that progressed following prior cisplatin-based chemotherapy.

The primary objective in Study Blu-667-1101 is ORR by per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Duration of response (DOR), PFS and overall survival (OS) are the secondary endpoints. All endpoints will be characterized using descriptive statistics.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).
- A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).
- An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.

Overall survival, progression-free survival and overall response rate are all considered clinically relevant endpoints for drugs intended to treat NSCLC. While OS is considered a direct clinical benefit, effects on PFS and ORR may provide evidence of clinical benefit if the magnitude of the treatment effects are very large and/or tumor responses are exceptionally durable.

None.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.
- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.
There are no therapies approved by FDA specifically for patients with RET fusion-positive NSCLC. Patients with RET-positive NSCLC are treated with conventional systemic therapies approved for the treatment of NSCLC. The following table summarizes available therapies for NSCLC in the second-line setting:
<table>
<thead>
<tr>
<th>Drug</th>
<th>indication</th>
<th>Regimen</th>
<th>Endpoint</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>after prior platinum-based chemotherapy</td>
<td>Docetaxel vs. Ifosfamide or vinorelbine</td>
<td>OS</td>
<td>5.7 vs. 5.6 mos (NI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>8.3 vs. 7.6 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>5.7% vs. 0.8%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>after prior platinum-based chemotherapy</td>
<td>Docetaxel vs. best supportive care</td>
<td>OS</td>
<td>7.5 vs. 4.6 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>12.3 vs. 7.0 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>5.5% vs. NR</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Non-Squamous NSCLC after prior chemotherapy</td>
<td>Pemetrexed vs. docetaxel</td>
<td>OS</td>
<td>8.3 vs. 7.9 mos (NI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>2.9 vs. 2.9 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>8.5% vs. 8.3%</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>after prior platinum-based chemotherapy</td>
<td>Ramucirumab + docetaxel vs. docetaxel alone</td>
<td>OS</td>
<td>10.5 vs. 9.1 mos</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td></td>
<td>PFS</td>
<td>4.5 vs. 3.0 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>23% vs. 14%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Non-Squamous NSCLC after prior chemotherapy</td>
<td>Nivolumab vs. Docetaxel</td>
<td>OS</td>
<td>12.2 vs 9.4 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>2.3 vs 4.2 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>19% vs 12%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Squamous NSCLC after prior chemotherapy</td>
<td>Nivolumab vs. Docetaxel</td>
<td>OS</td>
<td>9.2 vs 6.0 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>3.5 vs 2.0 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>20% vs 9%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC &gt; 1% PD-L1 after prior platinum-based chemotherapy</td>
<td>Pembrolizumab vs docetaxel 2mg/kg every 3 weeks</td>
<td>OS</td>
<td>14.9 vs 8.2 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>3.9 vs 4.0 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>18% vs 9%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC &gt; 1% PD-L1 after prior platinum-based chemotherapy</td>
<td>Pembrolizumab vs docetaxel 10mg/kg every 3 weeks</td>
<td>OS</td>
<td>12.7 vs 8.5 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>4.0 vs 4.0 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>19% vs 9%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>after prior platinum-based chemotherapy</td>
<td>Atezolizumab vs docetaxel</td>
<td>OS</td>
<td>13.8 vs 9.7 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>4.1 vs 2.8 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>14% vs 13%</td>
</tr>
</tbody>
</table>

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.

3 Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
LOXO-292, another investigational kinase inhibitor targeting the RET oncogene, was granted BTD in August 2018 for the treatment of patients with metastatic RET fusion-positive NSCLC who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy. The decision to grant BTD was based on demonstration of durable ORR in patients with NSCLC. Specifically, the confirmed ORR in 30 evaluable patients with RET fusion-positive NSCLC was 77% (95% CI: 58, 90). Of the 23 responders, 18 (78%) had durable responses of more than 6 months from the onset of response. In the 12 evaluable patients who were previously treated with both chemotherapy and immunotherapy, the ORR was 75% (95% CI: 46, 95). Eight of these nine responders demonstrated responses > 6 months (range 6.5 – 11.2 months).

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study Design
The data supporting the BTDR for BLU-667 comes from Study BLU-667-1101. This is an ongoing multicenter, first-in-human, dose-finding and activity-estimating, multiple disease-specific cohort study. The study schematic is presented in the figure below. The primary data supporting this BTD request is derived from Part 2/group 1 and those in Part 1 who met the same eligibility criteria and received BLU-667 at a dose of 400mg once daily.

Figure 1: BLU-667 Study Schema

Abbreviations: BOIN = Bayesian optimal interval, MTC = medullary thyroid cancer, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection, SOC = standard of care; TKI = tyrosine kinase inhibitor

4 Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Reference ID: 4582038
The primary efficacy endpoint for Part 2 of Study BLU-667-1101 is overall response rate (ORR) per RECIST v1.1 in all RET-altered patients. A central review of all imaging results will be conducted; however, the data included in the BTDR is based on investigator assessment of response.

Results

As of November 16, 2018, the dose escalation portion of the trial (Part 1) has been completed; the recommended phase 2 dose (RP2D) of BLU-667 was determined to be 400 mg once daily.

The original request contained data from a total of 33 patients with RET fusion-positive NSCLC (Part 2/Cohort 1) with disease progression on or after platinum-based chemotherapy and who received at least one dose of BLU-667 were enrolled and followed through a data cut-off date of March 1, 2019. In response to an information request from FDA, Blueprint provided updated data based on the enrollment cut-off date of Oct 11, 2018 (46 patients) and followup data cut-off date of March 1, 2019. The confirmed overall response rate in 46 patients with RET fusion-positive NSCLC with disease progression on or after platinum-based chemotherapy population is 48% (95% CI: 33, 63) (all partial responses); 36.3% of the 22 responders had a DoR ≥ 6 months.

b. Include any additional relevant information. Consider the following in your response:

- **Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.**

- **Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.**

- **Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.**

The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor involved in multiple cellular processes including cell proliferation, migration, differentiation, and neuronal maintenance. RET signaling leads to activation of multiple downstream pathways including MAPK and PI3K. According to Blueprint, oncogenic activation of RET can occur by two primary mechanisms: chromosomal rearrangements that lead to RET fusion proteins or mutations that directly or indirectly activate the kinase (RET mutations). Both mechanisms result in constitutively active RET kinase activity. The characteristics of patients with RET-rearranged NSCLC include predominantly adenocarcinoma histology, higher proportion of non-smoking patients and younger age than an unselected (non-genetically tested) population of patients with NSCLC.

**Safety Data**

In the dose-finding portion of Study BLU-667-1101, the determined RP2D was 400 mg daily. Dose-limiting toxicities occurred at the 300 and 100 mg twice daily dosing regimens and included Grade 3 hypertension and tumor lysis syndrome.

Of the 168 patients included in the safety summary, the most common AEs (>20%) regardless of causality are: constipation, aspartate aminotransferase increased, hypertension, anemia, diarrhea, alanine aminotransferase increased, fatigue and blood creatinine increased. As of December 19, 2018, treatment-related serious AEs (SAEs) have been reported in 15 (9%) of 168 patients. Two patients experienced related SAEs of Grade 2 pneumonitis, 2 patients experienced related SAEs of Grade 3 tumor lysis syndrome, and 2 patients experienced related SAEs of pneumonia/lung infection in which 1 event was Grade 3 and the other Grade 5.
12. Division’s recommendation and rationale (pre-MPC review):

**GRANT:**

Provide brief summary of rationale for granting:

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

A clinically meaningful improvement in durable ORR [48% (95% CI 33, 63); 37.5% durable ≥6 months] was observed in patients who received BLU-667 for the treatment of RET fusion NSCLC with progression on or after platinum-based chemotherapy when compared to patients with NSCLC following progression on or after platinum-based chemotherapy who received docetaxel or pemetrexed as single agents or ramucirumab plus docetaxel (ORRs: 6-23, median DoR of 4.6 to 9.1 months) or who received an anti-PD-(L)1 antibody as a single agent (ORRs: 14-20%; median DoR of 16-17 months).

**DENY:**

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

13. Division’s next steps and sponsor’s plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Blueprint plans to file BLU-667 for accelerated approval for the treatment of patients with RET-fusion positive NSCLC. Additionally, Blueprint plans on conducting a confirmatory trial in RET-fusion positive NSCLC study in the front-line setting. An End of Phase 2 meeting to discuss the study design, population, comparators, and endpoints of the Phase 3 RET-fusion positive NSCLC study has been scheduled for May 1, 2019 under preIND 143094 with DOP-2. This randomized study is targeted to begin by the end of 2019, in advance of Blueprint’s planned initial NDA filing in the first half of 2020. Blueprint is also developing a companion diagnostic for this development program with Thermo Fisher Scientific.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:


15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?  

- [X] YES  
- [ ] NO

16. Clearance and Sign-Off (after MPC review):

- Grant Breakthrough Therapy Designation  
- Deny Breakthrough Therapy Designation

Reviewer Signature:  
Team Leader Signature:  
Division Director Signature:

{ See appended electronic signature page}
{ See appended electronic signature page}
{ See appended electronic signature page}

Revised 3/18/19/M. Raggio
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/s/

LUCKSON N MATHIEU
05/01/2019 01:41:29 PM

ERIN A LARKINS
05/01/2019 01:49:12 PM

PATRICIA KEEGAN
05/01/2019 02:04:28 PM
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN A LARKINS
10/04/2019 04:55:27 PM

PATRICIA KEEGAN
10/05/2019 04:56:17 PM
Dear Ms. Sanchez:

Please refer to your Pre-Investigational New Drug Application (PIND) file for BLU-667.

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2019. The purpose of the meeting was to discuss the design of a confirmatory trial intended to verify and further describe the clinical benefit of BLU-667 in patients with RET fusion-positive non-small cell lung cancer, discuss the sourcing of the comparator for the proposed study, and discuss the overall nonclinical package to support a marketing application for BLU-667 in this population.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-5913.

Sincerely,

Autumn Zack-Taylor, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
ENCLOSURE:

Preliminary Meeting Comments
Table 1: Highlights of Clinical Pharmacology
Blueprint Medicines Corporation’s agenda, entitled “FDA EOP2 Agenda and Responses 30Apr2019.docx.”
Blueprint Medicines Corporation’s PowerPoint presentation, entitled “Effect of PPI drugs on BLU-667 Exposures - For FDA Meeting May 1 2019.pptx.”
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND/End of Phase 2

Meeting Date and Time: May 1, 2019; 2:00PM-3:00PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

Application Number: PIND 143094
Product Name: BLU-667

Indication: Treatment of patients with RET fusion-positive metastatic non-small cell lung cancer
Sponsor/Applicant Name: Blueprint Medicines Corporation

Meeting Chair: Luckson Mathieu, M.D.
Meeting Recorder: Autumn Zack-Taylor, M.S.

FDA ATTENDEES
Patricia Keegan, M.D. Director, OHOP/DOP2
Erin Larkins, M.D. Clinical Team Leader, OHOP/DOP2
Luckson Mathieu, M.D. Clinical Reviewer, OHOP/DOP2
Pallavi Mishra-Kalyani, Ph.D. Statistics Team Leader, OB/DBV
Somak Chatterjee, Ph.D. Statistics Reviewer, OB/DBV
Xiling Jiang, Ph.D. Clinical Pharmacology Reviewer, OCP/DCPV
Brian Booth, Ph.D. Clinical Pharmacology Reviewer, OCP/DCPV
Whitney Helms, Ph.D. Nonclinical Team Leader, OHOP/DHOT
Autumn Zack-Taylor, M.S. Regulatory Health Project Manager, OHOP/DOP2

SPONSOR ATTENDEES
Andy Boral, M.D., Ph.D. Chief Medical Officer
Christopher Turner, M.D. Vice President, Clinical Development
Sherwin Sattarzadeh, M.B.A. Vice President, Regulatory Affairs
Megan Sanchez, M.P.H. Director, Regulatory Affairs
Hongliang Shi, M.S. Director, Biostatistics
Hui Zhang, Ph.D. Associate Director, Biostatistics

Reference ID: 4431540
BACKGROUND

On April 11, 2018, Blueprint Medicines Corporation (Blueprint) received Orphan Drug Designation for the treatment of rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC).

Regulatory

IND

On November 21, 2016, Blueprint submitted IND including Protocol BLU-667-1101, entitled “A Phase 1 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer and Other Advanced Solid Tumors.” The IND went into effect on December 20, 2016.

On July 27, 2018, Blueprint submitted a Type B, End-of-Phase 1, meeting request to review the clinical data from the ongoing study, Study BLU-667-1101, in patients with unresectable or metastatic solid tumors with RET alterations and to discuss the study elements and registration path. This meeting was granted and took place on October 4, 2018. Key discussion points related to BLU-667 for the treatment of patients with NSCLC were:

- FDA stated that if the proposed study is used to support product registration, a bridging study may be required to demonstrate that the companion diagnostic (CDx) assay is safe and effective for the proposed indication for use because RET-positive patients are enrolled into the clinical trials using different assays from the final CDx assay. Therefore, FDA strongly recommends that the Blueprint bank all biomarker-positive specimens and a sufficient number of biomarker-negative specimens that were screened to conduct a bridging study with the final to-be-marketed test.
On October 19, 2018, Blueprint submitted a request for Breakthrough Therapy designation, amended October 22, 2018, for BLU-667 for the treatment of patients with RET fusion-positive NSCLC.

On February 15, 2019, Blueprint requested a separate Chemistry, Manufacturing and Controls (CMC) meeting. The meeting was held on April 23, 2019.

On February 11, 2019, Blueprint submitted a Type B, End-of-Phase 2, meeting request to discuss the design of a confirmatory trial in patients with RET fusion positive NSCLC, the sourcing of the comparator for the proposed study, and the overall nonclinical package to support a marketing application for BLU-667 in this population. On February 13, 2019, via an email correspondence, FDA requested that Blueprint withdraw the End-of-Phase 2 meeting request from IND and be resubmitted under a new NSCLC-specific pre-IND.

On March 5, 2019, Blueprint submitted a second request for Breakthrough Therapy designation for BLU-667 for the treatment of patients with RET fusion-positive NSCLC.

Pre-IND 143094

The Type B, End-of-Phase 2, meeting request was withdrawn on February 20, 2019. Blueprint resubmitted the meeting request on February 15, 2019, received February 21, 2019, under PIND 143094.

Chemistry, Manufacturing and Controls

BLU-667 is a small molecule new molecular entity (NME) supplied in clinical studies as 100 mg capsules for oral administration.

Nonclinical

BLU-667 is a kinase inhibitor that preferentially targets the rearranged during transfection (RET) surface receptor as well as several RET mutations. In vitro BLU-667 also showed activity against other kinases including JAK1-3, FLT 1-3, FGFR1, VEGFR2, KIT mutations, LCK, MEK3, PDGFRB, SRC, TRKA, B, and C, and TYK2. Blueprint has conducted GLP-compliant toxicology studies of up to 13 weeks duration in both Sprague Dawley rats and Cynomolgus monkeys. In the meeting package, Blueprint describes the results of a GLP-compliant embryofetal development study in rats showing embryofetal loss as well as both visceral and skeletal malformations/variations at doses resulting in exposures lower than the expected clinical exposure. To support a New Drug Application (NDA), Blueprint also plans to submit a full battery of genotoxicity studies and phototoxicity studies.
Clinical Pharmacology

Blueprint stated that the single dose and steady state pharmacokinetics (PK) of BLU-667 have been evaluated in Study BLU-667-1101. BLU-667 exhibited dose-dependent increase in systemic exposure was observed over the dose range of 30-400 mg; however, the increase was not dose proportional. The Tmax, volume of distribution and terminal half-life of BLU-667 after oral administration were approximately 2 to 4 hours, 289L and 14 hours, respectively. The observed accumulation ratio of BLU-667 was around 2 to 3-fold steady state.

In vitro studies suggested that CYP1A2, CYP2D6, CYP3A4 and UGT1A4 are involved in the metabolism of BLU-667, which also suggested that BLU-667 is a P-gp substrate and has some potential in inhibiting CYP2C8, CYP2C9 and CYP3A4. The effects of hepatic impairment, renal impairment, metabolic drug-drug interaction (DDI), and acid reducing agent DDI on BLU-667 will be evaluated.

Electrocardiogram (ECG) and time-matched data of BLU-667 has been collected in Study BLU-667-1101, and Blueprint will submit the cardiac safety report to the FDA QT-IRT when available.

The result from a food effect study under Protocol BLU-667-0101 suggested that a high-fat meal delayed Tmax of BLU-667 approximately 6 hours, which also increased Cmax and area under the curve (AUC) of BLU-667 approximated 104 % and 122%, respectively. Based on the results of the food effect study, Blueprint plans that BLU-667 continues to be administered in fasted conditions in all study protocols. The preliminary result from a bioequivalence Study BLU-667-0102 suggested that the BLU-667 tablet (Test) and capsule (Reference) formulation are not bioequivalent under fasted condition. The geometric mean ratio (GMR) of Test/Reference for Cmax and AUC are 1.70 and 1.75, respectively.

Clinical

Clinical Study BLU-667-1101

Study BLU-667-1101 is a first-in-human, international, dose-escalation, dose expansion study designed to evaluate the anti-tumor activity and safety of BLU-667 in patients with RET fusion-positive NSCLC and other solid tumors.

The study design for BLU-667-1101 at the time of initiation of protocol enrollment was to determine the maximum tolerated dose via a Bayesian optimal interval (BOIN) design and the dose expansion consisted of four cohorts: NSCLC with a RET rearrangement previously treated with a tyrosine kinase inhibitor (TKI), NSCLC with a RET rearrangement that was not previously treated with a TKI, medullary thyroid cancer (MTC), and solid tumors with a RET alteration other than NSCLC and MTC.

The protocol was amended multiple times. The current study design is presented in Figure 1 below, abstracted from the meeting package.
The primary objectives of the dose expansion portion are to determine the overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and to further define the safety and tolerability of BLU-667. Blueprint states that as of December 19, 2018, 66 patients with RET fusion-positive NSCLC received at least one dose of BLU-667 400 mg, 63 of whom were “evaluable for response” based on a data cut-off date of March 1, 2019, including 47 patients with disease progression on or after platinum-based chemotherapy. ORR is presented in the table below; all responses were partial responses (PR).

**Preliminary Results**

Based on the results of the dose escalation portion of Study BLU-667-1101, in which 62 patients were enrolled, the maximum tolerated dose (MTD) was determined to be 400 mg once daily.
Table 1: Confirmed ORR RET fusion-positive NSCLC*

<table>
<thead>
<tr>
<th>Responses</th>
<th>Total (N=63) n (%)</th>
<th>Prior Platinum (N=47) n (%)</th>
<th>No Prior Platinum (N=16) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>23 (36.5)</td>
<td>17 (36.2)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(25, 48)</td>
<td>(22, 50)</td>
<td>(14, 61)</td>
</tr>
</tbody>
</table>

Duration of response (DOR)

| % of responders with DOR≥6 months | 26% | 29% | 17% |

*includes patients who had received at least one dose of BLU-667 400 mg daily as of December 19, 2018, and were “evaluable for response” at the time of a data cut-off date of March 1, 2019.

As of the safety data cutoff date of December 19, 2018, 168 patients received at least one dose of BLU-667. The most common adverse events (≥20%) regardless of causality are: constipation, increased aspartate aminotransferase, hypertension, anemia, diarrhea, increased alanine aminotransferase, fatigue and increased blood creatinine.

**Proposed Study: BLU-667-2303**

Protocol BLU-667-2303 is an international, randomized, open label study to be conducted in patients with metastatic NSCLC harboring a RET fusion mutation. Randomization will be stratified by geography (Asia vs. Non-Asia), prior treatment with anti PD-1/PD-L1 therapy (yes vs. no), and presence of brain metastasis (yes vs. no). Eligible patients will be randomly assigned in a 1:1 ratio to two treatment arms:

- **Experimental (Arm A):** BLU-667 at 400 mg daily (orally)
- **Control (Arm B):**
  - Squamous histology: carboplatin 5-6 mg/ml min AUC intravenously every 3 weeks or cisplatin 75 mg/m² intravenously every 3 weeks and gemcitabine 1250 mg/m² intravenously on days 1 and 8 of each 21-day cycle
  - Non-squamous histology: carboplatin 5-6 mg/ml min AUC intravenously every 3 weeks or cisplatin 75 mg/m² intravenously every 3 weeks with gemcitabine or pemetrexed 500 mg/m² intravenously every 3 weeks and optional pemetrexed maintenance

Patients in the control arm who experience disease progression will be offered BLU-667 at the time of disease progression.

**Key Inclusion Criteria:**

- ≥ 18 years of age and performance status (PS) of 0-1
- Pathologically confirmed, definitively diagnosed, metastatic NSCLC
• Oncogenic RET fusion, as detected by local or central testing of tumor tissue or circulating tumor nucleic acid in blood. If archived tumor tissue is not available, patients are required to undergo a pretreatment biopsy. For patients with RET status determined locally for eligibility, the patient must also consent to submission of blood and tissue samples for retrospective confirmation of RET status by central testing. Patients with RET fusion detected by FISH may only be enrolled if central analysis confirms RET fusion in ctDNA prior to enrollment.

• Patients who previously received chemotherapy in the neoadjuvant or adjuvant setting must have experienced an interval of ≥ 6 months from completion of therapy to recurrence.

Key Exclusion Criteria:

• Any additional known primary driver alterations, such as targetable mutations of EGFR, ALK, ROS1, MET, and BRAF, as confirmed per local testing.

• Any prior anticancer therapy for metastatic disease, except for monotherapy PD-1 or PD-L1 targeted checkpoint inhibitor. Patients who have received a cycle of chemotherapy (i.e., ≤ 4 weeks) may be enrolled after discussion with, and approval by, the medical monitor, provided such therapy is completed at least 21 days prior to randomization.

• PD-1 or PD-L1 targeted checkpoint inhibitor within 28 days of randomization.

• Radiotherapy or radiosurgery to any site within 14 days prior to randomization and more than 30 gray (Gy) of radiotherapy to the lung in the 6 months prior to randomization.

• Presence of Grade 2 or worse interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis within 28 days prior to randomization.

• Patient has central nervous system (CNS) metastases or a primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease. If a patient requires corticosteroids for management of CNS disease, the dose must have been stable for the 2 weeks preceding C1D1.

The primary endpoint for this study is progression-free survival (PFS) assessed by central radiological assessment per RECIST v1.1. Disease assessments will be performed every 6 weeks for the first four assessments, every 9 weeks through the second year, and every 12 weeks thereafter, until documentation of progression disease.

Assuming the median PFS is 6 months in the control arm and 9.8 months in the experimental arm, a total of 178 events are needed to detect a hazard ratio (HR) of 0.61 with 90% power at a two-sided alpha level of 5%. Given non-uniform accrual, the total sample size needed for the study is approximately 258 patients (129 patients per arm) to achieve 178 total PFS events. The primary treatment comparison will be based on a stratified log-rank test in the intention-to-treat (ITT) population.

Secondary endpoints include ORR, EORTC-QLQ-LC13 dyspnea symptom scale, EORTC-QLQ-L13 peripheral neuropathy score, and EORTC-QLQ-C30 physical functioning score. To control
Type I error, the key secondary objectives will be tested sequentially, in the order listed. The study has 90% power to detect a difference in ORRs of 20% (ORR of 30% in the control arm and an ORR of 50% in the experimental arm). A stratified Cochran-Mantel-Haenszel (CMH) test will be performed to test the treatment difference of ORR.

Changes from baseline to week 12 will be compared between two treatment arms, for each of the EORTC-QLQ symptom scores. Assuming the difference of change in the proposed individual symptom scale scores from baseline to week 12 between the experimental arm and the standard of care (SOC) arm is 1 point, and the standard deviation of the difference is 2 points, the current study sample size will have > 90% power to show statistically significant difference between the two treatment arms. This change will be compared using a t-test. Post hoc analyses to explore thresholds for meaningful change using cumulative distribution function to determine clinical benefit will be outlined in the statistical analysis plan (SAP).

Differences in overall survival (OS) between two treatment arms will be analyzed in a same manner as for PFS based on a stratified log-rank test in ITT population.

One interim analysis will be conducted for futility and efficacy after 90 events (51% information). A Lan-DeMets spending function with O’Brien-Fleming type boundaries will be used to determine the alpha boundary for the interim analysis. If p-value ≤ 0.002, superiority will be claimed; if p-value > 0.392, futility will be claimed and if 0.002 < p ≤ 0.392, the trial will continue until the final database lock.

DISCUSSION

Chemistry, Manufacturing and Controls

1. To the extent possible, all of the investigator’s choice comparator treatments for use in the proposed Phase 3 clinical trial will be centrally sourced.

   Does the agency agree with Blueprint’s strategy for sourcing of the investigator’s choice comparators?

   FDA Response: FDA generally agrees with Blueprint’s proposal for drugs administered in the comparator arm. FDA does not object to use of comparators from a central source if they are approved for marketing in the US or if EU-approved comparators with equivalent quality to that of the US-approved comparators are to be used in the clinical study. Blueprint’s approach for stating equivalency appears reasonable; however, the quality information with an equivalency statement and data in the form of comparative certificates of analyses should be included in the original IND submission.

   Discussion during the meeting: Blueprint acknowledged FDA’s response; there was no further discussion of this item during the meeting.
Nonclinical

2.  *Does the Agency agree that the nonclinical safety data package per ICH S9 is supportive of registration of BLU-667 for the treatment of NSCLC?*

**FDA Response:** The completed and ongoing/planned nonclinical studies described in the meeting package appear sufficient to support the filing of a NDA marketing application in the proposed patient population. FDA will make a final determination of the adequacy of the data from these studies upon their review at the time of NDA submission. FDA acknowledges receipt of the final study reports for the 13-week chronic toxicology studies in rats and monkeys to IND [REDACTED] on March 1, 2019. The reports are under review.

**Discussion during the meeting:** Blueprint acknowledged FDA’s response; there was no further discussion of this item during the meeting.

Clinical

3.  *As discussed at the 04 Oct 2018 End-of-Phase 1 meeting with the Agency, Blueprint plans to enroll at least 80 evaluable patients with NSCLC who have been previously treated with platinum-containing chemotherapy into study BLU-667-1101 to support an initial accelerated approval.*

*As a confirmatory study in support of full approval, Blueprint proposes a Phase 3 randomized, open-label, superiority study of the efficacy of BLU-667 versus platinum-containing chemotherapy in platinum-naive patients with RET-fusion positive NSCLC.*

*Does the Agency agree with the open-label, active-comparator, 1:1 randomized design of the Phase 3 study?*

**FDA Response:** Please see FDA’s detailed response to Questions 4, 5, 6, 7, and 8. Clarify the criteria for determining which patients will be offered BLU-667 at the time of disease progression.

**Blueprint Response, received via email on April 30, 2019:** All patients who progress on the platinum-containing chemotherapy comparator arm which is confirmed by central radiology review may be offered BLU-667 at the time of disease progression. Patients must separately consent to cross-over to BLU-667 treatment after disease progression.

Can the Agency provide guidance on what additional clarifications are needed?

**Discussion during the meeting:** Blueprint clarified that all patients in the control arm who have confirmed disease progression and in whom toxicity from prior therapy has resolved will be offered BLU-667 at the time of disease progression.
4. *Does the Agency agree with the list of investigator’s choice comparator treatments?*

**FDA Response:** FDA does not object to the proposed options for investigator’s choice comparator treatments based on histology.

**Discussion during the meeting:** Blueprint acknowledged FDA’s response; there was no further discussion of this item during the meeting.

5. *Does the Agency agree with the proposed inclusion/exclusion criteria for this study?*

**FDA Response:** The proposed inclusion and exclusion criteria appear generally acceptable; however, FDA requests the following modifications.

- Exclude patients with blood bilirubin >1.5 ULN. Alternatively, if Blueprint intends to address the effect of hepatic impairment on BLU-667 PK based on a population PK analysis, the eligibility criteria may allow inclusion of patients with mild to moderate hepatic impairment.
- If Blueprint intends to address the effect of renal impairment on BLU-667 PK based on a population PK analysis, the eligibility criteria may allow inclusion of patients with mild to moderate renal impairment.
- If patients are eligible for enrollment after progressing on an anti-PD-(L)1 antibody randomization should be stratified by receipt of this prior therapy.

Blueprint Response, received via email on April 30, 2019: Blueprint is in agreement with the Agency’s requested inclusion/exclusion criteria, however, for patients with elevated bilirubin due to metastatic disease in the liver or Gilbert syndrome, Blueprint plans to allow total bilirubin ≤3x ULN for these patients. Does the Agency agree?

**Discussion during the meeting:** FDA agreed that inclusion of patients with Gilbert syndrome who have total bilirubin up to 3 times the ULN at baseline would be acceptable. However, patients with elevated bilirubin of greater than 1.5 times the ULN, where the increase in bilirubin is attributed to metastatic disease should be excluded from study entry.

6. *Does the Agency agree with the statistical assumptions and statistical power for the Phase 3 trial?*

**FDA Response:** The proposed statistical assumptions appear appropriate and the plan has adequate power based on these assumptions. However, the magnitude of the proposed treatment effect, which corresponds to a 3.8-month improvement in median PFS, may not demonstrate substantial evidence of effectiveness unless it is supported by an effect of overall survival or the treatment effect of PFS is underestimated by the difference in medians (e.g., hazard ratio ≤ 0.5).
In addition, FDA strongly discourages the conduct of an interim analysis for superiority at 50% information, since early analysis of the treatment effect on PFS tends to be liable to overestimation, is not robust, and is rarely reproducible at any interim analyses with immature data.

Blueprint Response, received via email on April 30, 2019: Based on recent investigator feedback, Blueprint plans to change the null hypothesis from 6-months to 7-months. This will correspond to a clinically meaningful treatment effect of 4.5 months improvement in median PFS assuming hazard ratio of 0.61. Blueprint agrees to remove the proposed interim analysis at 50% information.

Does the Agency agree that these changes address the above concerns?

**Discussion during the meeting:** FDA acknowledged Blueprint’s response. FDA stated that in order to potentially support a marketing application based on improvement of PFS, the treatment effect should be large in magnitude, statistically robust, and internally consistent within relevant subgroups with no evidence of a detrimental effect on overall survival and a favorable risk:benefit profile.

FDA also stated that the final statistical analysis plan (SAP) should reflect the updated assumptions as stated above.

7. *Does the Agency agree with the primary endpoint of progression-free survival?*

**FDA Response:** Please see FDA’s response to Question 6. Clarify if the central radiological assessment of PFS will be blinded to treatment assignment. PFS assessed by blinded independent review committee (BIRC) as the primary endpoint is acceptable, assuming that the trial demonstrates a large and clinically meaningful treatment effect.

Blueprint Response, received via email on April 30, 2019: Blueprint confirms that the central radiological assessment of PFS will be performed by a blinded independent review committee (BIRC).

**Discussion during the meeting:** FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

8. *Does the Agency agree with the key secondary endpoints and testing procedures?*

**FDA Response:** FDA recommends removing the key secondary endpoints of EORTC-QLQ-LC13 symptom scores (dyspnea, peripheral neuropathy, physical function) or making it the lower in the hierarchical testing procedure (after OS). In trials of similar size and population, these endpoints have not been able to demonstrate a statistically significant result at a clinically meaningful threshold. Blueprint may consider a separate statistical plan for assessment of patient-reported outcomes (PRO) endpoints.
Instead, FDA strongly recommends including overall survival (OS) as a key secondary endpoint in the sequential hypothesis testing procedure. Specify a statistical analysis plan for OS, including the hazard ratio to be detected, medians, power, the number of deaths for the final OS analysis, and the number of deaths for an interim OS analysis at the final PFS analysis.

Blueprint Response, received via email on April 30, 2019: Blueprint agrees to move OS to a key secondary endpoint. Blueprint also agrees to FDA’s recommendations regarding the statistical analysis plan for OS (1 Interim Analysis at the time of final PFS analysis and 1 Final Analysis). We propose to use rank preserving structural failure time (RPSFT) model as primary analysis of OS to account for cross-over effect. Does the Agency agree?

If we remove the PROs from the list of key secondary endpoints and analyze them under a separate statistical plan, could positive PRO results be included in a label?

Discussion during the meeting: FDA acknowledged Blueprint’s response; however, FDA discouraged the use of the preserving structural failure time model as the primary analysis of OS. FDA stated that the stratified or unstratified log rank test should be the primary analysis for OS, with any other proposed test as a sensitive analysis for the treatment effect of OS given cross-over of study treatment. FDA stated that they will use this approach (stratified or unstratified log rank test) when analyzing the data for assessment of clinical benefit.

The results of PRO endpoints may be considered for inclusion in the label if a pre-specified analysis plan is included in the SAP. While this analysis plan for PRO’s could be separate from those of the primary and secondary efficacy endpoints, the inclusion of p-values in the label will depend on strict type 1 error control for the entire study. FDA strongly recommended including this analysis plan in the protocol for FDA review prior to initiating the study.

Does the Agency agree that the proposed Phase 3 study, if positive, could support the approval of BLU-667 in first-line setting RET-fusion driven metastatic NSCLC and conversion from accelerated to full approval?

FDA Response: Discussion regarding approval of BLU-667 in first line setting is premature at this time.

Blueprint Response, received via email on April 30, 2019: Please see the Clinical Development Plan shown below. We understand that first-line approval depends on the results of the Phase 3 trial but with the elements of the study design as described, would this study support a first-line full approval and convert the initial accelerated approval?

Blueprint would also like to discuss the feedback the Agency provided in the March 11th advice/information (see below). Blueprint plans to modify protocol BLU-677-1101 to increase the number of treatment naïve patients (first-line) with metastatic RET-fusion

Reference ID: 4431540
positive NSCLC. Does the Agency agree that this supports an accelerated approval in the front-line setting assuming the BLU-667 response rate excludes the expected response rate with standard front-line therapy?

FDA Feedback (March 11th): “Regarding Group 2, which is limited to enrollment of patients with RET fusion-positive non-small cell lung cancer not previously treated with platinum-based chemotherapy, the proposed target response rate of 50%, for which the lower limit of the 95% confidence interval would be 34%, is unlikely to be considered adequate to demonstrate a substantial improvement over available therapy (i.e., pembrolizumab plus platinum-based chemotherapy).”

**Figure 1: BLU-667 clinical development plan in RET-driven mNSCLC**

**Discussion during the meeting:** FDA stated that the proposed randomized study for first line treatment of patients with metastatic RET-positive NSCLC is appropriate for a trial intended to verify the clinical benefit of BLU-667.
ADDITIONAL COMMENTS

Clinical Pharmacology

10. Include the following recommendations in the clinical program:

a. Clarify whether the capsule formulation or the tablet formulation will be used in the proposed Study BLU-667-2303, as the preliminary result from Study BLU-667-0102 suggested that these formulations were not bioequivalent under fasted condition.

Blueprint Response, received via email on April 30, 2019: The bioequivalence study (BLU-667-0102) comparing the capsule formulation that is currently being used in the ongoing Phase 1 Study BLU-667-1101 against the to-be-desired commercial tablet formulation failed to demonstrate bioequivalence.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

b. Restrict patients from acid reducing agents in the ongoing study and throughout the proposed Study BLU-667-2303, as the effect of acid reducing agents on BLU-667 PK has not been evaluated clinically:

- Patient should not use proton pump inhibitors, e.g., omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or dexamethasoprazole, at least 7 days prior and throughout the proposed study.

- When concurrent use of an H2 blocking agent is necessary, e.g., ranitidine, famotidine, or cimetidine, it must be administered only between 2 and 3 hours after the dose of BLU-667. If not taken during this time, the dose of H2 blocking agents should not be taken again until 2–3 hours after the next dose of BLU-667.

- When concurrent use of an antacid is necessary, e.g., aluminum hydroxide/magnesium hydroxide/simethicone or calcium carbonate, it must be administered 2 or more hours before and/or 2 or more hours after the dose of BLU-667.
Blueprint Response, received via email on April 30, 2019: Blueprint agrees to implement the restrictions in the Phase 3 (BLU-667-2303) until the results of the clinical pharmacology DDI PPI study are known. Based on preliminary data from the ongoing BLU-667-1101 study, BLU-667 exposure in patients receiving acid reducing agents is similar to that of patients not receiving acid reducing agents, therefore, we do not plan to implement these changes in the BLU-667-1101 study.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

FDA has the following recommendations for the clinical pharmacology studies to be included in the future NDA submission:

11. The effect of hepatic impairment on BLU-667 PK has not been evaluated. Propose a hepatic impairment study and submit the full protocol to obtain FDA’s agreement with the study design.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

12. The effect of renal impairment on BLU-667 PK has not been evaluated. Propose a renal impairment study and submit the full protocol to obtain FDA’s agreement with the study design.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

13. Blueprint’s plan of using population PK methods to understand the effect of proton pump inhibitors (PPIs) on the PK of BLU-667 is not accepted by FDA. Propose a clinical DDI study to evaluate the effect of PPIs on BLU-667 PK and submit the full protocol to obtain FDA’s agreement with the study design.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting
with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

**Discussion during the meeting**: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

14. Propose clinical DDI studies to evaluate the DDI potential of BLU-667 as either victim or perpetrator of drug metabolic enzymes and/or transporters. Submit the full protocols to obtain FDA’s agreement with the study design.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

**Discussion during the meeting**: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

15. Submit a detailed QTc data analysis plan within 60 days of this meeting to obtain FDA’s agreement with the study design.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

**Discussion during the meeting**: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

16. FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support the future NDA application be consistent with FDA Guidance for Industry, entitled “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at: [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

**Discussion during the meeting**: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.
17.  Address the following questions in the Summary of Clinical Pharmacology:

   a.  What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

   b.  What are the exposure-response relationships for efficacy, safety and biomarkers?

   c.  What is the effect of BLU-667 on the QT/QTc interval?

   d.  What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

   e.  What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.

   f.  How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

18.  Apply the following advice in preparing the clinical pharmacology sections of the original submission:

   a.  Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

   b.  Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

   c.  Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects’ unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
• Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

• Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

19. Submit the following for the population pharmacokinetic analysis reports:

a. Standard model diagnostic plots

b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line

c. Model parameter names and units in tables.

d. Summary of the report describing the clinical application of modeling results.


Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

20. Submit the following information and data to support the population pharmacokinetic analysis:
a. SAS transport files (*.xpt) for all datasets used for model development and validation

b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.


Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.
Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

22. If Blueprint plans to conduct physiologically based pharmacokinetic modelling (PBPK) analysis, include the following items when submitting the PBPK study report:
   
a. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report.
   
b. Provide the study report as PDF files (screenshots can be incorporated if required).
   
c. Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.
   
d. Include appropriate supporting documentations such as any special instructions and file definitions.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

23. Include the following items when submitting QT study report:
   
a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   
b. Electronic copy of the study report
   
c. Electronic or hard copy of the clinical protocol
   
d. Electronic or hard copy of the Investigator’s Brochure
   
e. Annotated CRF
   
f. A data definition file which describes the contents of the electronic data sets
   
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

j. Narrative summaries and case report forms for any:

- Deaths
- Serious adverse events
- Episodes of ventricular tachycardia or fibrillation
- Episodes of syncope
- Episodes of seizure
- Adverse events resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

l. A completed “Highlights of Clinical Pharmacology” table in this IND or a link to the cross-referenced information submitted to IND 131825.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.

Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

24. Advancing in this field, and possibly reducing the burden of conducting QT studies, depends critically upon obtaining the most comprehensive understanding of existing data. Blueprint should consider making the data, at least placebo and positive control data, available for further research purposes. For examples, refer to the Data Request Letter, available at: at http://cardiac-safety.org/ecg-database/.

Blueprint Response, received via email on April 30, 2019: No further discussion on FDA Comments 11 – 24 is requested at this time. Blueprint will request a separate meeting with the Agency to discuss the clinical pharmacology program in support of the future NDA submission.
Discussion during the meeting: FDA acknowledged Blueprint’s response; there was no further discussion of this item during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of this meeting or in the initial IND submission, whichever occurs earlier. The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format—Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data...
standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with SAMPLE STANDARDIZED DATASETS on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File (except Type III) and Commercial INDs must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content
for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:


NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
   • A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
   • Other significant changes
   • Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.
UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA’s assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProducts andTobacco/OCE/ucm612927.htm. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid:https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedical ProductsandTobacco/OCE/ucm612923.htm

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Attached is Blueprint Medicines Corporation’s agenda that was received via email on April 30, 2019, entitled “FDA EOP2 Agenda and Responses 30Apr2019.docx,” and a PowerPoint presentation received via email on May 1, 2019, entitled “Effect of PPI drugs on BLU-667 Exposures - For FDA Meeting May 1 2019.pptx.”
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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05/10/2019 08:19:53 AM