CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213217Orig1s007

Trade Name:	BRUKINSA
Generic or Proper Name:	(zanubrutinib)
Sponsor:	BeiGene USA LLC.
Approval Date:	January 19, 2023
Indication:	BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. • Waldenström's macroglobulinemia (WM). • Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

CENTER FOR DRUG EVALUATION AND RESEARCH

213217Orig1s007

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s007

APPROVAL LETTER

NDA 213217/S-007

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
COMMITMENT

BeiGene USA, Inc.
Attention: Qing (Veronica) Chen, PhD
Senior Director, Regulatory Affairs
1840 Gateway Drive
San Mateo, CA 94404

Dear Dr. Chen:

Please refer to your supplemental new drug application (sNDA) dated December 18, 2021, received December 20, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brukinsa (zanubrutinib) capsules.

We acknowledge receipt of your major amendment dated June 9, 2022, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication for Brukinsa for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

APPROVAL & LABEL

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated December 18, 2021, containing the final report for the following postmarketing commitment listed in the November 14, 2019, approval letter.

---

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] 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.

3735-4 Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of zanubrutinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing requirements listed in the November 14, 2019, approval letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of second primary malignancies.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4390-1 Conduct an integrated safety analysis of patients enrolled in Study BGB-3111-304 to further characterize the risk of second primary malignancies, including incidence and types, and other serious risks with extended follow-up in patients receiving zanubrutinib as first-line treatment for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Include incidence rates of second primary malignancies, including after receipt of subsequent anticancer therapy, types, time to onset, potential predisposing factors, and outcomes in patients who received zanubrutinib or bendamustine plus rituximab in Study BGB-3111-304, and an analysis of postmarketing reports of second primary malignancies in recipients of zanubrutinib as first-line treatment for CLL/SLL. Evaluate overall survival

in each treatment arm in Study BGB-3111-304, and include causes of death and narratives for death in the absence of treated disease progression, at least 8 years after randomization of the first subject in Cohort 1.

The timetable you submitted on December 5, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	06/2023
Final Protocol Submission (Analysis Plan):	12/2023
Study Completion:	11/2025
Final Report Submission:	05/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 125326 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Denise Felluca, Regulatory Project Manager, at

---

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

301-796-4574.

Sincerely,

{See appended electronic signature page}

Nicole J. Gormley, MD
Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

NICOLE J GORMLEY
01/19/2023 01:36:02 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRUKINSA safely and effectively. See full prescribing information for BRUKINSA.

BRUKINSA® (zanubrutinib) capsules, for oral use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.4)	1/2023
Dosage and Administration (2.3)	1/2023
Warnings and Precautions (5.4, 5.5)	1/2023

---------- INDICATIONS AND USAGE----------

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1.1)
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Waldenström's macroglobulinemia (WM). (1.2)
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen. (1.3)
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage: 160 mg orally twice daily or 320 mg orally once daily; swallow whole with water and with or without food. (2.1)
- Reduce BRUKINSA dose in patients with severe hepatic impairment. (2.2, 8.7)
- Advise patients not to open, break, or chew capsules. (2.1)
- Manage toxicity using treatment interruption, dose reduction, or discontinuation. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Capsules: 80 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hemorrhage: Monitor for bleeding and manage appropriately. (5.1)
- Infections: Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed. (5.2)
- Cytopenias: Monitor complete blood counts during treatment. (5.3)
- Second Primary Malignancies: Other malignancies have developed including skin cancers and non-skin carcinomas. Monitor and advise patients to use sun protection. (5.4)
- Cardiac Arrhythmias: Monitor for signs and symptoms of arrhythmias and manage appropriately. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to use effective contraception. (5.6)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥30%), including laboratory abnormalities, are neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BeiGene at 1-877-828-5596 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------

- CYP3A Inhibitors: Modify BRUKINSA dose with moderate or strong CYP3A inhibitors as described. (2.3, 7.1)
- CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers. (2.3, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.2)]*.

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of BRUKINSA is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

BRUKINSA can be taken with or without food. Advise patients to swallow capsules whole with water. Advise patients not to open, break, or chew the capsules. If a dose of BRUKINSA is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day.

2.2 Dosage Modification for Use in Hepatic Impairment

The recommended dosage of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Dosage Modifications for Drug Interactions

Recommended dosage modifications of BRUKINSA for drug interactions are provided in Table 1 *[see Drug Interactions (7.1)]*.

Table 1: Dosage Modifications for Use with CYP3A Inhibitors or Inducers

Coadministered Drug	**Recommended BRUKINSA Dosage** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Strong CYP3A inhibitor	80 mg once daily. Interrupt dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Moderate CYP3A inhibitor	80 mg twice daily. Modify dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Strong CYP3A inducer	Avoid concomitant use.
Moderate CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase BRUKINSA dose to 320 mg twice daily.

After discontinuation of a CYP3A inhibitor or moderate CYP3A4 inducer, resume previous dose of BRUKINSA *[see Dosage and Administration (2.1, 2.2) and Drug Interactions (7.1)]*.

2.4 Dosage Modifications for Adverse Reactions

Recommended dosage modifications of BRUKINSA for Grade 3 or higher adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modification for Adverse Reaction

Adverse Reaction	**Adverse Reaction Occurrence**	**Dosage Modification** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities *[see Warnings and Precautions (5.3)]*		
Grade 3 or Grade 4 febrile neutropenia Platelet count decreased to 25,000-50,000/mm^3 with significant bleeding	First	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.
	Second	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.

Adverse Reaction	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
Neutrophil count decreased to <500/mm^3 (lasting more than 10 consecutive days) Platelet count decreased to <25,000/mm^3 (lasting more than 10 consecutive days)	Third	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue BRUKINSA
Non-hematological toxicities *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*		
Severe or life-threatening non-hematological toxicities[a]	First	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.[a]
	Second	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
	Third	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue BRUKINSA

[a] Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.

3 DOSAGE FORMS AND STRENGTHS

Capsules: Each 80 mg capsule is a size 0, white to off-white opaque capsule marked with "ZANU 80" in black ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and

gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre and post surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%), and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (2.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single-agent in nine clinical trials, administered at 160 mg twice daily in 1445 patients and at 320 mg once daily in 105 patients. Among these 1550 patients, the median duration of exposure was 26 months, 80% of patients were exposed for at least 12 months, and 58% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, included neutrophil count decreased (42%), upper respiratory tract infection (39%), platelet count decreased (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86),

75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥75 × 10^9/L and an absolute neutrophil count ≥1 × 10^9/L independent of growth factor support, hepatic enzymes ≤2.5 × upper limit of normal, total bilirubin ≤1.5 × ULN. The BGB-3111-AU-003 trial required a platelet count ≥50 × 10^9/L and an absolute neutrophil count ≥1 × 10^9/L independent of growth factor support, hepatic enzymes ≤3 × upper limit of normal, total bilirubin ≤1.5 × ULN. Both trials required a CLcr ≥30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection, and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Infections and infestations	Upper respiratory tract infection[a]	39	0
	Pneumonia[b]	15	10[c]
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[d]	36	0
	Bruising[e]	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage[f]	11	3.4[c]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	14	3.4
Respiratory, thoracic and mediastinal disorders	Cough	12	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.
[b] Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
[c] Includes fatal adverse reaction.
[d] Rash includes all related terms containing rash.
[e] Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
[f] Hemorrhage includes all related terms containing hemorrhage, hematoma.
[g] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Other clinically significant adverse reactions that occurred in <10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), and headache (4.2%).

Table 4: Selected Laboratory Abnormalities[a] (>20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	45	20
Lymphocytosis[b]	41	16
Platelets decreased	40	7
Hemoglobin decreased	27	6
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

[a] Based on laboratory measurements.
[b] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (*MYD88^{MUT}*) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 (*MYD88^{WT}*) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in >2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%), and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in >2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in >2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia, and pneumonia in

Cohort 1. Adverse reactions leading to dosage interruption in >2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in >2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	44	0	40	2
	Pneumonia[b]	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders	Fatigue[c]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising[d]	20	0	34	0
	Rash[e]	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage[g]	42	4	43	9
	Hypertension	14	9	19	14

[a] Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.

[b] Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
[c] Fatigue includes asthenia, fatigue, lethargy.
[d] Bruising includes all related terms containing bruise, contusion, or ecchymosis.
[e] Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatoses, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
[f] Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
[g] Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post-procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter, and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities[a] (≥20%) that Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[b]		Ibrutinib[b]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry abnormalities				
Glucose increased	45	2.3	33	2.3
Creatinine increased	31	1	21	1
Calcium decreased	27	2	26	0
Potassium increased	24	2	12	0
Phosphate decreased	20	3.1	18	0
Urate increased	16	3.2	34	6
Bilirubin increased	12	1	33	1

[a] Based on laboratory measurements.
[b] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 *[see Clinical Studies (14.3)]*. The trials required an absolute neutrophil count ≥1 × 10^9/L, platelet count ≥50 or ≥75 × 10^9/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19–related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥10% Patients with MZL Who Received BRUKINSA

Body System	**Adverse Reaction**	**BRUKINSA (N=88)**	
		All Grades (%)	**Grade 3 or 4 (%)**
Infections and infestations	Upper respiratory tract infection[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c,d]	10	6
Gastrointestinal disorders	Diarrhea[e]	25	3.4
	Abdominal pain[f]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[g]	24	0
	Rash[h]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[i]	27	1.1
Vascular disorders	Hemorrhage[j]	23	1.1
General disorders	Fatigue[k]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[l]	10	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.

[b] Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.
[c] Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.
[d] Includes 2 fatalities from COVID-19 pneumonia.
[e] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[f] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[g] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[h] Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.
[i] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[j] Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.
[k] Fatigue includes fatigue, lethargy, asthenia.
[l] Cough includes cough and productive cough.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura, and atrial fibrillation or flutter.

Table 8 summarizes select laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with MZL

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

[a] The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The safety data described below reflect exposure to BRUKINSA (160 mg twice daily) in 675 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.4)]*. The trial required patients to be unsuitable for fludarabine, cyclophosphamide, and rituximab (FCR) therapy defined as age ≥65 years, or age 18 to <65 years with either a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or frequent infections. The trial excluded patients with AST or ALT ≥2 times the upper limit of normal (ULN) or bilirubin ≥3 times (ULN) and patients requiring a strong CYP3A inhibitor or inducer.

SEQUOIA

The safety of BRUKINSA monotherapy in patients with previously untreated CLL/SLL was evaluated in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. Patients without deletion of chromosome 17p13.1 (17p deletion) (Cohort 1) received either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=240) or bendamustine plus rituximab (BR) for 6 cycles (n=227). Bendamustine was dosed at 90 mg/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 on day 1 of Cycles 2 to 6.

Additionally, the same BRUKINSA regimen was evaluated in 111 patients with previously untreated CLL/SLL with 17p deletion in a non-randomized single arm (Cohort 2).

Randomized cohort: Previously untreated CLL/SLL without 17p deletion

In patients with previously untreated CLL/SLL without 17p deletion, the median age was 70, 62% were male, 89% were White, 2% were Asian, and 2% were Black. Most patients (93%) had an ECOG performance status of 0 to 1.

The median duration of exposure to BRUKINSA was 26 months, with 71% exposed for more than 2 years.

Serious adverse reactions occurred in 36% of patients who received BRUKINSA. Serious adverse reactions that occurred in ≥5% of patients were COVID-19, pneumonia, and second primary malignancy (5% each). Fatal adverse reactions occurred in 11 (4.6%) patients with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 9 summarizes select adverse reactions in this randomized cohort.

Table 9: Adverse Reactions in ≥10% Patients with Previously Untreated CLL/SLL Without 17p Deletion in SEQUOIA

	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		BR (N=227)	
System Organ Class Preferred Term	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	33	1.7	17	0.4
Infections and infestations				
Upper respiratory tract infection[b]	28	1.3	15	0.9
Pneumonia[c]	13*	5	8[†]	4
Vascular disorders				
Hemorrhage[d]	27*	4	4	0.4
Hypertension[e]	14	7	5	2.6
Skin and subcutaneous tissue disorders				
Rash[f]	24	1.3	30	5
Bruising[g]	24	0	2.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[e]	15	0	10	0
Gastrointestinal disorders				
Diarrhea	14	0.8	12[†]	0.9
Constipation	10	0.4	18	0.0
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8
Neoplasms				
Second primary malignancy[i]	13*	6	1.3	0.4
Nervous system disorders				
Headache[e]	12	0	8	0
Dizziness[j]	11	0.8	5	0

***** Includes 3 fatal outcomes.

[†] Includes 2 fatal outcomes.

[a] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, musculoskeletal discomfort, bone pain.

[b] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, laryngitis, tonsillitis and upper respiratory tract inflammation, and related terms.

[c] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.

[d] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.

[e] Includes multiple similar adverse reaction terms.

[f] Rash: Rash, dermatitis, drug eruption, and related terms.

[g] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.

[h] Fatigue: fatigue, asthenia, and lethargy
[i] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including lung, renal, genitourinary, breast, ovarian, and rectal), and chronic myeloid leukemia.
[j] Dizziness: dizziness and vertigo.

Other clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

Table 10 summarizes select laboratory abnormalities in this cohort.

Table 10: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA		BR	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	37	15	80	53
Hemoglobin decreased	29	2.5	66	8
Platelets decreased	27	1.7	61	11
Leukocytes increased	21[b]	21	0.4	0.4
Chemistry abnormalities				
Glucose increased[c]	55	7	67	10
Creatinine increased	22	0.8	18	0.4
Magnesium increased	22	0	14	0.4
Alanine aminotransferase increased	21	2.1	23	2.2

[a] The denominator used to calculate the rate was 239 in the BRUKINSA arm and 227 in the BR arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Lymphocytes increased in 15%.
[c] Non-fasting conditions.

Single-arm cohort: Previously untreated CLL/SLL and 17p deletion

In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months.

Fatal adverse reactions occurred in 3 (2.7%) patients, including pneumonia, renal insufficiency, and aortic dissection (1 patient each).

Serious adverse reactions occurred in 41% of patients treated with BRUKINSA. Serious adverse reactions reported in ≥5% of patients were pneumonia (8%) and second primary malignancy (7%).

Adverse reactions led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51%. The leading causes) of dose modification (≥5% of all patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Table 11 summarizes select adverse reactions in this cohort.

Table 11: Adverse Reactions in ≥10% of Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

	CLL/SLL with 17p Deletion	
	BRUKINSA (N=111)	
System Organ Class Preferred Term	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations		
Upper respiratory tract infection[a]	38	0.0
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0.0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4
Neoplasms		
Second primary malignancy[h]	22†	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0.0
Constipation	15	0.0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0.0
Dyspnea[g]	13	0.0
General disorders and administration site conditions		
Fatigue[i]	14	0.9
Nervous system disorders		
Headache	11	1.8

* Includes 1 fatal outcome.

† Includes non-melanoma skin cancer in 13%.

[a] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, upper respiratory tract inflammation, viral upper respiratory tract infection, and related terms.

[b] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, and related terms including specific types of infection.
[c] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, bone pain.
[d] Rash: Rash, dermatitis, toxic skin eruption, and related terms.
[e] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[f] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[g] Includes multiple similar adverse reaction terms.
[h] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including bladder, lung, renal, breast, prostate, ovarian, pelvis, and ureter), and malignant melanoma.
[i] Fatigue: fatigue, asthenia, and lethargy.

Clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 12 summarizes select laboratory abnormalities in this cohort.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	42	19[b]
Hemoglobin decreased	26	3.6
Platelets decreased	23	0.9
Chemistry abnormalities		
Glucose increased[c]	52	6
Magnesium increased	31	0
Creatinine increased	27	0.9

[a] The denominator used to calculate the rate varied from 110 to 111 based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Grade 4, 9%.
[c] Non-fasting conditions.

ALPINE

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. In ALPINE, 324 patients received BRUKINSA monotherapy, 160 mg orally twice daily and 324 patients received ibrutinib monotherapy, 420 mg orally daily until disease progression or unacceptable toxicity.

In ALPINE, the median duration of exposure was 24 months for BRUKINSA. Adverse reactions leading to death in the BRUKINSA arm occurred in 24 (7%) patients. Adverse reactions leading to death that occurred in >1% of patients were pneumonia (2.8%) and COVID-19 infection (1.9%).

One hundred and four patients in the BRUKINSA arm (32%) reported ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Table 13 summarizes select adverse reactions in ALPINE.

Table 13: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory CLL/SLL Who Received BRUKINSA in ALPINE

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	27	1.2	22	1.2
Pneumonia[b]	18*	9	19†	11
COVID-19[c]	14*	7	10†	4.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	26	0.6	28	0.6
Vascular disorders				
Hemorrhage[e]	24*	2.5	26†	3.7
Hypertension[f]	19	13	20	13
Skin and subcutaneous tissue disorders				
Rash[g]	20	1.2	21	0.9
Bruising[h]	16	0.0	14	0.0
Gastrointestinal disorders				
Diarrhea	14	1.5	22	0.9
General disorders				
Fatigue[i]	13	0.9	14	0.9
Respiratory, thoracic and mediastinal disorders				
Cough[f]	11	0.3	11	0.0
Nervous system disorders				
Dizziness[f]	10	0.0	7	0.0

***** Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).

† Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).

[a] Upper respiratory tract infection: upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, nasopharyngitis, laryngitis, tonsillitis, and related terms.

[b] Pneumonia: Pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.

[c] COVID-19: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, SARS-CoV-2 test positive.

[d] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, bone pain, and musculoskeletal discomfort.
[e] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[f] Includes multiple similar adverse reaction terms.
[g] Rash: Rash, Dermatitis, and related terms.
[h] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[i] Fatigue: asthenia, fatigue, lethargy.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

Table 14 summarizes select laboratory abnormalities in ALPINE.

Table 14: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in ALPINE

Laboratory Abnormality[a]	BRUKINSA		Ibrutinib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	43	15	33	16
Hemoglobin decreased	28	4	32	3.7
Lymphocytes increased	24	19	26	19
Platelets decreased	22	4	24	3.4
Chemistry abnormalities				
Glucose increased	52	5	29	2.8
Creatinine increased	26	0.0	23	0.0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	0.0

[a] The denominator used to calculate the rate was 321 in the BRUKINSA arm, and varied from 320 to 321 in the ibrutinib arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 15: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when coadministered with moderate or strong CYP3A inhibitors *[see Dosage and*

	Administration (2.3)].
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong CYP3A inducers *[see Dosage and Administration (2.3)]*. • Avoid coadministration of BRUKINSA with moderate CYP3A4 inducers *[see Dosage and Administration (2.3)]*. If these inducers cannot be avoided, increase BRUKINSA dosage to 320 mg twice daily *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2 or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1550 patients with MCL, MZL, WM, and CLL/SLL in clinical studies with BRUKINSA, 61% were ≥65 years of age, and 22% were ≥75 years of age. Patients <65 years of age had numerically higher rates of Grade 3 or higher adverse reactions and serious adverse reactions (63% and 47%, respectively) than patients <65 years of age (57% and 36%, respectively). No overall differences in effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

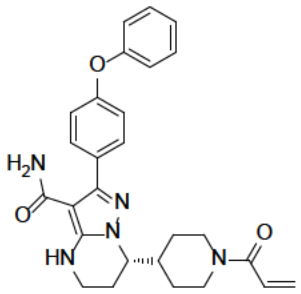
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

BRUKINSA (zanubrutinib) is a kinase inhibitor. The empirical formula of zanubrutinib is $C_{27}H_{29}N_5O_3$ and the chemical name is (*S*)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide. Zanubrutinib is a white to off-white powder, with a pH of 7.8 in saturated solution. The aqueous solubility of zanubrutinib is pH dependent, from very slightly soluble to practically insoluble.

The molecular weight of zanubrutinib is 471.55 Daltons.

Zanubrutinib has the following structure:



Each BRUKINSA capsule for oral administration contains 80 mg zanubrutinib and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The capsule shell contains edible black ink, gelatin, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanubrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

12.2 Pharmacodynamics

BTK Occupancy in PBMCs and Lymph Nodes

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over 24 hours at a total daily dose of 320 mg in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94% to 100% following the approved recommended dosage.

Cardiac Electrophysiology

At the approved recommended doses (160 mg twice daily or 320 mg once daily), there were no clinically relevant effects on the QTc interval. The effect of BRUKINSA on the QTc interval above the therapeutic exposure has not been evaluated.

12.3 Pharmacokinetics

Zanubrutinib maximum plasma concentration (C_{max}) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,099 (42%) ng·h/mL following 160 mg twice daily and 1,917 (59%) ng·h/mL following 320 mg once daily. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 295 (55%) ng/mL following 160 mg twice daily and 537 (55%) ng/mL following 320 mg once daily.

Absorption

The median t_{max} of zanubrutinib is 2 hours.

Effect of Food

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution

The geometric mean (%CV) apparent volume of distribution (Vz/F) of zanubrutinib is 537 (73%) L. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Elimination

The mean half-life ($t_{½}$) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib is 128 (58%) L/h.

Metabolism

Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Excretion

Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (less than 1% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of zanubrutinib were observed based on age (19 to 90 years), sex, race (Asian, Caucasian, and Other), body weight (36 to 144 kg) or mild, moderate or severe renal impairment (creatinine clearance [CLcr] ≥15 mL/min as estimated by Cockcroft-Gault). The effect of dialysis on zanubrutinib pharmacokinetics is unknown.

Hepatic Impairment

The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child-Pugh class A), by 21% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child-Pugh class A), by 43% in subjects with moderate hepatic impairment (Child-Pugh class B) and by 194% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

CYP3A Inhibitors: Coadministration of multiple doses of CYP3A inhibitors increases zanubrutinib C_{max} and AUC (Table 16).

Table 16: Observed or Predicted Increase in Zanubrutinib Exposure After Coadministration of CYP3A Inhibitors

Coadministered CYP3A Inhibitor	**Increase in Zanubrutinib C_{max}**	**Increase in Zanubrutinib AUC**
	Observed	
Itraconazole (200 mg once daily)	157%	278%
	Predicted	
Clarithromycin (250 mg twice daily)	175%	183%
Diltiazem (60 mg three times daily)	151%	157%
Erythromycin (500 mg four times daily)	284%	317%
Fluconazole (200 mg once daily)	179%	177%
Fluconazole (400 mg once daily)	270%	284%

CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92% and AUC by 93%. Coadministration of multiple doses of rifabutin (moderate CYP3A inducer) decreased the zanubrutinib C_{max} by 48% and AUC by 44%.

Coadministration of multiple doses of efavirenz (moderate CYP3A inducer) is predicted to decrease zanubrutinib C_{max} by 58% and AUC by 60%.

CYP3A Substrates: Coadministration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%.

CYP2C19 Substrates: Coadministration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%.

Other CYP Substrates: No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics when coadministered with zanubrutinib.

Transporter Systems: Coadministration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34% and AUC by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when coadministered with zanubrutinib.

Gastric Acid Reducing Agents: No clinically significant differences in zanubrutinib pharmacokinetics were observed when coadministered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

In Vitro Studies

CYP Enzymes: Zanubrutinib is an inducer of CYP2B6 and CYP2C8.

Transporter Systems: Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with zanubrutinib.

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats.

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 10 times the human recommended dose, based on body surface area.

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The efficacy of BRUKINSA was assessed in BGB-3111-206 [NCT03206970], a Phase 2, open-label, multicenter, single-arm trial of 86 previously treated patients with MCL who had received

at least one prior therapy. BRUKINSA was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.

The median age of patients was 60.5 years (range: 34 to 75) and the majority were male (78%). The median time since diagnosis to study entry was 30 months (range: 3 to 102) and the median number of prior therapies was 2 (range: 1 to 4). The most common prior regimens were CHOP-based (91%) followed by rituximab-based (74%). The majority of patients had extranodal involvement (71%) and refractory disease (52%). Blastoid variant of MCL was present in 14% of patients. The MIPI score was low in 58%, intermediate in 29%, and high risk in 13%.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003 [NCT02343120], a Phase 1/2, open-label, dose-escalation, global, multicenter, single-arm trial of B cell malignancies including 32 previously treated MCL patients treated with BRUKINSA. BRUKINSA was given orally at doses of 160 mg twice daily or 320 mg daily. The median age of patients with previously treated MCL was 70 years (range: 42 to 86) and 38% of patients were ≥75 years old. Most patients were male (69%) and Caucasian (78%). The MIPI score was low in 28%, intermediate in 41%, and high risk in 31%.

Tumor response was according to the 2014 Lugano Classification for both studies, and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee.

Table 17: Efficacy Results in Patients with MCL by Independent Review Committee

	Study BGB-3111-206 (N=86)	**Study BGB-3111-AU-003 (N=32)**
ORR (95% CI)	84% (74, 91)	84% (67, 95)
CR	59%	22%[a]
PR	24%	62%
Median DoR in months (95% CI)	19.5 (16.6, NE)	18.5 (12.6, NE)

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable.

[a] FDG-PET scans were not required for response assessment.

14.2 Waldenström's Macroglobulinemia

The efficacy of BRUKINSA was evaluated in ASPEN [NCT03053440], a randomized, active control, open-label trial, comparing BRUKINSA and ibrutinib in patients with MYD88 L265P mutation (*MYD88*^{MUT}) WM. Patients in Cohort 1 (n=201) were randomized 1:1 to receive BRUKINSA 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (0 versus 1-3 versus >3) and CXCR4 status (presence or absence of a WHIM-like mutation as measured by Sanger assay).

The major efficacy outcome was the response rate defined as PR or better as assessed by IRC based on standard consensus response criteria from the International Workshop on Waldenström's Macroglobulinemia (IWWM)-6 criteria. An additional efficacy outcome measure was duration of response (DOR).

The median age was 70 years (range: 38 to 90) and 68% were male. Of those enrolled, 2% were Asian, 91% were White, and 7% were of unknown race. ECOG performance status of 0 or 1 was present in 93% patients at baseline and 7% had a baseline ECOG performance status of 2. A total of 82% had relapsed/refractory disease with 85% having received prior alkylating agents and 91% prior anti-CD20 therapy. The median number of prior therapies in those with relapsed/refractory disease was 1 (range: 1 to 8). A total of 91 (45%) patients had International Prognostic Scoring System (IPSS) high WM.

The study did not meet statistical significance for the prespecified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN.

Table 18 shows the response rates in ASPEN based on IRC assessment.

Table 18: Response Rate and Duration of Response Based on IRC Assessment in ASPEN

Response Category	Standard IWWM-6[a]		Modified IWWM-6[b]	
	BRUKINSA (N=102)	**Ibrutinib (N=99)**	**BRUKINSA (N=102)**	**Ibrutinib (N=99)**
Response rate (CR+VGPR+PR), (%)	79 (77.5)	77 (77.8)	79 (77.5)	77 (77.8)
95% CI (%)[c]	(68.1, 85.1)	(68.3, 85.5)	(68.1, 85.1)	(68.3, 85.5)
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very Good Partial Response (VGPR)	16 (15.7)	7 (7.1)	29 (28.4)	19 (19.2)
Partial Response (PR), (%)	63 (61.8)	70 (70.7)	50 (49.0)	58 (58.6)
Duration of response (DOR), Event-free at 12 months (95% CI)[d]	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)

[a] IWWM-6 criteria (Owen et al, 2013) require complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed.
[b] Modified IWWM-6 criteria (Treon, 2015) require a reduction in EMD if present at baseline for VGPR to be assessed.
[c] 2-sided Clopper-Pearson 95% confidence interval.
[d] Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

ASPEN Cohort 2

Cohort 2 enrolled patients with MYD88 wildtype (*MYD88*^{WT}) or MYD88 mutation unknown WM (N=26 and 2, respectively) and received BRUKINSA 160 mg twice daily. The median age was 72 years (range: 39 to 87) with 43% >75 years, 50% were male, 96% were White, and 4% were not reported (unknown race). 86% patients had a baseline ECOG performance status 0 or 1 and 14% had a baseline performance status of 2. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease.

In Cohort 2, response (CR+VGPR+PR) as assessed by IRC using IWWM-6 or modified IWWM-6 was seen in 50% (13 out of 26 response evaluable patients; 95% CI: 29.9, 70.1).

14.3 Marginal Zone Lymphoma

The efficacy of BRUKINSA was assessed in Study BGB-3111-214 [NCT03846427], an open-label, multicenter, single-arm trial that evaluated 66 patients with MZL who received at least one

prior anti–CD20-based therapy. BRUKINSA was given orally at a dosage of 160 mg twice daily until disease progression or unacceptable toxicity. The median age was 70 years (range: 37 to 85); 55% were male; 38% had extranodal MZL, 38% nodal, 18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 27% having 3 or more lines of systemic therapy; 88% had prior rituximab-based chemotherapy; 32% had refractory disease at study entry.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003 [NCT02343120], an open-label, multicenter, single-arm trial that included 20 patients with previously treated MZL (45% having extranodal MZL, 25% nodal, 30% splenic). BRUKINSA was given orally at dosages of 160 mg twice daily or 320 mg once daily. The median age was 70 years (range: 52 to 85); 50% were male. The median number of prior systemic therapies was 2 (range: 1 to 5), with 20% having 3 or more lines of systemic therapy; 95% had prior rituximab-based chemotherapy.

Efficacy was based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using 2014 Lugano criteria (Table 19).

Table 19: Efficacy Results per IRC in Patients with MZL

Parameter	Study BGB-3111-214 (N=66)	Study BGB-3111-AU-003 (N=20)
Overall Response Rate (CT-based)[a]		
ORR, n	37 (56%)	16 (80%)
(95% CI, %)	(43, 68)	(56, 94)
CR, n	13 (20%)	4 (20%)
PR, n	24 (36%)	12 (60%)
Time to Response		
Median (range), months	2.9 (1.8, 11.1)	2.9 (2.6, 23.1)
Duration of Response[b]		
Median DoR (95% CI), months	NE (NE, NE)	NE (8.4, NE)
Rate at 12 months (95% CI)	85% (67, 93)	72% (40, 88)

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable

[a] Per 2014 CT-based Lugano criteria. FDG-PET scans were not considered for this response assessment.

[b] Based on Kaplan-Meier estimation. Estimated median follow-up for DoR was 8.3 months for Study BGB-3111-214 and 31.4 months for Study BGB-3111-AU-003.

In study BGB-3111-214, ORR prioritizing PET-CT when available (55 patients, with the remainder assessed by CT scan) was 67% (95% CI: 54, 78) with a CR rate of 26%.

14.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The efficacy of BRUKINSA in patients with CLL/SLL was evaluated in two randomized controlled trials.

SEQUOIA

The efficacy of BRUKINSA in patients with previously untreated CLL/SLL was evaluated in a multicenter, open-label trial (SEQUOIA; NCT0333633). The trial required patients to be unsuitable for FCR therapy defined as either age ≥65 years or age 18 to <65 with a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or recurrent infection. Patients without 17p deletion (17p del) were randomized to receive either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=241) or bendamustine plus rituximab (BR) for 6 cycles (n=238). Bendamustine was dosed at 90 mg/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 on day 1 of Cycles 2 to 6 with a 28-day cycle length. Randomization was stratified by age, Binet stage, immunoglobulin variable region heavy chain (IGHV) mutational status, and geographic region.

Additionally, the same BRUKINSA regimen was evaluated in 110 patients with previously untreated, 17p del CLL/SLL in a non-randomized cohort.

Efficacy is summarized according to cohort.

Randomized cohort: Previously untreated CLL/SLL without 17p deletion

In the randomized cohort of patients with previously untreated CLL/SLL without 17p deletion, the median age was 70 years; 62% were male, 89% were White, 3% were Asian, 1% were Black. Fifty-three percent of patients had an unmutated IGHV gene and 29% had Binet Stage C disease. Baseline characteristics were generally similar between treatment arms.

Efficacy in this cohort was based on progression-free survival as assessed by an IRC. Efficacy results are presented in Table 20 and Figure 1.

Table 20: Efficacy Results per IRC in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA (Randomized Cohort)

Parameter[a]	**CLL/SLL without del(17p)**	
	BRUKINSA (N=241)	**Bendamustine + Rituximab (N=238)**
Progression-free survival		
Number of Events, n	36 (15%)	71 (30%)
Disease Progression	27 (11%)	59 (25%)
Death	9 (3.7%)	12 (5%)
Median PFS (95% CI), months[b]	NE (NE, NE)	33.7 (28.1, NE)
HR (95% CI)[c]	0.42 (0.28, 0.63)	
P-value[d]	<0.0001	
Overall response rate[e]		
ORR, n (%)	225 (93)	203 (85)
95% CI, %	(89, 96)	(80, 90)
CR, n (%)	16 (7)	36 (15)
nPR, n (%)	3 (1.2)	14 (6)
PR, n (%)	206 (85)	153 (64)

CI=Confidence interval, CR=complete response, CRi=complete response with incomplete hematopoietic recovery, HR=hazard ratio, NE=not estimable, nPR=nodular partial response, ORR=overall response rate, PFS=progression-free survival, PR=partial response.

[a] Efficacy was assessed using the 2008 International Workshop for Chronic Lymphocytic Leukemia (iwCLL) guidelines and 2014 Lugano criteria for SLL.

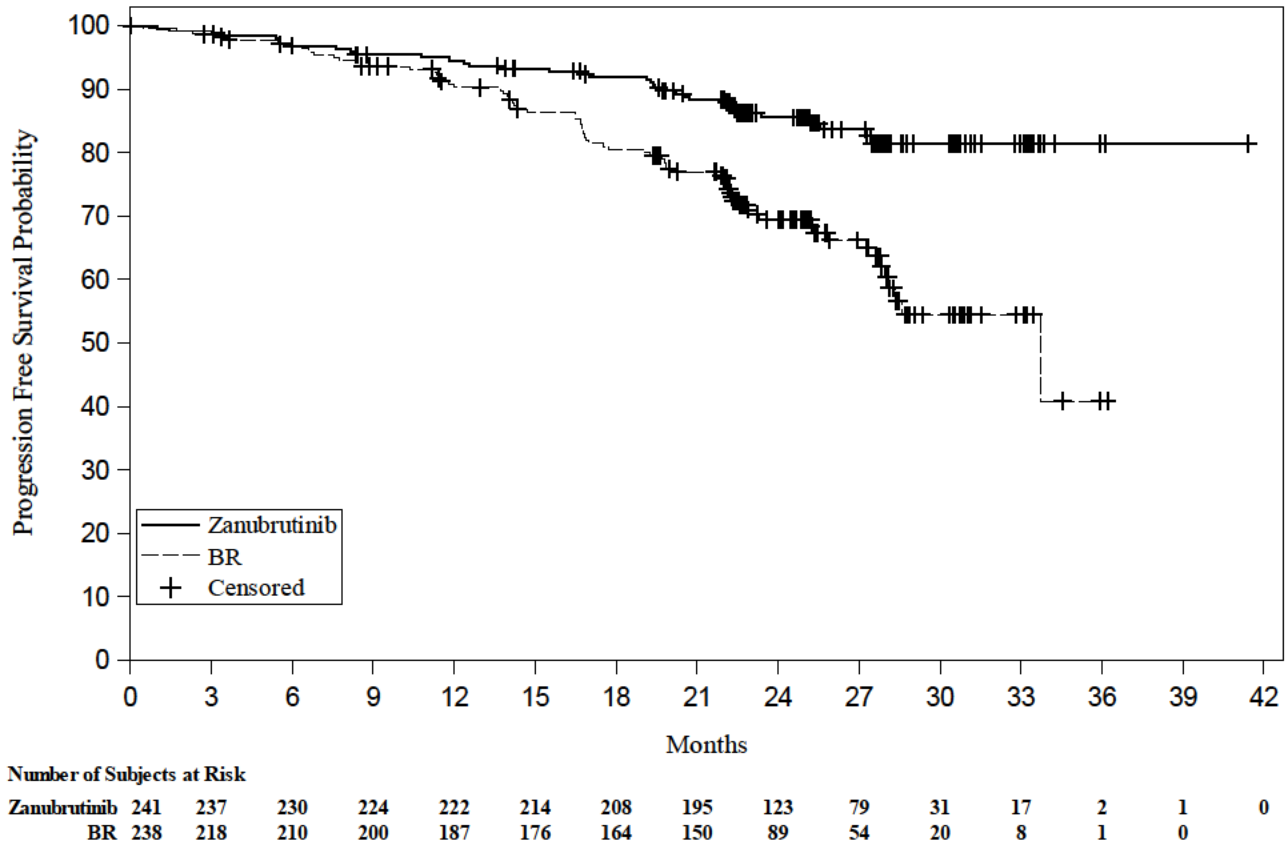
[b] Based on Kaplan-Meier estimation. Estimated median follow-up for PFS was 25.0 months.

[c] Based on a stratified Cox-regression model with bendamustine + rituximab as the reference group.

[d] Based on a stratified log-rank test, with a 2-sided significance level of 0.0372.

[e] Defined as CR, CRi, PR and nPR. No patients had CRi as best response.

Figure 1: Kaplan-Meier Plot of IRC-Assessed Progression-Free Survival in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA



At the time of analysis, overall survival data were immature. With an estimated median follow-up of 25.7 months, median overall survival was not reached in either arm, with fewer than 7% of patients experiencing an event.

Single-arm cohort: Previously untreated CLL/SLL with 17p deletion

In this cohort, 110 patients with previously untreated CLL/SLL and centrally confirmed 17p deletion received BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity.

The median age was 70, 71% were male, 95% were White, and 1% were Asian. Sixty percent of patients had an unmutated IGHV gene and 35% had Binet Stage C disease.

Efficacy was based on overall response rate and duration of response as assessed by an IRC. Efficacy results are presented in Table 21.

Table 21: Efficacy Results Per IRC in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Parameter[a]	**del(17p) CLL/SLL N=110**
Overall response rate[b]	
ORR, n (%)	97 (88)
(95% CI, %)	(81, 94)
CR, n (%)	7 (6)
nPR, n (%)	2 (1.8)
PR, n (%)	88 (80)
Time to response	
Median (range), months	2.9 (1.9 to 13.9)
Duration of response	
Median DOR (95% CI),[c] months	NE (NE, NE)
Range, months	(5.6 to 35.9+)
Rate at 12 months, % (95% CI)[c]	96 (89, 98)
Rate at 18 months, % (95% CI)[c]	95 (88, 98)

DOR=duration of response. A + sign indicates a censored observation.

[a] Efficacy was assessed using the 2008 iwCLL guidelines and Lugano criteria for SLL.

[b] Defined as CR, CRi, PR and nPR. No patients had CRi as best response.

[c] Kaplan-Meier estimate. Estimated median follow-up for DOR was 25.1 months.

ALPINE

The efficacy of BRUKINSA in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE, a randomized, multicenter, open-label, actively controlled trial (NCT03734016). The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 systemic therapy. The patients were randomized in a 1:1 ratio to receive either BRUKINSA 160 mg orally twice daily (n=327) or ibrutinib 420 mg orally once daily (n=325), each administered until disease progression or unacceptable toxicity.

Randomization was stratified by age, geographic region, refractoriness to last therapy, and 17p deletion/*TP53* mutation status.

Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years, 68% were male, 81% were White, 14% were Asian, 1% were Black. Forty-three percent had advanced stage disease, 73% had an unmutated IGHV gene, and 23% had 17p deletion or *TP53* mutation. Patients had a median of one prior line of therapy (range: 1-8), 18% of patients had ≥3 prior lines of therapy, 78% had prior chemoimmunotherapy, and 2.3% had prior BCL2 inhibitor.

Efficacy was based on overall response rate and duration of response as determined by an IRC. Efficacy results are shown in Table 22.

Table 22: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL/SLL in ALPINE

Outcome [a]	**Zanubrutinib (N=327)**	**Ibrutinib (N=325)**
Overall response rate[b]		
ORR, n (%)	263 (80)	237 (73)
(95% CI, %)	(76, 85)	(68, 78)
CR, n (%)	13 (4.0)	8 (2.5)
nPR, n (%)	1 (0.3)	0 (0)
PR, n (%)	249 (76)	229 (70)
Response Rate Ratio (95% CI)[c]	1.10 (1.01, 1.20)	
2-sided p-value[d]	0.0264	
Time to response		
Median (range), months	5.5 (2.6 to 22.1)	5.6 (2.3 to 19.8)
Duration of response		
Median DOR (95% CI)[e]	NE (NE, NE)	NE (NE, NE)
Range, months	(1.4 to 30.4+)	(1.9+ to 30.8+)
Rate at 12 months, % (95% CI)[e]	92 (87, 95)	86 (80, 91)

CI=Confidence interval, CR=complete response, CRi=complete response with incomplete hematopoietic recovery, DOR=duration of response, HR=hazard ratio, NE=not estimable, nPR=nodular partial response, ORR=overall response rate, PR=partial response. A + sign indicates a censored observation.

[a] Efficacy was based on 2008 iwCLL guidelines for CLL and the Lugano criteria for SLL.

[b] Defined as CR + CRi + nPR + PR. No patients had CRi as best response.

[c] Estimate stratified by randomization stratification factors.

[d] 2-sided significance level of 0.0469 was allocated for ORR superiority testing.

[e] Based on Kaplan-Meier estimate. Estimated median follow-up for DOR was 14.1 months.

At the time of analysis, overall survival data were immature. With an estimated median follow-up of 24.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Package Size	Content	NDC Number
120-count	Bottle with a child-resistant cap containing 120 capsules 80 mg, white to off-white opaque capsule, marked with “ZANU 80” in black ink	72579-011-02

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that BRUKINSA may need to be interrupted for major surgeries or procedures *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.2)]*.

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with BRUKINSA *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with BRUKINSA, including skin cancer and other solid tumors. Advise patients to use sun protection and have monitoring for development of other cancers *[see Warnings and Precautions (5.4)]*.

Cardiac Arrhythmias

Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise women of the potential hazard to a fetus and to use effective contraception during treatment and for 1 week after the last dose of BRUKINSA *[see Warnings and Precautions (5.6)]*. Advise males with female sexual partners of reproductive potential to use effective contraception during BRUKINSA treatment and for 1 week after the last dose of BRUKINSA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with BRUKINSA and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Administration Instructions

BRUKINSA may be taken with or without food. Advise patients that BRUKINSA capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of BRUKINSA, they may still take it as soon as possible on the same day with a return to the normal schedule the following day *[see Dosage and Administration (2.1)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

Manufactured for:
BeiGene USA, Inc.
1840 Gateway Dr., FL 3
San Mateo, CA 94404

PATIENT INFORMATION
BRUKINSA® (BROO-kin-sah)
(zanubrutinib)
capsules

What is BRUKINSA?

BRUKINSA is a prescription medicine used to treat adults with:

- Mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.
- Waldenström's macroglobulinemia (WM).
- Marginal zone lymphoma (MZL) when the disease has come back or did not respond to treatment and who have received at least one certain type of treatment.
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

It is not known if BRUKINSA is safe and effective in children.

Before taking BRUKINSA, tell your healthcare provider about all of your medical conditions, including if you:

- have bleeding problems.
- have had recent surgery or plan to have surgery. Your healthcare provider may stop BRUKINSA for any planned medical, surgical, or dental procedure.
- have an infection.
- have or had heart rhythm problems.
- have high blood pressure.
- have liver problems, including a history of hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. BRUKINSA can harm your unborn baby. If you are able to become pregnant, your healthcare provider may do a pregnancy test before starting treatment with BRUKINSA.
  - **Females** should avoid getting pregnant during treatment and for 1 week after the last dose of BRUKINSA. You should use effective birth control (contraception) during treatment and for 1 week after the last dose of BRUKINSA.
  - **Males** should avoid getting female partners pregnant during treatment and for 1 week after the last dose of BRUKINSA. You should use effective birth control (contraception) during treatment and for 1 week after the last dose of BRUKINSA.
- are breastfeeding or plan to breastfeed. It is not known if BRUKINSA passes into your breast milk. Do not breastfeed during treatment with BRUKINSA and for 2 weeks after the last dose of BRUKINSA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking BRUKINSA with certain other medications may affect how BRUKINSA works and can cause side effects.

How should I take BRUKINSA?

- Take BRUKINSA exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking BRUKINSA unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking BRUKINSA if you develop certain side effects.
- Take BRUKINSA with or without food.
- Swallow BRUKINSA capsules whole with a glass of water. Do not open, break, or chew the capsules.
- If you miss a dose of BRUKINSA, take it as soon as you remember on the same day. Return to your normal schedule the next day.

What are the possible side effects of BRUKINSA?

BRUKINSA may cause serious side effects, including:

- **Bleeding problems (hemorrhage)**. Bleeding problems are common with BRUKINSA, and can be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - pink or brown urine
  - unexpected bleeding, or bleeding that is severe or you cannot control
  - vomit blood or vomit that looks like coffee grounds
  - cough up blood or blood clots
  - increased bruising
  - dizziness
  - weakness
  - confusion
  - change in speech
  - headache that lasts a long time
- **Infections** that can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, or flu-like symptoms.

- **Decrease in blood cell counts** (white blood cells, platelets, and red blood cells). Your healthcare provider should do blood tests during treatment with BRUKINSA to check your blood counts.
- **Second primary cancers.** New cancers have happened in people during treatment with BRUKINSA, including cancers of the skin or other organs. Your healthcare provider will check you for other cancers during treatment with BRUKINSA. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems** (atrial fibrillation, atrial flutter, and ventricular arrhythmias) that can be serious and may lead to death**.** Tell your healthcare provider if you have any of the following signs or symptoms:
  - your heartbeat is fast or irregular
  - feel lightheaded or dizzy
  - pass out (faint)
  - shortness of breath
  - chest discomfort

The most common side effects of BRUKINSA include:

- decreased white blood cell count
- upper respiratory tract infection
- decreased platelet count
- muscle, bone, or joint pain

These are not all the possible side effects of BRUKINSA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BRUKINSA?

- Store BRUKINSA capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- BRUKINSA comes in a bottle with a child-resistant cap.

Keep BRUKINSA and all medicines out of the reach of children.

General information about the safe and effective use of BRUKINSA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BRUKINSA for a condition for which it was not prescribed. Do not give BRUKINSA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about BRUKINSA that is written for healthcare professionals.

What are the ingredients in BRUKINSA?

Active ingredient: zanubrutinib
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.
Capsule shell contains edible black ink, gelatin, and titanium dioxide.

Manufactured for: BeiGene USA, Inc., 1840 Gateway Dr., FL 3, San Mateo, CA 94404

For more information, go to www.BRUKINSA.com or call 1-833-969-2463.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental NDA
Application Number(s)	213217/S-007
Priority or Standard	Standard
Submit Date(s)	December 20, 2021
Received Date(s)	December 20, 2021
PDUFA Goal Date	January 20, 2023
Division/Office	Division of Hematologic Malignancies II
Review Completion Date	January 16, 2023
Established Name	Zanubrutinib
(Proposed) Trade Name	Brukinsa
Pharmacologic Class	Kinase Inhibitor
Code name	BGB-3111
Applicant	BeiGene, USA, Inc.
Formulation(s)	Capsule
Dosing Regimen	160 mg orally twice daily or 320 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Denise Felluca, PharmD, MBA
Office of Clinical Pharmacology Reviewer(s)	Yue Xiang, PharmD Hongshan Li, PhD
Office of Clinical Pharmacology Team Leader(s)	Vicky Hsu, PharmD Jiang Liu, PhD
Clinical Reviewer	Margret Merino, MD
Clinical Team Leader	Yvette Kasamon, MD
Statistical Reviewer(s)	Kun Wang, PhD Mingyu Xi, PhD
Statistical Team Leader	Lisa Rodriguez, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Yvette Kasamon, MD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Mark Levenson, PhD
Division Director (OOD)	Nicole Gormley, MD

Additional Reviewers of Application

OPDP	Jessica Chung, PharmD/Barbara Fuller
OSI	Anthony Orencia, MD
OSE/DEPI	Emily Dvorsky/Louisa Bako
OSE/DMEPA	Nicole Iverson/Hina Mehta

OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BCR	B-cell receptor
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CCOD	clinical cutoff date
CIRS	Cumulative Illness Rating Scale
CLL	Chronic Lymphocytic Leukemia
CMC	chemistry, manufacturing, and controls
CRi	complete response with incomplete blood count recovery
CRF	case report form
CSR	clinical study report
DDI	drug-drug interaction
del	deletion
DOR	duration of response
ECI	event of clinical interest
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ICH	International Conference on Harmonization
IGHV	immunoglobulin heavy-chain variable
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MZL	marginal zone lymphoma
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NE	not estimable
nPR	nodular parital remission
ORR	overall response rate
OS	overall survival
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PFS	progression-free survival
PI	prescribing information

PK	pharmacokinetics
PMR	postmarketing requirement
PR	partial response
PR-L	partial response with lymphocytosis
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
SPM	second primary malignancy
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TN	treatment naïve
WM	Waldenström's macroglobulinemia

1 Executive Summary

1.1. Product Introduction

The review team recommends regular approval of zanubrutinib for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Zanubrutinib is a small-molecule kinase inhibitor that forms a covalent bond with a cysteine residue in the Bruton tyrosine kinase (BTK) active site, leading to inhibition of BTK activity. The recommended dosage of zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily, continued until disease progression or unacceptable toxicity.

This application provides for expansion of the indications for zanubrutinib, which has accelerated approval for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, regular approval for the treatment of adult patients with Waldenström's macroglobulinemia (WM) and accelerated approval for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20 based regimen. The recommended indication for patients with CLL or SLL is based on the totality of data from two phase 3 trials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy in treatment-naïve CLL/SLL without 17p deletion (17p del) is based on progression-free survival (PFS) per independent review committee (IRC) in study BGB-3111-304 (SEQUOIA), an open label, phase 3 trial that randomized 479 patients (1:1) to zanubrutinib monotherapy at the intended dosage until disease progression or unacceptable toxicity or bendamustine plus rituximab (BR) for six cycles. On a prespecified interim analysis, the zanubrutinib arm had a statistically significantly improved PFS with a HR of 0.42 (95% CI: 0.28, 0.63; 1-sided $p < 0.0001$, with a boundary of 0.0186). After an estimated 25.0 month median follow-up, the median PFS had not been reached for the zanubrutinib arm (95% CI: NE, NE) and was 33.7 months (95% CI: 28.1, NE) for the BR arm.

Efficacy in treatment-naïve CLL/SLL with 17p del is based on overall response rate (ORR) and duration of response (DOR) in a single-arm cohort of study BGB-3111-304, which treated 110 patients with centrally confirmed 17p del with zanubrutinib monotherapy. The ORR per IRC was 88% (95% CI: 81, 94), and the median DOR had not been reached (95% CI: NE, NE) after an estimated 25.1 month median follow-up.

Efficacy in patients with relapsed or refractory CLL/SLL is based on ORR per IRC with durability in study BGB-3111-305 (ALPINE), an open-label, phase 3 trial that randomized 652 patients to zanubrutinib monotherapy at the intended dosage or ibrutinib monotherapy. The median number of prior lines of therapy was 1 (range: 1 to 8), 73% had an unmutated immunoglobulin

heavy-chain variable (IGHV) gene, and 23% had 17p del or TP53 mutation. On a prespecified final analysis of ORR per IRC, the ORR was statistically significantly higher in the zanubrutinib arm (80.4%) than the ibrutinib arm (72.9%), with a response ratio of 1.10 (95% CI: 1.01, 1.20; 2-sided p-value 0.0264 with a significance level of 0.0469). At the time of the final analysis of ORR, a prespecified interim analysis of PFS was conducted. Although the interim PFS analysis is considered descriptive, it showed a trend towards an improvement in PFS per IRC in the zanubrutinib arm, with a PFS HR of 0.61 (95% CI: 0.44, 0.86).

The totality of data supports the determination that zanubrutinib has clinically meaningful efficacy in adult patients with previously untreated and relapsed or refractory CLL/SLL, including patients with 17p del or TP53 mutated CLL/SLL. Coupled with an acceptable safety profile, the PFS results from study BGB-3111-304 represent a clinically beneficial treatment effect with zanubrutinib compared to BR, and are the primary basis for the recommended regular approval of zanubrutinib in the first-line setting. Additional follow-up for overall survival and longer-term safety will be obtained through a post-marketing requirement. The ORR superiority of zanubrutinib compared to ibrutinib in study BGB-3111-305, with durability and supported by the PFS results from study BGB-3111-304, are the basis for also recommending regular approval of zanubrutinib for patients with CLL or SLL in the relapsed or refractory setting.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Efficacy: Efficacy supporting a broad CLL/SLL indication is based on two multicenter, randomized open-label trials: study BGB-3111-304 (SEQUOIA) in treatment-naïve (TN) CLL/SLL and study BGB-3111-305 (ALPINE) in relapsed or refractory (R/R) CLL/SLL.

Efficacy in the treatment naïve CLL/SLL setting in patients without 17p del is based on SEQUOIA Cohort 1, a multicenter, open-label trial that included 479 patients with previously untreated CLL/SLL without 17p del randomized (1:1) to receive zanubrutinib monotherapy 160mg twice daily continuously until disease progression or unacceptable toxicity or BR administered for 6 cycles. The treatment arms were generally balanced with regards to baseline characteristics. The median age was 62 years, 30% had Binet stage C, and 51% had an unmutated IGHV status. The median duration of treatment was 26 months in the zanubrutinib arm and 5.5 months in the BR arm. The primary endpoint was PFS per IRC. On a prespecified interim analysis with a median follow-up time of 25.0 months, the zanubrutinib arm had a statistically significantly improved PFS with a HR of 0.42 (95% CI: 0.28, 0.63; $p < 0.0001$). The median PFS had not been reached for the zanubrutinib arm and was 33.7 months (95% CI: 28.1, NE) for the BR arm. The secondary endpoints of overall response rate (ORR) and complete response (CR) rate were also higher in the zanubrutinib arm with an ORR of 93.4% (95% CI: 89.4, 96.2) vs. 85.2% (95% CI: 80.1, 89.5) in the BR arm.

Cohort 2 of SEQUOIA evaluated 111 patients with TN CLL with 17p del treated with zanubrutinib monotherapy 160mg twice daily until disease progression or unacceptable toxicity. In Cohort 2, ORR was evaluated by IRC as a secondary endpoint. The ORR was 88% (95% CI: 81, 94), with a median follow-up time of 25.1 months (95% CI 24.9, 25.6), the median duration of response (DOR) had not been reached (95% CI: NE, NE).

Efficacy in patients with R/R CLL/SLL is based on ALPINE, a multicenter, open-label trial that included 652 patients with previously treated CLL/SLL, including those with 17p del (15%), randomized (1:1) to receive either zanubrutinib 160mg twice daily or ibrutinib 420mg once daily, continuously until disease progression or unacceptable toxicity. The primary endpoint (per the U.S. statistical analysis plan) was ORR per IRC in the ITT population, to be tested for noninferiority then superiority. The treatment arms were generally balanced with regards to baseline characteristics. The median number of prior therapies was 1 (range: 1, 8), 43% of the patients had Binet stage C or Ann Arbor stage III/IV disease, 15% had 17p del, and 73% had an unmutated IGHV status.

At the final ORR analysis of the ITT population, the ORR per IRC was statistically significantly higher in the zanubrutinib arm compared to the ibrutinib arm (80.4% vs. 72.9%, respectively). The response ratio was 1.10 (95% CI: 1.01, 1.20) with a 2-sided p-value for superiority of 0.0264 (significance level, 0.0469). With a median follow-up time for DOR of 14.1 months, median DOR had not been reached for either arm. Efficacy results from SEQUOIA were also considered to support the results from ALPINE.

Safety in TN CLL/SLL is based on SEQUOIA supported by the safety from the ALPINE trial and an expanded safety population of 1,550 patients with B-cell malignancies who received zanubrutinib monotherapy at 160mg twice daily or 320mg daily. In SEQUOIA Cohort 1, the median duration of zanubrutinib was 26 months. In the zanubrutinib arm, treatment-emergent serious adverse events (SAEs) occurred in 36% of patients with fatal TEAEs occurring in 4.6%. The most common TEAEs with zanubrutinib (≥ 25%) were neutropenia, anemia, thrombocytopenia, musculoskeletal pain, hemorrhage, and upper respiratory tract infection. Other common TEAEs that occurred in ≥ 15% were pneumonia, rash, bruising, and cough. In Cohort 2, SAEs occurred in 41% of patients with fatal TEAEs occurring in 2.7%. The most common TEAEs in Cohort 2 (≥ 25%) were neutropenia, anemia, thrombocytopenia, musculoskeletal pain, hemorrhage, and upper respiratory tract infection. Other common TEAEs that occurred in ≥ 15% of patients were pneumonia, rash, bruising, hemorrhage, second primary malignancy, cough, diarrhea, and nausea.

Safety in R/R CLL/SLL is based on ALPINE and supported by safety from the SEQUOIA trial and the expanded safety population of 1,550 patients with B-cell malignancies who received zanubrutinib monotherapy at 160mg twice daily or 320mg daily. In ALPINE, the median duration of zanubrutinib therapy was 24 months. In the zanubrutinib arm, treatment emergent SAEs occurred in 41% of patients with fatal TEAEs occurring in 2.7%. The most common AEs with zanubrutinib (≥ 25%) were neutropenia, anemia, thrombocytopenia, upper respiratory infection, musculoskeletal pain, rash, bruising and hemorrhage. Other common TEAEs that occurred in ≥ 15% of patients were pneumonia, diarrhea, nausea, and cough.

The overall safety profile observed in SEQUOIA and ALPINE was similar to safety profile of the larger ISS (N = 1550 safety set). The most common AEs (≥ 30%) were neutropenia, upper respiratory tract infection, thrombocytopenia, hemorrhage and musculoskeletal pain. Events of clinical interest in the expanded safety population included serious or ≥ grade 3 infections, major hemorrhage, cytopenias, second primary malignancies, and cardiac arrhythmias.

Overall benefit-risk assessment: In patients with TN and R/R CLL/SLL, zanubrutinib has a favorable benefit-risk balance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CLL and SLL are generally incurable malignancies. • With successive treatment regimens, many patients have diminished response rates and shorter response duration. •Patients with high-risk cytogenetic features have an especially poor prognosis.	CLL/SLL is a serious and life-threatening condition
Current Treatment Options	• Available therapy for treatment naïve and relapsed and refractory CLL/SLL includes chemotherapy or chemo-immunotherapy, monoclonal anti-CD20 antibodies, ibrutinib, acalabrutinib, venetoclax, and one PI3K inhibitor: duvelisib (after two prior therapies). CLL almost invariable relapses after treatment, although some patients may have prolonged remission prior to relapse. • Available therapies have significant toxicities, with some toxicities leading to treatment discontinuation.	Effective, yet tolerable, treatment options are needed for the intended populations, including chemotherapy-free options.
Benefit	• The SEQUOIA trial demonstrated clinically meaningful and statistically significant improvement in progression-free survival for zanubrutinib [hazard ratio 0.42 (95% CI: 0.28, 0.63) compared to BR in patients with previously untreated CLL/SLL without 17p del. In patients with CLL/SLL with 17p del, efficacy was demonstrated by an ORR of 88% with durability; the median DOR not reached, with an estimated 1-year DOR rate of 95%. • There were a similar number of overall survival events between the two arms at the time of the PFS analysis and the impact of zanubrutinib in patients with previously untreated CLL/SLL compared to BR with longer follow-up is unknown • In patients with R/R CLL/SLL, the ALPINE trial demonstrated superior ORR per IRC in the zanubrutinib arm compared to the	Substantial evidence of efficacy was demonstrated for zanubrutinib over bendamustine plus rituximab in patients with previously untreated CLL/SLL Substantial evidence of efficacy was demonstrated for zanubrutinib over ibrutinib in patients with previously treated CLL/SLL based on the ALPINE study and supported by the SEQUOIA study

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ibrutinib arm (80.4% vs. 72.9%) with a response rate ratio of 1.10 (95% CI: 1.01, 1.20; 2-sided p=0.0264). In addition, a trend towards an improvement in PFS in the zanubrutinib arm was observed at an interim analysis. The median DOR had not been reached in either arm, with median DOR follow-up of 14.1 months.	
Risk and Risk Management	• In SEQUOIA and ALPINE, AEs in ≥ 25% were cytopenias, musculoskeletal pain, upper respiratory infection, and hemorrhage. Other common AEs (incidence ≥ 15%) were pneumonia, rash, bruising, and hypertension. • In SEQUOIA, at the interim analysis for PFS, there was an increase in deaths due to AEs in the zanubrutinib arm compared to the control arm. At subsequent follow-up there were a similar number of deaths due to AEs in both arms, however overall survival data are immature. • Events of clinical interest with zanubrutinib include infections, bleeding, grade 3-4 cytopenias, SPMs, and cardiac arrhythmias.	• The overall safety profile of zanubrutinib in patients with CLL/SLL is similar to the safety profile described previously for the approved indications in R/R mantle cell lymphoma, WM, and R/R marginal zone lymphoma. • The risks are acceptable in patients with CLL/SLL who have an indication for treatment. • Additional follow-up for overall survival and longer-term toxicities is warranted in the TN population despite the observed PFS advantage.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				
	□	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.1 and 8.1.2 *Secondary endpoints: study BGB-3111-304 and BGB-3111-305* *EORTC QLQ-C30* *EQ-5D-5L*
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader

APPEARS THIS WAY ON ORIGINAL

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) is the most common leukemia in the Western world, representing approximately 25% to 35% of all leukemias in the United States (US) (Siegel et al 2021) with incidence rates among men and women of approximately 6.75 and 3.65 cases per 100,000 population per year, respectively (Yamamoto et al 2008). It is estimated that 21,250 new cases of CLL/SLL will be diagnosed in the United States in 2021 (Siegel et al 2021) and that there are approximately 191,000 cases and 61,000 deaths per year attributed to CLL/SLL (Global Burden of Disease Cancer Collaboration, 2017). The World Health Organization (WHO) classification considers CLL and SLL to be different clinical manifestations of the same disease (Swerdlow et al 2008Swerdlow et al 2008); therefore, CLL and SLL are considered collectively.

CLL/SLL may often be initiated by the loss or addition of large chromosomal elements, eg, deletion 13q (approximately 55%), deletion 11q (approximately 25%), or trisomy 12 (10% to 20%), followed by additional mutations that may render the leukemia more aggressive (Landau et al 2015). The loss of the TP53 locus on chromosome 17p13.1 (del(17p)) is the most significant poor prognostic feature in this disease

CLL is considered a treatable but essentially incurable disease. While the overall 5-year survival rate is high (> 85% in the USA) for those who receive appropriate treatment, fewer than 25% of the highest-risk subset of patients (based on *TP53* gene dysfunction and clinical factors) would be expected to survive 5 years (Hallek 2019; Hallek 2019; NCI SEER 2020). Until recent decades, the treatment of CLL was based on chemotherapy, particularly the alkylating agents chlorambucil, cyclophosphamide, and more recently, bendamustine. In the 1990s, the purine analogue fludarabine was shown in clinical trials to improve progression-free survival (PFS) compared to chlorambucil, except for elderly CLL patients, and became a standard initial therapy in younger patients with CLL (Rai et al 2000). The addition of anti-CD20 antibodies, such as rituximab, to chemotherapy resulted in significant improvements in the clinical outcomes of previously untreated CLL (Bauer et al 2012; Goede et al 2015; Bryan and Borthakur 2010; Reff et al 1994). Treatment standards for CLL/SLL have transformed since the advent of effective inhibitors of B-cell receptor (BCR) signaling, allowing for several choices of treatment regimens and single agent therapies for the general population of both treatment-naïve (TN) and previously treated CLL/SLL.

The FDA's Assessment:
The Agency agrees with the Applicant's position. The BTK inhibitors acalabrutinib and ibrutinib are approved for the treatment of CLL/SLL including patients with CLL/SLL with 17p del. Approvals were supported by multiple randomized trials evaluating clinically meaningful endpoints including PFS and OS.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Current Standard of Care for Treatment of TN CLL/SLL

Treatment options for CLL/SLL patients include multiagent chemoimmunotherapy, such as fludarabine/cyclophosphamide/rituximab (FCR), bendamustine/rituximab (B+R), and chlorambucil/obinutuzumab (Cl+O). Such treatments, however, are less effective in patients with high-risk disease; furthermore, many patients cannot tolerate multiagent chemoimmunotherapy due to age and comorbidities. Other treatment options include first-generation BTK inhibitors such as ibrutinib or acalabrutinib and PI3K inhibitors; these also have significant toxicities, such as atrial fibrillation for ibrutinib and colitis for PI3K inhibitors, which limit tolerability and may lead to treatment discontinuation.

First-line therapy for CLL/SLL is influenced by the presence or absence of del(17p). For patients with the mutation, chemotherapy is no longer recommended. Recent studies have demonstrated that inhibitors of BCR signaling, either alone or in combination with anti-CD20 antibodies, result in deep responses with improved PFS as compared to chemotherapy (Al-Sawaf et al 2020; Sharman et al 2020; Shanafelt et al 2019). The National Comprehensive Cancer Network (NCCN) guidelines (NCCN Guidelines for CLL, version 4.2021NCCN Guidelines for CLL, version 4.2021) list acalabrutinib (+/- obinutuzumab), ibrutinib, and venetoclax (+/- rituximab) as category 1 therapies for first line treatment of CLL independent of prognostic risk and medical comorbidity. Clinical trials summarizing efficacy of these agents in patients with TN CLL/SLL are detailed in Table 1 in Module 2.7.3.

Current Standard of Care for Treatment of Relapsed/Refractory (R/R) CLL/SLL

Management of progressive CLL/SLL following first-line therapy is guided by the duration of first remission. For patients with a duration of remission > 36 months, the regimen used in the first line may be administered again. For patients who are refractory or whose disease progresses within 3 years, the choice of subsequent therapy is guided by patient fitness and the regimen that was used in the first line (Hallek et al 2019).Hallek et al 2019). Additionally, special consideration is required for patients with treatment-refractory disease (defined by an early relapse within 6 months after the last treatment) or whose CLL/SLL expresses the del(17p) mutation. Treatment options for these patients include venetoclax-based regimens, ibrutinib regimens, idelalisib + rituximab, alemtuzumab or lenalidomide + rituximab (Hallek et al, 2019).Hallek et al, 2019). The NCCN guidelines list acalabrutinib (alone or in combination with obinutuzumab), ibrutinib, and venetoclax (alone or in combination with rituximab) as Category

1 therapies for the second line and subsequent treatment of CLL/SLL independent of prognostic risk and medical comorbidity; these 3 drugs are approved in the US for treatment of TN and R/R CLL/SLL.

All 3 drugs have proven efficacy in R/R CLL/SLL. Ibrutinib was approved in R/R CLL/SLL from the RESONATE trial with a median follow-up of 9.4 months and an ORR of 42.6%. With over 5 years of follow-up median PFS was found to be 44 months. Acalabrutinib treatment in patients with R/R CLL/SLL had an ORR of 81% and venetoclax in combination with rituximab an ORR of 92%.

While the BTK inhibitors ibrutinib and acalabrutinib have shown acceptable tolerability profiles and superior efficacy when compared to prior therapies (Woyach et al, 2018Woyach et al, 2018; Shanafelt et al, 2019; Sharman et al, 2020; Ghia et al, 2020; Fischer et al, 2019), there remains an unmet medical need for a highly tolerable and effective BTK inhibitor that can be administered with commonly used concurrent medications such as proton pump inhibitors. Current NCCN guidelines list acalabrutinib (+/- obinutuzumab), ibrutinib, and venetoclax (+/- rituximab) as category 1 therapies for first line and subsequent treatment of CLL/SLL independent of prognostic risk and for treatment of patients who are fit or frail.

The FDA's Assessment:
The Agency agrees with the Applicant's position.

2 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
BRUKINSA® (zanubrutinib, also known as BGB-3111) was first approved on 14 November 2019 by the US Food and Drug Administration (FDA) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Additionally, zanubrutinib received regular approval on 31 August 2021 for adult patients with Waldenström macroglobulinemia (WM), and on 14 September 2021 for adult patients with R/R Marginal Zone Lymphoma (MZL) through the accelerated approval pathway. Zanubrutinib received Orphan Drug Designation (ODD) from the FDA for the treatment of CLL/SLL on 20 July 2016 (ODD #16-5275).

The FDA's Assessment:
The Agency agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Key interactions with the Agency related to the development of zanubrutinib for CLL/SLL are summarized in Table 1.

Table 1: Summary of Regulatory Communications

Regulatory Events	Date	Description
End-of-Phase 1 meeting	12 May 2016	Present data from the ongoing Phase 1/2 Study BGB-3111-AU-003 and to obtain input on registrational pathways and study designs for the MCL, Waldenström macroglobulinemia (WM), and CLL/SLL indications.
Type C written response	06 Apr 2017	Discuss data from the Phase 1 BGB-3111-AU-003 study, especially the efficacy and safety data in patients with CLL/SLL, and to propose a plan to evaluate BGB-3111 in potential registrational trials in CLL/SLL.
Type B meeting	11 May 2018	Discuss the proposed protocol for Study BGB-3111-305 and the registration pathways for BGB-3111 in CLL/SLL. PFS was agreed as the primary endpoint for regulatory assessment.

Type B meeting preliminary response	17 May 2019	Discuss and obtain Agency feedback regarding the regulatory pathway in patients with treatment-naïve (TN) CLL/SLL with the del(17p) mutation and potential registration strategy for zanubrutinib under the accelerated approval provision (12 CFR 314 Subpart H).
Type B pre-sNDA meeting	17 Sep 2021	Provide a summary of data for zanubrutinib in adult patients with CLL/SLL, and to seek agreement from the Agency on the regulatory pathway for the approval of zanubrutinib in this patient population.
Type C meeting	22 Oct 2021	A follow-up to the pre-sNDA meeting on 17 September 2021, to discuss proposed additional overall survival (OS) analyses and revisions to the statistical analysis plan (SAP) to support an sNDA for CLL/SLL

Agency interactions also included FDA information requests and advice related to protocols for Studies BGB-3111-304 and BGB-3111-305, which have all been properly responded to and implemented.

The FDA's Assessment:
The Agency agrees with the Applicant's position. Additional key details regarding prior regulatory interactions include:

May 17, 2019 - Type B meeting: The Agency informed the Applicant that an indication for previously untreated CLL should be supported by a randomized study comparing zanubrutinib to standard therapy and should demonstrate superiority of zanubrutinib for PFS.

September 17, 2021 - pre sNDA meeting: The Agency expressed concerns about uncertainty regarding a potential for harm based on limited information, and increased deaths due to TEAEs in the zanubrutinib arm compared to the BR arm. The Agency advised the Applicant that additional follow-up on OS would be required to fully assess the benefit risk of zanubrutinib in patients with previously untreated CLL.

3 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA Office of Scientific Investigations was consulted to perform an audit of one of the highest enrolling U.S. sites for studies BGB-3111-304 and BGB-3111-305. The division also requested an audit of the Applicant's U.S. office.

Clinical site 0146, Dr. Mazyar Shadman at the Fred Hutchinson Cancer Center Seattle, Washington, was selected for inspection based on having one of the highest accrual numbers for United States sites for studies BGB-3111-304 and BGB-3111-305. The clinical site inspection included a review of study administrative files, including FDA 1572 (Statement of Investigator) completion, financial disclosure forms, IRB approvals, clinical site training documentation, and monitoring reports. The Applicant had pre-designated vendors for central laboratory analysis (b) (4), clinical pathology, biomarkers (b) (4) central imaging (b) (4) (b) (4) study management and monitoring.

The site audit involved review of the electronic medical record printouts, electronic data capture for study subject enrollment per inclusion and exclusion criteria, informed consent, treatment assignment, adverse events reporting, concomitant medications, vitals, and study drug accountability and disposition.

Source records for the enrolled study patients were examined. The primary efficacy data were verified against the data line listings, including the investigator's response assessment and independent review committee as part of the endpoint data. Adverse and serious adverse events were assessed for reporting adequacy.

The Applicant's office inspection included review of the trial master files, organizational charts, standard operating procedures, operational manuals, contracts, transfers of obligations, site monitoring, case report forms, handling of adverse events, data collection, and how the Applicant brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, monitoring procedures and frequency, and other monitoring-related activities, test articles, test accountability records.

No significant issued were identified during the clinical site or Applicant's office inspection.

4.2. Product Quality

Not applicable, as this sNDA does not contain CMC-related changes.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

The FDA approved Vysis FISH assay was utilized to determine 17p deletion status for patients in the studies supporting the indication.

APPEARS THIS WAY ON ORIGINAL

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

No new non-clinical pharmacology/toxicology data were provided in this submission.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Reference is made to original zanubrutinib NDA 213217 submitted on 27 June 2019 and approved on 14 November 2019. The non-clinical pharmacology/toxicology profile for zanubrutinib has not changed and results support the treatment of patients with CLL/SLL with the intended dose regimen of 320 total daily dose.

5.3 Pharmacology

Primary pharmacology
Data:
No new information is provided in the current supplemental submission.

The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Secondary Pharmacology
Data:
No new information is provided in the current supplemental submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Safety Pharmacology
Data:
No new information is provided in the current supplemental submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

5.4 ADME/PK

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

5.5 Toxicology

5.5.1 General Toxicology

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Genetic Toxicology

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Carcinogenicity

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Reproductive and Developmental Toxicology

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

Other Toxicology Studies

Data:
No new information is provided in the current submission.
The Applicant's Position:
Not applicable

The FDA's Assessment:
Agree

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant submitted this efficacy supplement to support the approval of the following new indication for zanubrutinib: treatment of adult patients with chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL). Efficacy and safety data to support the proposed indication were derived from Studies BGB-3111-304 and Study BGB-3111-305 (see Sections 7 and 8 for details on these clinical trials). The proposed recommended dosage is 160 mg BID or 320 mg QD with or without food in patients with CLL/SLL.

The clinical pharmacology review focused on the dosing, population PK (popPK) analysis, exposure response (E-R) analyses, and drug-drug interaction (DDI) evaluation. The proposed recommended dosage of 160 mg BID or 320 mg QD is acceptable in patients with CLL/SLL, and aligns with previously demonstrated and approved dosages of 160 mg BID and 320 mg QD zanubrutinib in patients with mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), and marginal zone lymphoma (MZL). The popPK analysis was also consistent with previous submissions: no clinically meaningful covariates that impact the PK of zanubrutinib were identified. The E-R analyses found no evidence indicative of relationship for safety or efficacy.

Additionally, the Applicant submitted results from DDI Study BGB-3111-112 (a phase 1 study to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib in healthy male subjects). This DDI study was intended to fulfill post-marketing commitment **(PMC) #3735-4**. The results showed that multiple doses of rifabutin (a moderate CYP3A inducer) decreased zanubrutinib Cmax by 48% and AUC by 44%. Based on the results of the study, the labeling will be updated to recommend increasing zanubrutinib dose to 320 mg BID (from 160 mg BID) if concomitant administration of moderate CYP3A4 inducers cannot be avoided.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the information and data submitted in this supplemental NDA 213217 (S-007). This supplemental NDA is approvable from a clinical pharmacology perspective. Additionally, **PMC #3735-4** is considered fulfilled.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Reference is made to original zanubrutinib NDA 213217 submitted on 27 June 2019 and approved on 14 November 2019.

Updated clinical pharmacology results in the sNDA since the last new drug application (NDA) approval include:

- An updated population PK analysis (N = 1291) based on additional data from studies BGB-3111-304 and BGB-3111-305 as compared to prior population PK reporting (N = 632).
- Exposure-efficacy analysis using data from studies BGB-3111-304 and BGB-3111-305 to understand the relationship between exposure and efficacy endpoints in patients with CLL/SLL.
- Exposure-safety analysis using pooled data from studies BGB-3111-304 and BGB-3111-305 to understand the relationship between exposure and safety endpoints in patients with CLL/SLL
- A summary of study results from Study BGB-3111-112, a Phase 1, open-label, fixed-sequence study to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib in healthy male subjects. This is a postmarketing commitment (PMC) study by the FDA for the approval of zanubrutinib for treatment of adult patients with R/R MCL.

Please refer to Module 2.7.2 Summary of Clinical Pharmacology for more details.

The Applicant's Position:

Zanubrutinib PK characteristics in patients with CLL/SLL are overall consistent with the data from the previously established population PK analysis in patients with B-cell malignancies, with the exception of age, which was identified as a statistically significant covariate in the updated analysis but is not considered to be clinically meaningful. The impact of age on zanubrutinib exposure was relatively small (with an absolute change of less than 15% from baseline) compared with the overall variability of exposures in the study population. E-R analyses showed no statistically significant relationship between steady-state PK exposure (maximum observed plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC] at steady-state [$AUC_{0-24,ss}$], and minimum observed plasma concentration [C_{min}]) and efficacy in patients with CLL/SLL. There was no evidence of E-R relationships for adverse events of interests across dose levels from 40 to 320 mg.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. No evident E-R relationship between exposure (AUC_{0-24h}, C_{max}, or C_{min}) was found for safety or efficacy. However, the exposure-efficacy analysis is limited by single dose level 160 mg BID from Studies BGB-3111-304 and BGB-3111-305. Population PK analysis identified no clinically meaningful covariates that may impact the PK of zanubrutinib.

The 320 mg QD dosage is supported by totality of safety, PK (similar exposures (AUC) between 160 mg BID and 320 mg QD), PD (near 100% BTK occupancy in PBMCs and lymph node tissue between 160 mg BID and 320 mg QD) and efficacy data from CLL/SLL dataset in Phase 1/2 dose-escalation Study BGB-311-AU-003. Among the patients with CLL/SLL, 83(67%) patients received a starting dose of 160 mg twice daily and 40 (32%) patients received 320 mg once daily (comparative ORR = 93% for 160 mg BID and 100% for 320 mg QD). Additionally, the acceptability of both 160 mg BID and 320 mg QD dosing regimens has been previously demonstrated in the currently approved indications of B-cell malignancies, MCL and WM.

6.2.2 **General Dosing and Therapeutic Individualization**

6.2.2.1 **General Dosing**

Data:

Reference is made to original zanubrutinib NDA 213217 submitted on 27 June 2019 and approved on 14 November 2019.

The results of the pivotal Phase 3 studies, BGB-3111-304 and BGB-3111-305, provided the primary evidence of effectiveness in patients with CLL/SLL and supported the proposed zanubrutinib dose of 160 mg twice daily. Additionally, there is now extensive experience at the 160 mg twice-daily and 320 mg once-daily doses with both schedules showing a high level of activity in patents with B-cell malignancies. In patients with CLL/SLL in Study BGB-3111-AU-003, the overall response rate was 100% (n = 40 of 40 patients) for the 320 mg once-daily dose compared to 92.8% (n = 77 of 83 patients) for the 160 mg twice-daily dose. The complete response (CR) rate was 22.5% (n = 9 of 40 patients) for the 320 mg once-daily dose compared with 14.5% (n = 12 of 83 patients) for the 160 mg twice-daily dose (Table 14.2.1.1.3 in BGB-3111-AU-003 clinical study report). Objective responses have been observed in patients with various B-cell malignancies (including CLL/SLL, MCL, WM, MZL, and follicular lymphoma) at all tested dose levels from 40 to 320 mg. Furthermore, no remarkable difference in adverse events between the 2 regimens in the safety population in study BGB-3111-AU-003 were observed (Ou et al 2021).

The Applicant's Position:

The proposed dose regimen in patients with CLL/SLL is a 320 mg total daily dose (administered as 160 mg BID or 320 mg QD).

This is based on the totality of safety, efficacy, pharmacokinetic and pharmacodynamic (BTK occupancy data) results from previous studies including registrational trials of zanubrutinib in other indications as well as from patients with CLL/SLL in Studies BGB-3111-AU-003, BGB-3111-304, and BGB-3111-305.

The FDA's Assessment:

FDA agrees with the Applicant's position. A total daily dose of 320 mg (as 160 mg BID or 320 mg QD) is acceptable in patients with CLL/SLL.

6.2.2.2 **Therapeutic Individualization**

Data:

No new information is provided in the current submission.

The Applicant's Position:
Not applicable

The FDA's Assessment:
N/A.

6.2.2.3 **Outstanding Issues**

Data:

NDA 213217 Post Marketing Commitment (PMC) 3735-4 Study BGB-3111-112, a Phase 1, open-label, fixed-sequence study to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib in healthy male subjects was completed in November 2020 (b) (6) and the CSR was submitted to the FDA on 26 April 2021.

The Applicant's Position:

PMC 3735-4, Final CSR for Study BGB-3111-112 is included in this sNDA submission.

Based on the emergent data from Study BGB-3111-112, a revision to the current dose recommendation for concomitant use of moderate CYP3A inducers is proposed; it is recommended that patients use caution with concomitant use of moderate CYP3A inducers. This updated recommendation is based on the totality of data including (1) less than 50% decrease in zanubrutinib AUC for concurrent use of a moderate CYP3A inducer, (2) an efficacy signal at doses as low as 40 and 80 mg (BGB-3111-AU-003 CSR), (3) maximal BTK inhibition (median BTK occupancy of 100%) in PBMC samples starting at doses of 40 mg once a day, and (5) no identifiable E-R relationships for efficacy or safety endpoints (see Module 2.7.2 Summary of Clinical Pharmacology for more details).

The FDA's Assessment:
There are no outstanding clinical pharmacology-related issues in this current submission.

6.3.1 **General Pharmacology and Pharmacokinetic Characteristics**

The Applicant's Position:

The clinical pharmacology and PK data submitted in the original NDA 213217 supports a 160 mg twice daily or 320 mg once daily zanubrutinib dose for the treatment of adult patients with CLL/SLL. Results from additional bioanalytical and PopPK data remain consistent with the data provided in the original NDA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Reference is made to original zanubrutinib NDA 213217 submitted on 27 June 2019 and approved on 14 November 2019 and exposure-response analyses in patients with CLL/SLL (please see Module 2.7.2 Summary of Clinical Pharmacology for more details).

The Applicant's Position:

The results of Studies BGB-3111-304 and BGB-3111-305 support the effectiveness of zanubrutinib inpatients with CLL/SLL.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Reference is made to original zanubrutinib NDA 213217 submitted on 27 June 2019 and approved on 14 November 2019 and exposure-response analyses in patients with CLL/SLL (please see Module 2.7.2 Summary of Clinical Pharmacology for more details).

The Applicant's Position:

Yes. The proposed dose regimen of 320 mg total daily dose (administered as 160 mg BID or 320 mg QD) remains suitable in patients with CLL/SLL.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable

The FDA's Assessment:
N/A.

6.3.2.4 **Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Data:
No new food-drug interactions were observed with zanubrutinib. Zanubrutinib can be taken with or without food as stated in the original NDA 213217.

Study results from PMC Study BGB-3111-112 (a Phase 1, open-label, fixed-sequence study to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib in healthy male subjects) showed that there was a less than a 50% reduction of systemic exposures (AUC) of zanubrutinib following coadministration zanubrutinib with rifabutin, a moderate CYP3A inducer compared to administration of zanubrutinib alone.

The Applicant's Position:

There was no new food-drug interaction finding in the current submission. For drug-drug interaction (DDI) with CYP3A inducers, please see Section 6.2.2.3 Outstanding Issues for further details.

The FDA's Assessment:
Based on Study BGB-3111-112 results, approximately 50% decreases in zanubrutinib AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were observed with coadministration of rifabutin (a moderate CYP3A inducer) compared to administration of zanubrutinib alone(Table 2). While the Applicant did not propose a dose adjustment with concomitant moderate CYP3A inducers, FDA's exposure-efficacy analysis could not adequately cover a 50% lower exposure given the analysis was performed on a single dose level of 160 mg BID in patients with CLL/SLL. As such, the ER relationship was too limited to adequately support that a lack of dose adjustment of zanubrutinib with concomitant moderate CYP3A inducer will not compromise zanubrutinib efficacy. FDA therefore recommended increasing the zanubrutinib dose to 320 mg BID (from 160 mg BID) with concomitant administration of moderate CYP3A4 inducers if use of these inducers is unavoidable.

Table 2: BGB-3111-112 Pharmacokinetic Parameters of Zanubrutinib Alone and After Coadministration with 300 mg Rifabutin

Parameter	N	320 mg Zanubrutinib + 300 rifabutin (Test)	320 mg Zanubrutinib (reference)	Ratio of Geometric Mean (Test/Reference)
AUC0-t (ng.h/mL)	13	1530	2700	0.57
AUC0-∞ (ng.h/mL)	12	1560	2780	0.57
Cmax (ng.h/mL)	13	253	489	0.51

Source: Applicant's Study BGB-3111-112 CSR, Table 6

X X

Primary Reviewer
Yue Xiang

Team Leader
Vicky Hsu

X X

Pharmacometrics Reviewer
Hongshan Li

Pharmacometrics Team Leader
Jiang Liu

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 3: Summary of Key Design Features in Clinical Studies Contributing Efficacy and/or Safety Data in the Submission

Study Location	Study Design	Population	Zanubrutinib Dose	Number of Treated Patients [a]			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				CLL/SLL	All		
Pivotal Studies							
BGB-3111-304 (AU, China, EU [AT, BE, CZ, ES, FR, IT, PO, SW], NZ, UK, RUS, US)	Phase 3, randomized, open-label, multicenter study	Patients with TN CLL/SLL	160 mg BID	240 in Cohort 1/ 40 in Cohort 1a [b]/ 111 in Cohort 2	240 in Cohort 1/ 40 in Cohort 1a/ 111 in Cohort 2	227 in Cohort 1/ 38 in Cohort 1a (B+R)	31 October 2021 / 07 May 2021 / Ongoing
BGB-3111-305 (AU, China, EU [BE, CZ, ES, FR, GE IT, NL, PO, SW], TR, NZ, UK, US)	Phase 3, randomized, open-label, multicenter study	Patients with R/R CLL/SLL	160 mg BID	324	324	324 (Ibrutinib)	05 November 2018 31 December 2020/ Ongoing

Study Location	Study Design	Population	Zanubrutinib Dose	Number of Treated Patients [a]			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				CLL/SLL	All		
Supportive Studies							
BGB-3111-AU-003 (AU, NZ, SK, US, IT, UK)	Phase 1/2, single-arm, dose escalation and cohort expansion	Patients with R/R or TN CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	160 mg BID 320 mg QD	123 (101 R/R, 22 TN)	373	NA	16 September 2014/ 31 March 2021/ Closed
BGB-3111-205 China	Phase 2, single-arm	Patients with R/R CLL/SLL	160 mg BID	91	91	NA	09 March 2017/ 11 September 2020/ Closed
BGB-3111-1002 China	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL or nGCB DLBCL	160 mg BID 320 mg QD	9	44	NA	05 July 2016/ 30 August 2020/ Closed
BGB-3111-206 China	Phase 2, single-arm	Patients with R/R MCL	160 mg BID	NA	86	NA	02 March 2017/ 08 September 2020/ Closed

Study Location	Study Design	Population	Zanubrutinib Dose	Number of Treated Patients [a]			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				CLL/SLL	All		
BGB-3111-210 China	Phase 2, single-arm	Patients with R/R WM	160 mg BID	NA	44	NA	31 August 2017/ 11 January 2021/ Closed
BGB-3111-214 (AU, China, EU [CZ, FR, IT], NZ, SK, UK US)	Phase 2, open-label, single-arm study	Patients with R/R MZL	160 mg BID	NA	68	NA	19 February 2019/ 16 April 2021/ Ongoing
BGB-3111-302 (AU, UK, US, EU [CZ, ES, GE, FR, GR, IT, NL, PO, SW])	Phase 3, randomized, open-label, multicenter study	Patients with R/R or TN WM	160 mg BID	NA	129	98 (Ibrutinib)	25 January 2017/ 01 February 2021/ Ongoing

Study Location	Study Design	Population	Zanubrutinib Dose	Number of Treated Patients [a]			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				CLL/SLL	All		
BGB-3111-LTE1 [c]	Long-term extension	Patients with B-cell malignancies who were previously enrolled in a BeiGene parent study	Initial dosing regimen of 160mg BID or 320mg QD in parent study	BGB-3111-AU-003 n = 82 BGB-3111-1002 n = 3 BGB-3111-205 n = 60	337 BGB-3111-AU-003 n = 201 BGB-3111-1002 n = 11 BGB-3111-205 n = 60 BGB-3111-206 n = 40 BGB-3111-210 n = 25	NA	Ongoing
Total Patients in the Integrated Safety Population				**938**	**1550**	NA	NA

Source: Table 1 in Module 2.7.4

Abbreviations: AU, Australia; AT, Austria; BE, Belgium; BID, twice a day; B+R, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; CZ, Czech Republic; DLBCL, diffuse large B-cell lymphoma; EU, European Union; ES, Spain; FL, follicular lymphoma; FR, France; GE, Germany; GR, Greece; HCL, hairy cell leukemia; IT, Italy; LPL, lymphoplasmacytic lymphoma; LTE, long-term extension; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, Number of patients treated with zanubrutinib; NA, not applicable; nGCB, non-germinal center B-cell-like; NHL, non-Hodgkin lymphoma; NL, Netherlands; NZ, New Zealand; QD, once a day; PO, Poland; R/R, relapsed or refractory; RT, Richter's transformation; RUS, Russia; SK, South Korea; SLL, small lymphocytic lymphoma; SW, Sweden; TN, treatment-naive; TR, Turkey; UK, United Kingdom; US, United States; WM, Waldenström macroglobulinaemia

Note:

[a] Reflects patients who received at least one dose of study drug and are included in the integrated safety analyses; for the number of patients randomized and included in the individual CLL/SLL efficacy studies (BGB-3111304, BGB-3111-305, BGB-3111-205, and BGB-3111-AU-003).

[b] Patients from Cohort 1 and Cohort 1a treated with zanubrutinib were included in this analysis. Patients in Cohort 3 treated with venetoclax + zanubrutinib were not included in this analysis because this cohort is a combination study separate from the primary analysis.

[c] Safety data collected from LTE1 study for 337 patients who were dosed at either 160mg BID or 320 mg QD in the parent studies (BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, and BGB-3111-210) are grouped with data from the parent studies in all data summaries and analysis described herein. The LTE data of 1 patient (Study BGB-3111-AU-003, patient (b) (6) who discontinued the parent study due to "patient diagnosed with other cancer that needed treatment" on (b) (6) and then enrolled in LTE study for zanubrutinib treatment was not included.

APPEARS THIS WAY ON ORIGINAL

The Applicant's Position:

Substantial efficacy evidence to support the proposed indication is primarily established from 2 randomized, active-controlled pivotal Phase 3 trials, Study BGB-3111-304 and Study BGB-3111-305.

The safety database to support the proposed indication includes 1550 zanubrutinib-treated patients with B-cell malignancies contributed from 9 clinical studies, as summarized in Table 3. All studies have completed enrollment, with 5 studies closed and 4 studies ongoing. The studies providing safety data for this application were pooled from 9 clinical studies, including the 4 studies in patients with CLL/SLL. The primary safety evaluation is based on the two pivotal Phase 3 trials conducted in patients with CLL/SLL.

The FDA's Assessment:

The Agency agrees with the Applicant's description of the studies included originally in this submission. For study BGB-3111-305, which was submitted with an original clinical cutoff date (CCOD) of December 20, 2021, updated safety and efficacy data were submitted at the Agency's request. The revised CCOD for safety and efficacy for study BGB-3111-305 is 1 December 2021, reflecting the prespecified primary ORR analysis and interim PFS and OS analysis. For study BGB-3111-304, submitted with an original CCOD of 7 May 2021. Additional follow-up for OS was requested by the Agency and provided by the Applicant with a CCOD for OS of 7 March 2022.

The study populations and the revised CCODs for efficacy and safety are summarized in the table below.

Table 4: Summary of Studies Supporting FDA's Efficacy and Safety Review

Study Name	Study Design	Population	Zanubrutinib Dose	N Zanubrutinib	Data Cutoff for Efficacy	Data Cutoff for Safety
BGB-3111-304	Phase 3, randomized, open-label, multicenter study	Patients with TN CLL/SLL	160 mg BID	240 without 17p del in Cohort 1 (randomized) 111 with 17p del in Cohort 2	07 May 2021	07 May 2021
					Additional OS 7 Mar 2022	

Study Name	Study Design	Population	Zanubrutinib Dose	N Zanubrutinib	Data Cutoff for Efficacy	Data Cutoff for Safety
BGB-3111-305	Phase 3, randomized, open-label, multicenter study	Patients with R/R CLL/SLL	160 mg BID	324	1 December 2021	1 December 2021
Total Patients in the ISS Safety Population						
BGB-3111-304		Patients with B-cell malignancies	160mg BID or 320mg daily	1550	NA	7 May 2021
BGB-3111-305						1 Dec 2021
BGB-3111-AU-003						3 May 2021
BGB-3111-205						11 Sept 2020
BGB-3111-1002						30 Aug 2020

Source: Reviewer generated from Applicant SCS in module 2.7.4 and CSR addendums submitted on May 23, 2022 and June 30, 2022.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

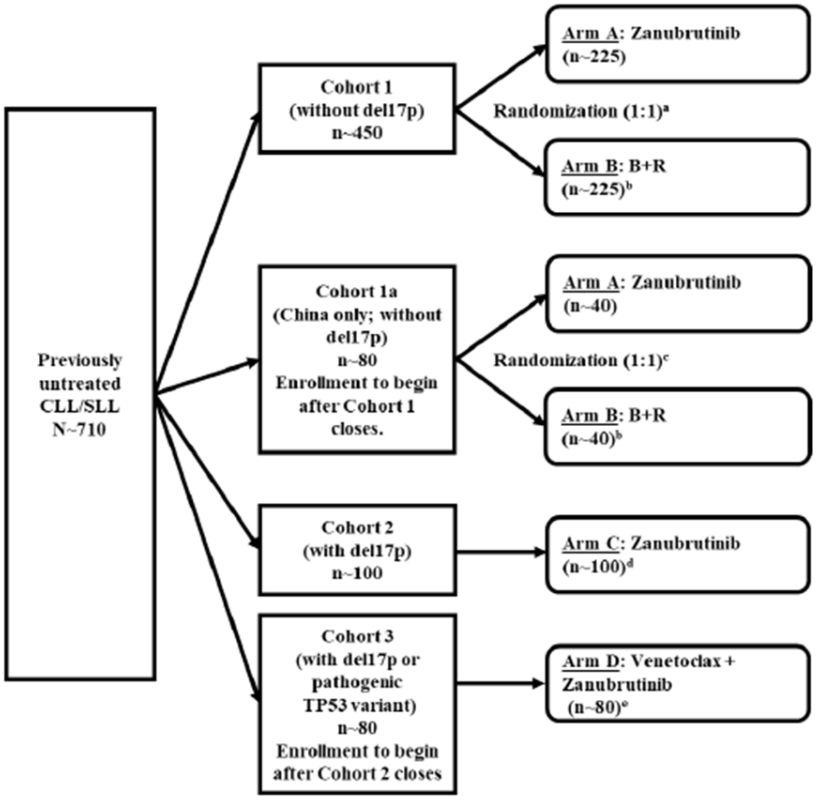
The Applicant's Description

8.1.1 BGB-3111-304

8.1.1.1 Trial Design

Study BGB-3111-304 is an ongoing, international, Phase 3, open-label, randomized study designed to evaluate the efficacy of zanubrutinib versus B+R in patients with previously untreated CLL/SLL (refers to BGB-3111-304 Protocol and CSR Body). Approximately 710 patients will be enrolled in the study. The schema for this study is presented in Figure 1.

Figure 1: Study BGB-3111-304 Study Schema (Planned)



Abbreviations: B+R = bendamustine and rituximab; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.

[a] Randomization for Cohort 1 will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific).

[b] Crossover for patients in Arm B to receive next-line zanubrutinib is allowed after disease progression is confirmed by independent central review.
[c] The same stratification factors used for Cohort 1 will also be used for Cohort 1a, except for geographic region.
[d] Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached.

The FDA's Assessment:
The Agency agrees with the Applicant's description of the study design. Only patients from Cohort 1 and 2 from study BGB-3111-304 were included in FDA's efficacy and safety assessment for the proposed indication.

Trial Location

The study was conducted at 153 study centers in 15 countries and regions (Austria; Australia; Belgium; France; Italy; Spain; Czech Republic; Poland; Sweden; the United Kingdom; Russia; the United States; China; New Zealand; and Taiwan, China).

Choice of Control Groups

This study was designed to test whether treatment with zanubrutinib could prolong PFS as compared with a standard first-line chemoimmunotherapy regimen, B+R, in patients with previously untreated CLL/SLL. Prolongation of PFS is likely to delay or prevent symptoms of progressive CLL/SLL and delay the need for subsequent therapies to treat CLL/SLL and was the basis of regulatory approval for several new therapeutic agents, including ibrutinib. The appropriate standard initial treatment regimen for CLL/SLL was dependent upon patient age, presence or absence of comorbidities, and molecular features, particularly the presence of del17p. Infections are a common complication of the disease and of treatment, and the risk of recurrent infection can limit treatment choices. At the time of study design, although BTK or phosphoinositide-3-kinase delta inhibitors were considered appropriate for patients without or with del17p, the more global standard for first-line treatment remained chemoimmunotherapy, and the most commonly used chemoimmunotherapy regimens were B+R and fludarabine, cyclophosphamide, and rituximab (FCR).

Selection of study population

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria Included:

- Unsuitable for treatment with FCR
- Confirmed diagnosis of CD20-positive CLL or SLL that met the iwCLL criteria
- Measurable disease by CT/MRI

- ECOG Performance Status of 0, 1, or 2
- Life expectancy ≥ 6 months
- Adequate bone marrow and organ function
- Must have FISH results from the study-specified central laboratory confirming the presence or absence of del17p

Key Exclusion Criteria Included:

- Previous systemic treatment for CLL/SLL
- Requires ongoing need for corticosteroid treatment
- Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation
- Clinically significant cardiovascular disease
- Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
- History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
- History of stroke or intracranial hemorrhage within 6 months before first dose of study drug
- Severe or debilitating pulmonary disease
- Active fungal, bacterial and/or viral infection requiring systemic therapy
- Known central nervous system involvement by leukemia or lymphoma
- Known infection with HIV, or serologic status reflecting active hepatitis B or C infection
- Ongoing alcohol or drug addiction
- Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (e.g., idiopathic thrombocytopenia purpura).

A complete list of inclusion and exclusion criteria are presented in Section 4 of the study protocol in BGB-3111-304 CSR Appendix 16.1.1.

Zanubrutinib dose modification for hematologic toxicity

Hematologic toxicity was based on the Grading Scale for Hematologic Toxicity in CLL Studies (Appendix 9 of the study protocol in BGB-3111-304 CSR Appendix 16.1.1).

Dosing was to be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness:

- Grade 4 neutropenia that is persistent for at least 10 consecutive days
- Grade 4 thrombocytopenia that is persistent for at least 10 consecutive days
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

The dose hold should start on the day that 1 of the above conditions was met. For the first occurrence of hematologic toxicity, treatment might restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

If the same event reoccurred, patients were` to restart at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline. A maximum of 2 dose reductions were to be allowed. Patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention should be discussed with medical monitor.

Asymptomatic treatment-related lymphocytosis should not be considered an adverse event. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Zanubrutinib dose modification for nonhematologic toxicity

Zanubrutinib dose modifications for nonhematological toxicity are described in Table 5.

Table 5: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Restart Dose[a]
≥ Grade 3 bleeding not considered related to study drug	Hold until recovery to less than or equal to Grade 1	Re-start at either the original dose or dose level (-1), at the discretion of the treating investigator
≥ Grade 3 bleeding considered related to study drug	Hold until underlying condition has fully resolved. If underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib. The drug should be permanently discontinued for any related ≥ Grade 3	Re-start at dose level (-1)

Toxicity	Action for Zanubrutinib	Restart Dose[a]
	hemorrhage with the exception of those where the underlying condition or reason for the bleeding can be fully treated (e.g., gastric ulcer resulting in GI bleed, use of anti-coagulation) and the risk of a re-bleed is deemed acceptable by the medical monitor and investigator.	
Any grade intracranial hemorrhage	Hold and assess the risk of rebleeding; if the risk of rebleeding is deemed unacceptable, permanently discontinue.	May be re-started only with medical monitor approval. See below.
AF that is symptomatic and/or incompletely controlled	Hold until AF is controlled	Re-start at either the original dose or dose level (-1), at the discretion of the treating investigator
Other ≥ Grade 3 toxicity considered related to study drug, including inadequately controlled HTN and/or liver or renal laboratory value abnormalities	Hold until recovery to less than or equal to baseline (BL) if BL is greater than Grade 1; hold until less than or equal to Grade 1 if BL is less than or equal to Grade 1.	Re-start at the original dose level
TLS	Hold until resolution or TLS resolves to at least Grade 0.	In the event of clinical TLS, contact the medical monitor.

Abbreviations: AF, atrial fibrillation; BL, baseline; HTN, hypertension; TLS, tumor lysis syndrome
[a] These zanubrutinib dose modifications apply to Arms A and C during the zanubrutinib monotherapy run-in.

Administrative structure

The sponsor of the trial is BeiGene Ltd. and the trial was conducted under Sponsor IND. Study management and monitoring was performed by BeiGene (b) (4) (b) (4). An independent Data Monitoring Committee (DMC) was established to monitor safety data periodically throughout the study. An Independent Review Committee (IRC) was established to provide the independent assessment of clinical data and imaging.

Concomitant medications

Concomitant medications in Cohort 1
Medications that were prohibited and restricted, as well as medications whose use was to be considered cautionary while participating in the trial, are discussed in Section 9.4.7 of the BGB-3111-304 CSR.

Treatment compliance
Compliance was assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian, including patient's diary and pill count on returned study drug containers.

Subject Completion, Discontinuation, or Withdrawal
Zanubrutinib was taken as prescribed from Cycle 1 Day 1 until disease progression, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or termination of the study by the sponsor. Bendamustine or rituximab were administered intravenously for 6 cycles. Patients who continued to receive benefit from zanubrutinib after disease progression may have remained in the study upon discussion with the medical monitor or designee. Patients could voluntarily withdraw consent from treatment at any time and continue into the follow-up phase if the patient withdrew consent from the treatment phase.

The FDA's Assessment:
The Agency agrees with the Applicant's description of the study population and treatment plan. The protocol specified definition of unsuitable for the treatment with FCR was:

- ≥ 65 years of age at the time of informed consent OR
- 10-64 years of age and one or more of the following:
  - Cumulative Illness Rating Scale > 6
  - Creatinine clearance < 70mL/min
  - History of previous serious infection or multiple infections in the past 2 years

Per the study protocol, patients randomized to the zanubrutinib arm were to receive zanubrutinib 160mg orally, twice daily, continuously until unacceptable toxicity, progressive disease or death.

Study Endpoints

The Applicant's Description:

Primary Endpoint: The primary endpoint was PFS in Cohort 1 (patients without del17p) determined by independent central review. Disease assessment for CLL was based on the iwCLL2008 guidelines with modification for treatment-related lymphocytosis and other modifications specified in the study protocol response criteria and for SLL was based on the

Lugano Classification for NHL. A PFS event was defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first.

Secondary Endpoints:

- Overall response rate in Cohort 1, defined as the proportion of patients who achieve a CR, complete response with incomplete bone marrow recovery, partial response, or partial response with lymphocytosis (PR-L), determined by independent central review and by investigator assessment
- Overall survival in Cohort 1 defined as the time from randomization to the date of death due to any reason
- Duration of response in Cohort 1 determined by independent central review and by investigator assessment, using the iwCLL criteria with modification for treatment-related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL), and defined as the time from the date that criteria for response (i.e., PR-L or better) are first met to the date that disease progression is objectively documented or death, whichever occurs first
- PFS in Cohort 1 determined by investigator assessment
- Patient-reported outcomes in Cohort 1 measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires.
- Overall response rate in Cohort 2 (patients with del17p), Arm C, determined by independent central review and investigator review
- PFS in Cohort 2 (Arm C), determined by independent central review and investigator review
- Duration of response in Cohort 2 (Arm C), determined by independent central review and investigator review
- Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical examinations, and vital signs
- Pharmacokinetic parameters of zanubrutinib such as apparent clearance of the drug from plasma (CL/F) and AUC from time 0 to 12 hours postdose (AUC_{0-12}) for Arms A and C

The FDA's Assessment:

The Agency agrees with the Applicant's description of the primary endpoint of PFS. The Agency does not agree with the Applicant's definition of the secondary endpoint of objective response, referred to by the Applicant as objective response. For regulatory purposes partial response with lymphocytosis, which could represent treatment effect or active disease is not included in the definition of objective response. The Agency's considered objective response as complete response (CR), complete response with incomplete bone marrow recovery (CRi), partial response (PR), and nodal partial response (nPR). The Agency agrees with Applicant's description of the remainder of the secondary and exploratory endpoints.

Statistical Analysis Plan

The Applicant's Description:
The statistical analysis plan was finalized before the conduct of the prespecified interim analysis. The plan is written in accordance with protocol version 4.0 dated 10 Feb 2021. Finally, a SAP addendum was included in the filing package per request from FDA and the OS analysis from the data cut off from September 7, 2021 is included as an addendum in the CSR.

Sample Size

In Cohort 1, a total of 118 PFS events were determined to provide approximately 83.5% power to detect a hazard ratio (HR) of 0.58 using a two-sided 5% overall significance level with one interim analysis for both efficacy and futility planned at 73% events. The study design employed the O'Brien-Fleming alpha spending function (Lan and DeMets 1983) for efficacy and Haybittle-Peto method (Haybittle 1971; Peto et al 1976) for futility. The futility boundary of this study was non-binding.

Analyses sets

- **Intent-to-Treat (ITT) Analysis Set**: All enrolled patients who are assigned a treatment group by the IRT system. The ITT Analysis Set will be the primary population for Cohort 1 and Cohort 1a efficacy analyses. Patients will be included in the treatment group originally assigned in the analysis.
- **Safety Analysis Set**: All enrolled patients who received any dose of study drug. Patients will be included in the treatment group corresponding to the actual treatment received. The Safety Analysis Set will be used for all safety analyses.

Primary efficacy endpoint analysis

Primary inference of comparing PFS assessed by independent central review between the 2 arms in Cohort 1 was based on log-rank test stratified by randomization stratification factors (age [< 65 years versus ≥ 65 years], Binet stage [C versus A or B], and IGHV mutational status [mutated versus unmutated) per IRT in the ITT Analysis Set.

The censoring rules for PFS in the primary analysis followed the FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).Alternative censoring rules, such as not censoring PFS due to receipt of new anticancer therapy for CLL/SLL, were used in sensitivity analyses of PFS. Another sensitivity analysis of PFS was based on all patients randomized to Cohort 1 and Cohort 1a. Additional details are provided in Appendix 16.1.9 of the BGB-3111-304 CSR.

Secondary Efficacy Endpoint Analyses

Overall Response Rate

Overall response rate was calculated for each treatment group with Clopper-Pearson 95% CI. The odds ratio in overall response rate was calculated along with its 2-sided 95% CI using the stratified Cochran-Mantel-Haenszel method.

Overall Survival

Primary inference of comparing overall survival between the 2 arms in Cohort 1 was based on a log-rank test stratified by the randomization stratification factors age (< 65 years versus ≥ 65 years), Binet stage (C versus A or B), and IGHV mutational status (mutated versus unmutated) in the ITT Analysis Set.

Duration of Response

Distribution of duration of response was summarized using the Kaplan-Meier method for each arm.

Progression-Free Survival by Investigator Assessment

PFS was calculated based on investigator-assessed tumor responses. PFS by investigator assessment was analyzed using the same methods as the primary endpoint of PFS by independent central review.

Patient Reported Outcomes (PRO)

The EORTC QLQ-C30 questionnaire was summarized for each assessment timepoint. The scale was compared between treatment groups using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) to account for missing data under Missing at Random (MAR) assumption (Mallinckrodt et al 2008). The analysis was based on the ITT population.

Change of EQ-5D-5L score was summarized descriptively.

Cohort 2

PFS, overall response rate, and duration of response of Cohort 2 (Arm C) were summarized descriptively. Independent central review data as well as investigator assessed response data were used for PFS, overall response rate, and duration of response. The Kaplan-Meier method was used to summarize the distribution of PFS and duration of response including quartiles and event-free rates at selected timepoints. An estimate of overall response rate with 95% Clopper-Pearson CI was generated.

Changes to planned analyses: None

The FDA's Assessment:

FDA generally agrees with the description of the statistical analysis plan. Although inferential testing was planned for two secondary endpoints (OS and the QLQ-C30 Global Health Status), there were no key secondary endpoints or prespecified hypotheses for secondary endpoints in the SAP (version date May 13, 2021). Therefore, all analyses of secondary endpoints, including OS and ORR, are considered descriptive.

FDA notes that, in protocol amendment V4.0, there was one interim analysis of PFS per IRC prespecified in Cohort 1, planned when approximately 86 events (73% of the target number of events at final analysis) in total from Arms A and B were observed. It was estimated that it

would take approximately 33 months to observe 86 events under the assumption made for the sample size consideration. The final analysis of PFS was planned after 118 events were observed in Cohort 1, estimated at approximately 41 months from study start. The alpha boundaries stated for efficacy at the interim and final analyses were 0.009 and 0.022, respectively. The boundaries were to be adjusted based on actual number of events observed at the interim analysis. If the efficacy boundary was met and the DMC recommended stopping the study for efficacy, the sponsor could stop Cohort 1.

In Cohort 1, OS would only be tested if the primary endpoint, PFS, is significant. There were two interim OS analyses prespecified in the protocol: one at the interim analysis of PFS with 1-sided alpha=0.00005, and another at the final analysis of PFS with 1-sided alpha=0.00005. The planned interim OS analyses are not expected to have sufficient power to show a statistical difference between the two arms. The final analysis of OS will be performed at the end of the study with a 1-sided alpha=0.0001, approximately five years after the first patient was randomized (planned November 2022).

For the secondary endpoints in Cohort 1, only OS and PROs (QLQ-C30 Global Health Status) were to be tested if the PFS primary endpoint was significant. No inferential testing was to be done for other secondary endpoints including ORR and DOR.

Protocol Amendments

The Applicant's Description:

The protocol was amended 4 times before the data cutoff date for the BGB-3111-304 CSR. Additional country specific amendments for eligibility criteria or study conduct may apply based on local medical practices or input from regional health authorities. A total of 506 patients enrolled under the original protocol (dated 28 June 2017).

Amendment 1 (27 November 2018):

A total of 84 patients enrolled in the study under Amendment 1. The main purpose of this amendment was to increase the sample size, to allow use of slides from a previously performed diagnostic bone marrow biopsy, to revise inclusion criterion 1, and allow patients from Arm B in Cohort 1 to receive crossover treatment.

Amendment 2 (01 April 2019):

A total of 590 patients enrolled before Amendment 2 of the study protocol, and a total of 63 patients enrolled in the study under Amendment 2. The main purpose of this amendment was to add an additional study arm (Cohort 3, Arm D) that will explore the benefits of treatment with venetoclax + zanubrutinib. Cohort 3, Arm D will assess undetectable minimal residual disease at $< 10^{-4}$ sensitivity (undetectable MRD4) at various timepoints. Treatment with venetoclax and/or zanubrutinib may be permanently discontinued based on patients meeting undetectable MRD4 requirements. Cohort 3, Arm D will only be open for enrollment at select sites in select countries.

Amendment 3 (11 February 2020):

A total of 653 patients enrolled before Amendment 3 of the study protocol, and a total of 53 patients enrolled in the study under Amendment 3. The main purpose of this amendment is to add a cohort (Cohort 1a) to the study to allow for continuing enrollment of patients from Chinese sites to support further analysis in the Chinese population and to add a pharmacokinetic sub-study to evaluate potential drug-drug interactions between venetoclax and zanubrutinib in patients assigned to Cohort 3 (Arm D).

Amendment 4 (10 February 2021):

A total of 706 patients enrolled before Amendment 4 of the study protocol, and a total of 4 patients enrolled in the study under Amendment 4.

The primary purposes of this amendment are as follows:

- Updated the number of PFS events planned for the interim analysis to increase statistical power at the interim analysis.
- Added a requirement to record all second primary malignancies until the end of the study.
- Updated the requirements for start of next line "crossover" treatment with zanubrutinib.
- Allowed for enrollment and evaluation of patients with pathogenic TP53 variants in Cohort 3 (Arm D).

The FDA's Assessment:
The Agency agrees with the Applicant's description of the protocol amendments. Amendment 2 included cohort 3 which is not part of the efficacy or safety population for the proposed indication.

8.1.1.2 Study Results

Compliance with Good Clinical Practices

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor or designee conducted quality assurance audit. The protocol, any amendments, and informed consent form were reviewed and approved by the Institutional Review Board/Independent Ethics Committee in conformance with Good Clinical Practice (GCP) and applicable regulatory requirements.

The Applicant's Position:

A total of 18 sites were audited by BeiGene. No significant findings were observed. This study was conducted in accordance with sponsor procedures, which comply with the principles of GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals

for Human Use (ICH) Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

The FDA's Assessment:
The Agency agrees with the Applicant's description of methods used to evaluate compliance with Good Clinical Practices. Audit certificates were included in the application.

Financial Disclosure
Data:

Per 21 CFR Part 54, all disclosable financial interests and arrangements with the clinical investigators in Study BGB-3111-304 was tracked and evaluated by Applicant. The submission reports Financial Disclosures for 20 investigators out of total of 1419 in Study BGB-3111-304.

The Applicant's Position:

The Applicant minimized the potential for bias that could be associated with reported Financial Disclosures. The design of the studies aimed to mitigate the potential for investigator bias. Study BGB-3111-304 was a randomized controlled study with primary endpoint PFS assessed by Independent Review Committees (IRCs). The IRC members were completely blinded to treatment arm. Safety and efficacy data were reviewed by an independent data monitoring committee (DMC). In addition, sensitivity analyses taking into account the Financial Disclosures demonstrated that the efficacy and safety data are robust, and patient data from these investigators are consistent with the conclusions drawn from the study results. The applicant concludes that the Financial Disclosures have no impact on the overall benefit/risk analysis for this NDA.

The FDA's Assessment:
The Agency agrees that the financial disclosure information provided for the 20 investigators do not indicate a conflict of interest and measure to mitigate potential for investigator bias were undertaken.

Patient Disposition
Data and Applicant's Position:

Patient disposition for Study BGB-3111-304 are summarized in Table 6.

The most common reasons for study discontinuation were death and withdrawal by subject. The median follow-up times in Study BGB-3111-304 zanubrutinib Arm A, B+R Arm B, and zanubrutinib in del(17p) Arm C patients were 26.35, 25.92, and 30.59 months, respectively. The most common reasons for discontinuing study treatment were adverse event and progressive disease.

Table 6: Patient Disposition and Reasons for Discontinuation (BGB-3111-304)

	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)
Number of Patients Enrolled, n (%)	241 (100.0)	238 (100.0)	110 (100.0)
Number of patients treated	240 (99.6)	227 (95.4)	110 (100.0)
Number of patients discontinued from treatment	34 (14.1)	227 (95.4)	18 (16.4)
Reason for discontinuation			
Completed	0 (0.0)	188 (79.0)	0 (0.0)
Adverse Event	20 (8.3)	31 (13.0)	6 (5.5)
Related to COVID-19	5 (2.1)	0 (0.0)	0 (0.0)
Progressive Disease	11 (4.6)	1 (0.4)	10 (9.1)
Withdrawal by Subject	2 (0.8)	1 (0.4)	2 (1.8)
Investigator's Discretion	1 (0.4)	3 (1.3)	0 (0.0)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (1.3)	0 (0.0)
Number of patients remained on treatment	206 (85.5)	0 (0.0)	92 (83.6)
Number of patients discontinued from study	22 (9.1)	36 (15.1)	9 (8.2)
Reason for discontinuation			
Death	16 (6.6)	14 (5.9)	8 (7.3)
Related to COVID-19	5 (2.1)	1 (0.4)	0 (0.0)
Withdrawal by Subject	5 (2.1)	16 (6.7)	1 (0.9)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Physician Decision	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	6 (2.5)	0 (0.0)
Number of patients remained in study	219 (90.9)	202 (84.9)	101 (91.8)
Study Follow-up Time (Months)			
N	241	238	110
Median	26.35	25.92	30.59
Q1, Q3	24.18, 29.54	23.39, 29.60	27.76, 33.05
Min, Max	0.3, 42.2	0.0, 38.9	5.0, 39.1

Source: ADSL. Data cutoff: 07MAY2021(304), 31DEC2020(305). Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: Study follow-up time is defined as the time from study entry (randomization date for randomized studies; otherwise, date of first dose) to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients; In this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on arm c was not included in this summary.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-ds-i.sas 08SEP2021 02:53 t-1-ds-itt-i.rtf

The FDA's Assessment:
The Agency agrees with the Applicant's description of the patient disposition in Cohort 1 and Cohort 2. There was an imbalance in the number of patients who were enrolled but not treated (1/241 in the zanubrutinib arm compared to 11/238 in the BR arm) potentially related to investigator or physician decision post randomization.

In Cohort 2, 111 patients received zanubrutinib; one treated patient was later found to not have 17p del confirmed by central review and was excluded from the efficacy analysis.

Protocol Violations/Deviations

Data:
Study conduct was monitored by the CRO and the sponsor's medical monitor. In China, these activities were conducted by BeiGene. Protocol deviations were assessed as either protocol deviation (non-important) or important and reviewed by the CRO or BeiGene's clinical operations team (China) in consultation with the medical monitor before a final determination was made. Important protocol deviations were defined as those that were likely to have had a major impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis. The final determination of important protocol deviations was made by the medical monitor, using the criteria that define important protocol deviation in the ICH E3 guidelines as follows: eligibility criteria not satisfied, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications.

Deviations were assessed for their impact on analyses and data integrity or patient safety. Critical protocol deviations were identified and used to define the Per-protocol Analysis Set.

Protocol Deviations – Cohort 1
Important protocol deviations were reported in 10 (4.1%) patients in the zanubrutinib arm and 2 (0.8%) patients in the B+R arm. Three patients in the zanubrutinib arm and 1 patient in the B+R arm reported critical protocol deviations. Important protocol deviation that related to COVID-19 were reported in 2 (0.8%) patients in the zanubrutinib arm and 0 (0.0%) patient in the B+R arm.

Important protocol deviations are summarized as follows:

- Missed four consecutive response assessments for efficacy and did not perform required safety assessments over the same interval. *(Critical IPD – removed from per-protocol analysis)*: a total of 1 protocol deviation was recorded in 1 patient.
- Missed four or more required consecutive safety assessments for hepatitis B monitoring: a total of 7 protocol deviations were recorded in 7 patients.
- Incorrect selection of central laboratory result for del(17p) in IRT, leading to incorrect assignment of study cohort, during randomization. *(Critical IPD – removed from per-protocol analysis):* a total of 2 protocol deviations were recorded in 2 patients.

- Did not perform seven consecutive required imaging studies to assess efficacy due to severe claustrophobia. *(Critical IPD–removed from per-protocol analysis)*: a total of 1 protocol deviation was recorded in 1 patient.
- Received study drug while having an active Grade 3 adverse event, which per protocol required dose hold for safety reasons: a total of 1 protocol deviation was recorded in 1 patient.

Protocol Deviations – Cohort 2

Important protocol deviations were reported in 2 (1.8%) patients in the zanubrutinib arm: one patient entered by mistake as "with del17p" in the IRT system during randomization process by site staff and was assigned to Cohort and the other patient missed four or more required consecutive safety assessment for Hepatitis B monitoring. One patient (0.9%) in the zanubrutinib arm reported critical protocol deviation (Table 14.1.1.4.3 in Study BGB-3111-304). No important protocol deviation that related to COVID-19 was reported in the zanubrutinib arm (Table 14.1.1.5.3 in Study BGB-3111-304).

The Applicant's Position:

None of the protocol deviations identified were considered to have the potential to impact the overall interpretation of efficacy or safety conclusions from the study.

The FDA's Assessment:

The Agency agrees with the Applicant's position that the protocol deviations are unlikely to impact the overall study results and conclusions.

Table of Demographic Characteristics

Patient demographics and baseline characteristics in BGB-3111-304 are summarized in Table 7.

Table 7: Demographics and Baseline Characteristics (BGB-3111-304)

	Zanubrutinib Arm A (N = 241)	**Bendamustine + Rituximab Arm B (N = 238)**	**Zanubrutinib Arm C in del(17p)+ (N = 110)**
Sex, n (%)			
Male	154 (63.9)	144 (60.5)	78 (70.9)
Female	87 (36.1)	94 (39.5)	32 (29.1)
Race, n (%)			
Asian	4 (1.7)	9 (3.8)	1 (0.9)
White	221 (91.7)	206 (86.6)	104 (94.5)
Black or African American	4 (1.7)	1 (0.4)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Not Reported	9 (3.7)	21 (8.8)	4 (3.6)
Unknown	2 (0.8)	1 (0.4)	1 (0.9)

	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)
Age (years)			
N	241	238	110
Mean (SD)	69.8 (7.74)	69.3 (7.39)	69.8 (7.78)
Median	70.0	70.0	70.0
Min, Max	40, 86	35, 87	42, 86
Age Group, n (%)			
< 65 years	45 (18.7)	46 (19.3)	16 (14.5)
≥ 65 and < 75 years	133 (55.2)	139 (58.4)	67 (60.9)
≥ 75 years	63 (26.1)	53 (22.3)	27 (24.5)
Geographic Region*, n (%)			
Asia	3 (1.2)	6 (2.5)	1 (0.9)
Australia/New Zealand	30 (12.4)	32 (13.4)	46 (41.8)
Europe	174 (72.2)	172 (72.3)	51 (46.4)
North America	34 (14.1)	28 (11.8)	12 (10.9)

Source: ADSL, ADBASE. Data cutoff: 07MAY2021(304), 31DEC2020(305). Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.
Note: Baseline value was the last non-missing result before first dose of study drug (or randomization date if not dosed); In this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized;
+ one patient without del (17p) enrolled on arm c was not included in this summary.
* Geographic region includes sites in Austria; Australia; Belgium; France; Italy; Spain; Czech Republic; Poland; Sweden; United Kingdom; Russia; United States; China; New Zealand; and Taiwan, China.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-dm-i.sas 08SEP2021 02:53 t-4-dm-itt-i.rtf

The Applicant's Position:
Overall, demographics were generally comparable between the treatment arms.

The FDA's Assessment:
The Agency agrees with the Applicant's position that the demographic characteristics of Cohorts 1 and 2 were generally balanced between the study arms. Excluding Cohort 1a, the majority of patients (67%) were enrolled in Europe with 12% of patients enrolled in the United States. There is an underrepresentation of patients of Black or African American race (0.8%), Asian race (0.2%), and Hispanic ethnicity 0.2%.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs
Patient disease characteristics in BGB-3111-304 are summarized in Table 8.

Table 8: Disease Characteristics (BGB-3111-304)

	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)
Time from Initial Diagnosis to Study Entry (years)			
N	241	238	110
Mean (SD)	4.0 (4.14)	3.2 (3.22)	3.4 (4.62)
Median	2.6	2.4	1.8
Q1, Q3	0.7, 5.6	0.6, 4.5	0.6, 4.6
Min, Max	0, 19	0, 19	0, 27
Disease Type, n (%)			
CLL	221 (91.7)	218 (91.6)	99 (90.0)
SLL	20 (8.3)	20 (8.4)	11 (10.0)
Staging at Study Entry[a], n (%)			
Low Risk	33 (13.7)	31 (13.0)	18 (16.4)
Intermediate Risk	138 (57.3)	137 (57.6)	53 (48.2)
High Risk	70 (29.0)	70 (29.4)	39 (35.5)
Bulky Disease, n (%)			
Any target lesion longest diameter ≥ 5 cm	69 (28.6)	73 (30.7)	43 (39.1)
Any target lesion longest diameter ≥ 10 cm	14 (5.8)	10 (4.2)	12 (10.9)
Splenomegaly, n (%)			
Yes	146 (60.6)	143 (60.1)	75 (68.2)
No	95 (39.4)	95 (39.9)	35 (31.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hepatomegaly, n (%)			
Yes	60 (24.9)	50 (21.0)	36 (32.7)
No	181 (75.1)	188 (79.0)	74 (67.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Absolute Lymphocyte Count ($x10^9$/L)			
N	241	238	110
Mean (SD)	80.49 (81.651)	75.80 (66.316)	83.84 (79.573)
Median	63.43	60.98	63.16
Q1, Q3	18.14, 111.21	20.45, 111.07	23.81, 109.81
Min, Max	0.9, 715.8	0.5, 300.0	1.3, 345.3
Hemoglobin (g/L)			
N	241	238	110
Mean (SD)	119.83 (19.298)	119.63 (18.534)	117.81 (20.078)
Median	120.00	120.00	121.00
Q1, Q3	108.00, 133.00	106.00, 133.00	101.00, 130.00
Min, Max	58.0, 181.0	63.0, 159.0	75.0, 166.0
Hemoglobin, n (%)			
≤ 110 g/L	75 (31.1)	81 (34.0)	43 (39.1)

	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)
> 110 g/L	166 (68.9)	157 (66.0)	67 (60.9)
Platelets (x10^9/L)			
N	241	238	110
Mean (SD)	156.6 (65.41)	158.9 (64.93)	156.8 (67.32)
Median	150.0	149.0	155.0
Q1, Q3	107.0, 193.0	108.0, 201.0	100.0, 203.0
Min, Max	23, 577	49, 355	38, 358
Platelets, n (%)			
≤ 100 x 10^9/L	51 (21.2)	50 (21.0)	29 (26.4)
> 100 x 10^9/L	190 (78.8)	188 (79.0)	81 (73.6)
Absolute Neutrophil Count (x10^9/L)			
N	241	238	110
Mean (SD)	5.35 (3.573)	5.23 (2.852)	4.91 (3.186)
Median	4.68	4.95	4.58
Q1, Q3	2.98, 6.64	3.22, 6.53	2.84, 5.92
Min, Max	0.5, 30.8	0.7, 21.1	0.2, 20.2
Absolute Neutrophil Count, n (%)			
≤ 1.5 x 10^9/L	12 (5.0)	7 (2.9)	8 (7.3)
> 1.5 x 10^9/L	229 (95.0)	231 (97.1)	102 (92.7)
Any cytopenia[b], n (%)			
Yes	102 (42.3)	109 (45.8)	61 (55.5)
No	139 (57.7)	129 (54.2)	49 (44.5)
Constitutional symptoms, n (%)			
Yes	100 (41.5)	97 (40.8)	45 (40.9)
No	141 (58.5)	141 (59.2)	65 (59.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Beta 2 microglobulin (mg/L)			
N	234	229	100
Mean (SD)	4.49 (3.186)	4.97 (6.935)	5.17 (2.208)
Median	3.80	3.81	4.80
Q1, Q3	3.10, 5.20	3.00, 5.15	3.60, 6.30
Min, Max	1.5, 38.0	0.0, 93.0	1.9, 13.0
Beta 2 microglobulin, n (%)			
≤ 3.5 mg/L	99 (41.1)	98 (41.2)	23 (20.9)
> 3.5 mg/L	135 (56.0)	131 (55.0)	77 (70.0)
Missing	7 (2.9)	9 (3.8)	10 (9.1)
Lactate Dehydrogenase (U/L)			
N	238	237	110
Mean (SD)	223.87 (76.802)	237.21 (111.911)	248.53 (90.076)
Median	210.00	216.00	232.00
Q1, Q3	178.00, 245.00	176.00, 255.00	180.00, 285.00
Min, Max	116.0, 643.0	106.0, 1174.0	97.0, 573.0
del(17p) mutation status, n (%)			

	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)
Deleted / Abnormal	2 (0.8)	0 (0.0)	110 (100.0)
Not deleted / Normal	239 (99.2)	238 (100.0)	0 (0.0)
del(11q) mutation status, n (%)			
Deleted / Abnormal	43 (17.8)	46 (19.3)	37 (33.6)
Not deleted / Normal	198 (82.2)	192 (80.7)	73 (66.4)
del(13q) mutation status, n (%)			
Deleted / Abnormal	136 (56.4)	129 (54.2)	73 (66.4)
Not deleted / Normal	105 (43.6)	109 (45.8)	37 (33.6)
TP53 mutation status, n (%)			
Mutated	15 (6.2)	13 (5.5)	47 (42.7)
Unmutated	217 (90.0)	210 (88.2)	62 (56.4)
Missing	9 (3.7)	15 (6.3)	1 (0.9)
del(17p) or TP53 mutation, n (%)			
Yes	17 (7.1)	13 (5.5)	110 (100.0)
No	215 (89.2)	210 (88.2)	0 (0.0)
Missing	9 (3.7)	15 (6.3)	0 (0.0)
IGHV mutation status, n (%)			
Mutated	109 (45.2)	110 (46.2)	36 (32.7)
Unmutated	125 (51.9)	121 (50.8)	66 (60.0)
Missing	7 (2.9)	7 (2.9)	8 (7.3)
Trisomy 12 mutation status, n (%)			
Abnormal	45 (18.7)	49 (20.6)	20 (18.2)
Normal	196 (81.3)	189 (79.4)	90 (81.8)

Source: ADSL, ADBASE. Data cutoff: 07MAY2021(304), 31DEC2020(305). Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: In this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on Arm C was not included in this summary.
[a] If available, Binet stage is summarized; otherwise, Rai stage is summarized. Low risk includes Binet stage A, Rai stage 0 and Ann Arbor stages I/II; intermediate risk includes Binet stage B, Rai stages I/II; high risk includes Binet stage C, Rai stages III/IV and Ann Arbor stages III/IV.
[b] Cytopenia is defined as any of the following: hemoglobin ≤ 110 g/L or platelet count ≤ 100 x10^9/L or ANC ≤ 1.5 x10^9/L.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-dh-i.sas 08SEP2021 02:51 t-7-dh-itt-i.rtf

The Applicant's Position:

Disease history was generally comparable between the zanubrutinib and B+R arms in the ITT Analysis Set in Cohort 1. In the ITT Analysis Set, the cancer type in most patients was CLL (221 [91.7%] patients in the zanubrutinib arm and 218 [91.6%] patients in the B+R arm); patients

with SLL accounted for 8.3% in the zanubrutinib arm and 8.4% in the B+R arm. The median time from initial diagnosis of CLL/SLL to randomization was 31.28 months in the zanubrutinib arm and 28.67 months in the B+R arm. Across both treatment groups, approximately 85% of patients had CLL or SLL that was Stage B or Stage C.

The FDA's Assessment:
The Agency agrees with the Applicant's position. The study population for BGB-3111-304 appears reasonably reflective of the general U.S. population of patients with previously untreated CLL/SLL, with the notable exception of the underrepresentation of racial and ethnic minorities in this study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Data:
Compliance with study drug administration was measured using review of patient diaries and tablet counts at each study visit.

Concomitant Medications in Cohort 1

Almost all patients in the Cohort 1 received ≥ 1 concomitant medication (99.2% in the zanubrutinib arm; 99.1% in the B+R arm). The most common concomitant medications in both arms were antibacterials for systemic use (167 [69.6%] patients in the zanubrutinib arm and 171 [75.3%] patients in the B+R arm). The use of vaccines was more common in the zanubrutinib arm (75 [31.3%] patients) compared with the B+R arm (8 [3.5%] patients). The use of below-mentioned medications was less common in the zanubrutinib arm compared with the B+R arm.

- Analgesics: 99 (41.3%) patients in the zanubrutinib arm versus 192 (84.6%) patients in the B+R arm (category includes premedication prior to infusion of study drugs)
- Antigout preparations: 114 (47.5%) patients versus 145 (63.9%) patients
- Corticosteroids for systemic use: 49 (20.4%) patients versus 187 (82.4%) patients (category includes premedication prior to infusion of study drugs)
- Antihistamines for systemic use: 45 (18.8%) patients versus 188 (82.8%) patients (category includes premedication prior to infusion of study drugs)
- Antivirals for systemic use: 85 (35.4%) patients versus 144 (63.4%) patients
- Immunostimulants: 26 (10.8%) patients versus 132 (58.1%) patients
- Blood substitute and perfusion solutions: 40 (16.7%) patients versus 83 (36.6%) patients
- Antiemetics and antinauseants: 27 (11.3%) patients versus 190 (83.7%) patients

Concomitant Medication in Cohort 2

Almost all patients in the Cohort 2 received ≥ 1 concomitant medication (98.2% in the zanubrutinib arm).

The most common concomitant medications used in the zanubrutinib arm in Cohort 2 were antibacterials for systemic use (83 [74.8%] patients), analgesics (60 [54.1%] patients), agents acting on the renin-angiotensin system (52 [46.8%] patients), antigout preparations (45 [40.5%] patients), antithrombotic agents (42 [37.8%] patients), drugs for acid-related disorders (38 [34.2%] patients), antivirals for systemic use (34 [30.6%] patients), vaccines (34 [30.6%] patients), and lipid modifying agents (33 [29.7%] patients).

The Applicant's Position:
Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results.

The FDA's Assessment:
The Agency agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Primary Endpoint: Progression-free Survival by Independent Central Review in Cohort 1

The primary efficacy endpoint for this study was PFS assessed by independent central review for zanubrutinib (Arm A) compared with B+R (Arm B) in patients without the del(17p+) mutation (Cohort 1). As of data cutoff date in Cohort 1 with a median follow-up of 25.1 months in the zanubrutinib arm and 24.6 months in the B+R arm, the median PFS was not reached in the zanubrutinib arm and was 33.7 (95% CI: 28.1, NE) months in the B+R arm (Table 9). The hazard ratio for PFS in Cohort 1 assessed by independent central review was 0.42 (95% CI: 0.28, 0.63) for zanubrutinib Arm A compared with B+R Arm B in the ITT Analysis Set. Overall, the event-free rates at 12 months for patients in the zanubrutinib Arm A and in the B+R Arm B were 94.5% and 90.2%, respectively; at 24 months were 85.5% and 69.5%; and at 36 months were 81.5% and 40.8%.

All prespecified sensitivity analyses (Analyzing in Per-Protocol Analysis Set, including initiation of subsequent anti-CLL/SLL treatment as event, including events after missing for more than one response assessment, including events after subsequent anti-CLL/SLL treatment, censoring for hospitalization due to COVID-19) were supportive of the results of the primary analysis of PFS (Section 11.4.1.1 of CSR).

Zanubrutinib demonstrated improved PFS compared with BR in all high-risk subgroups with sufficient number of patients for analyses including the more difficult to treat subgroup of patients harboring unmutated IGHV and del11q (hazard ratios: 0.24 [95% CI: 0.13, 0.43] and 0.21 [95% CI: 0.09, 0.50], respectively) (Section 11.4.1.1.2 of CSR).

With a median follow-up of 27.9 months, the median PFS assessed by the independent central review was not reached with zanubrutinib among the patients with del(17p) CLL/SLL in Cohort 2. The event-free rates at 12, 24, and 36 months for patients in Cohort 2 were 93.6%, 88.9%, and 84.9%, respectively.

Kaplan-Meier curves for PFS assessed by independent central review are provided in

Figure 2 for Cohort 1 and Figure 3 for Cohort 2.

Table 9: Progression-Free Survival Assessed by Independent Central Review, Cohort 1 and Cohort 2 (ITT Analysis Set)

	Cohort 1 (without del(17p)		Cohort 2 (with del(17p))
	Zanubrutinib (N = 241)	**B+R (N = 238)**	**Zanubrutinib (N = 110)**
Progression-Free Survival			
Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)
Progressive disease	27 (11.2)	59 (24.8)	14 (12.7)
Death	9 (3.7)	12 (5.0)	1 (0.9)
Censored, n (%)	205 (85.1)	167 (70.2)	95 (86.4)
No documented progressive disease/death	195 (80.9)	140 (58.8)	93 (84.5)
No baseline/post-baseline assessment	2 (0.8)	16 (6.7)	0 (0.0)
No documented progressive disease/death: Withdrew consent/lost to follow-up	3 (1.2)	6 (2.5)	1 (0.9)
Progressive disease/death after missing 2 consecutive planned disease assessments	4 (1.7)	4 (1.7)	0 (0.0)
No documented progressive disease/death: Non-protocol anti-cancer therapy	1 (0.4)	1 (0.4)	0 (0.0)
Progressive disease/death after new anti-cancer therapy	0 (0.0)	0 (0.0)	1 (0.9)
Follow-up Time (Month)			
Median (95% CI) [a]	25.1 (24.9, 25.4)	24.6 (22.8, 25.2)	27.9 (27.7, 29.2)
(Min, Max)	(0.0, 41.4)	(0.0, 36.2)	(1.0, 38.8)
Hazard Ratio (95% CI) [b]	0.42 (0.28, 0.63)	N/A	N/A
1-sided p-value (Log-Rank) [c]	<.0001 (-4.349)	N/A	N/A
Progression Free Survival (Month) [d]			
Median (95% CI)	NE (NE, NE)	33.7 (28.1, NE)	NE (NE, NE)

	Cohort 1 (without del(17p)		Cohort 2 (with del(17p))
	Zanubrutinib (N = 241)	**B+R (N = 238)**	**Zanubrutinib (N = 110)**
Q1 (95% CI)	NE (27.5, NE)	22.1 (17.5, 25.2)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (33.7, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI) [e]			
12 Month	94.5 (90.8, 96.8)	90.2 (85.4, 93.5)	93.6 (87.0, 96.9)
18 Month	91.9 (87.7, 94.8)	80.5 (74.4, 85.2)	89.9 (82.5, 94.3)
24 Month	85.5 (80.1, 89.6)	69.5 (62.4, 75.5)	88.9 (81.3, 93.6)
30 Month	81.5 (74.6, 86.6)	54.4 (43.8, 63.9)	84.9 (76.0, 90.8)
36 Month	81.5 (74.6, 86.6)	40.8 (17.5, 63.1)	84.9 (76.0, 90.8)

Source: Table 8 and Table 16 in Module 2.7.3.

Abbreviation: B+R, Bendamustine and Rituximab; CI, confidence interval; IRT, Interactive Response Technology; N/A, not applicable; NE = not estimable.

Stratification factors: age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated) per IRT

[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.

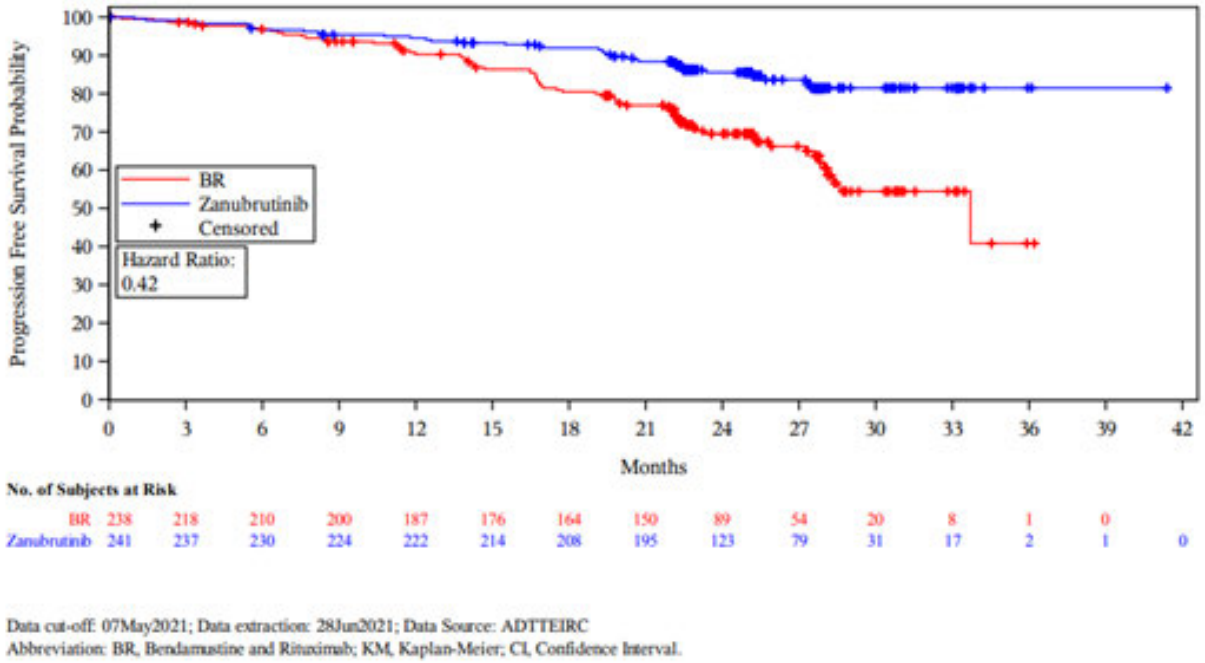
[b] Hazard ratio and 95% CI were from stratified Cox regression model with B+R arm as the reference group.

[c] From stratified log-rank test.

[d] Medians and other quartiles of progression free survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[e] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

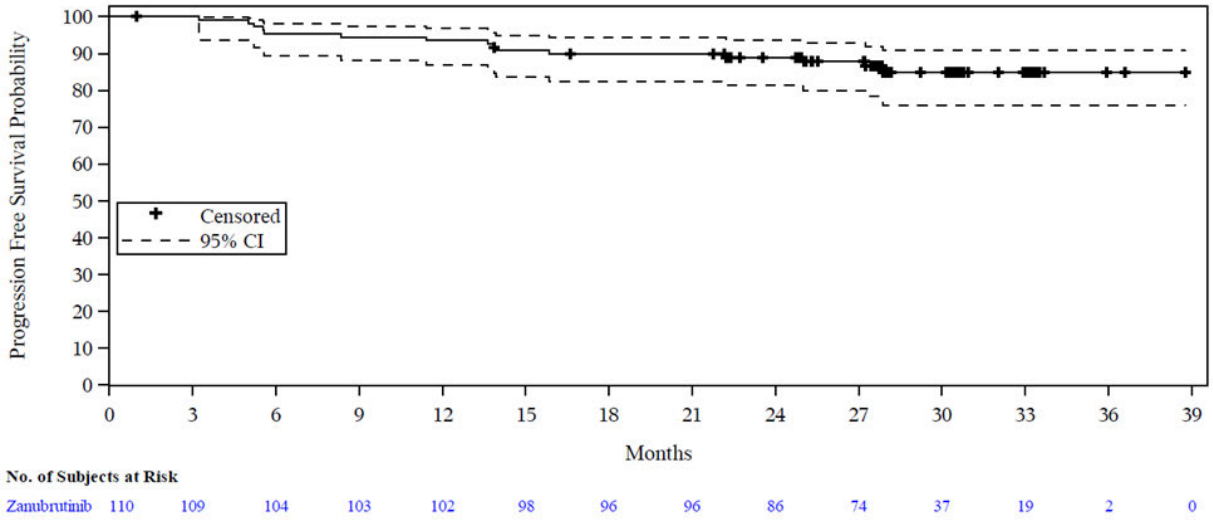
Figure 2: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review in Cohort 1 (ITT Analysis Set)



Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADTTEIRC
Abbreviation: BR, Bendamustine and Rituximab; KM, Kaplan-Meier; CI, Confidence Interval.

Source: Figure 2 in Module 2.7.3.

Figure 3: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review Committee in Cohort 2 (Safety Analysis Set in del(17p) Patients)



Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADTTEIRC
Abbreviation: CI, confidence interval
The 95% CI is based on Greenwood's formula and a generalize Brookmeyer and Crowley method with log-log transformation.

Source: Figure 6 in Module 2.7.3.

The Applicant's Position:

Study BGB-3111-304 met its primary endpoint with a HR of 0.42 (95% CI: 0.28, 0.63), demonstrating zanubrutinib was superior to B+R for IRC assessed PFS. The sensitivity analyses of PFS were consistent with the primary analysis and showed similar improvement in PFS for zanubrutinib compared with BR. The PFS benefit of zanubrutinib compared with BR was consistent across all prespecified subgroups, including the more difficult to treat subgroup of patients harboring unmutated IGHV and del11q.

The FDA's Assessment:

Cohort 1:
FDA generally agrees with the description of the analysis results of PFS per IRC in Cohort 1, which was the prespecified primary endpoint and primary analysis.

FDA notes that the interim analysis of PFS per IRC was prespecified when approximately 86 PFS events were observed, the date of the approximate 86th event was to be used as the data cutoff date. However, at the time of interim analysis (May 07, 2021), there were a total of 107 PFS events observed in the zanubrutinib and BR arms. The actual interim analysis conducted as above was based on the data with a cutoff date of May 07, 2021, when 107 PFS events were observed in total. Based on the actual number of events observed at the interim analysis (n=107), the O'Brien-Fleming boundaries were adjusted to be 0.0186 and 0.02 (1-sided) for the interim efficacy analysis and final efficacy analysis of PFS. At the interim analysis timepoint, the study met the superiority criteria with a PFS HR of 0.42 (95% CI: 0.28, 0.63), p<0.0001 versus the boundary of 0.0186, demonstrating improvement in PFS in the zanubrutinib arm. The HR and 95% C.I. were based on a stratified Cox regression model, and there was no violation of the proportional hazards assumption.

In addition, the Applicant submitted updated PFS results per investigator based on a data cutoff date of March 07, 2022. The results were consistent with the previous analysis, with a PFS HR of 0.33 (95% CI: 0.22, 0.48) favoring zanubrutinib (Appendix, Table 120).

There were several sensitivity analyses of the primary endpoint prespecified in the SAP. In summary, the primary analysis results were supported by these prespecified sensitivity analyses:

- The unstratified estimate of HR (Zan vs BR) obtained from the unstratified Cox proportional hazard regression model was 0.41 (95% CI: 0.28, 0.62)
- the estimate of HR based on per-protocol analysis set, other than ITT set, was 0.43 (95% CI: 0.29, 0.64)
- treating initiation of non-protocol CLL/SLL related therapy as a PFS event, other than a mechanism for censoring, led to a HR of 0.40 (95% CI: 0.27, 0.60)
- treating initiation of non-protocol CLL/SLL related therapy as neither a PFS event nor a censoring event led to a HR of 0.42 (95% CI: 0.28, 0.63)
- treating death or disease progression immediately after 2 or more missed consecutive

disease as a PFS event led to a HR of 0.45 (95% CI: 0.31, 0.67)
- adding hospitalization due to COVID-19 as a mechanism for censoring led to a HR of 0.34 (95% CI: 0.22, 0.53)
- assuming date of progressive disease as interval censored led to a HR of 0.40 (95% CI: 0.27, 0.60)
- using stratification factors collected in eCRF, instead of by IRT, in the PFS analysis results in a HR of 0.42 (95% CI: 0.28, 0.63).

The PFS HR per Investigator in Cohort 1 was 0.42 (95% CI: 0.27, 0.66) and was highly concordant (91.4%) with PFS per IRC.

In summary, at the interim analysis timepoint, with 107 PFS events observed by May 07, 2021, the analysis of the primary endpoint of PFS per IRC in Cohort 1 demonstrated the superiority of zanubrutinib compared to BR in patients with previously untreated CLL/SLL without 17p del; the finding was supported by the sensitivity analyses, subgroup analyses and the analysis of PFS by investigator prespecified in the protocol.

Cohort 2:
Although PFS was a prespecified secondary endpoint in Cohort 2, time-to-event efficacy endpoints such as PFS have limited interpretability in single-arm cohorts, are considered exploratory, and cannot be used to support efficacy claims.

Quality and Integrity

Data:

The applicant submitted this sNDA including the data to the FDA CDER Electronic Document Room (EDR).The data in this submission are in electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submission. The data sets are well documented and included definition files.

The Applicant's Position:
No issues were identified with the data quality or integrity from Study BGB-3111-304 which could affect the study results.

The FDA's Assessment:
The Agency agrees with the Applicant's position. No data integrity or quality issues were identified during the review.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:
Overall Response Rate by Independent Central Review

In Cohort 1, the overall response rate assessed by independent central review was higher for patients in zanubrutinib Arm A (94.6% [95% CI: 91.0, 97.1]) compared with the B+R Arm B (85.3% [95% CI: 80.1, 89.5]) (Table 10). The odds ratio was 3.162 (95% CI: 1.608, 6.220); p-value = 0.0006. The CR/CRi rate was 6.6% in the zanubrutinib arm and 15.1% in the B+R arm.

The PR or higher rate in Cohort 1 was also higher in the zanubrutinib arm (93.4% [95% CI: 89.4, 96.2] compared with the B+R arm (85.3% [95% CI: 80.1, 89.5]). The odds ratio was 2.526 (95% CI: 1.341, 4.757).

In Cohort 2, the overall response rate with zanubrutinib was 90.0% (95% CI: 91.0, 97.1). The CR/CRi rate for this group was 6.4% (95% CI: 2.6; 12.7). The proportion of patients with best overall response of PR or higher was 88.2% (95 CI: 80.6; 93.6). Thus, zanubrutinib administration resulted in a high overall response in patients with del(17p) CLL/SLL.

Table 10: Analysis of Disease Response by Independent Central Review in Cohorts 1 and 2 (ITT Analysis Set)

	Cohort 1 (without del(17p))		**Cohort 2 (with del(17p))**
	Zanubrutinib ARM A (N = 241)	**B+R ARM B (N = 238)**	**Zanubrutinib ARM C (N = 110)**
Best Overall Response, n (%)			
Complete Response	16 (6.6)	36 (15.1)	7 (6.4)
Nodular Partial Response	3 (1.2)	14 (5.9)	2 (1.8)
Partial Response	206 (85.5)	153 (64.3)	88 (80.0)
Partial Response with Lymphocytosis	3 (1.2)	0 (0.0)	2 (1.8)
Stable Disease	7 (2.9)	14 (5.9)	11 (10.0)
Progressive Disease	2 (0.8)	1 (0.4)	0
Not Evaluable	1 (0.4)	1 (0.4)	0
Discontinued Prior to First Assessment	3 (1.2)	19 (8.0)	0
Overall Response [a] Rate, n (%)	228 (94.6)	203 (85.3)	99 (90.0)
(95% CI)	(91.0, 97.1)	(80.1, 89.5)	(82.8, 94.9)
Odds ratio (95% CI)	3.162 (1.608, 6.220)	N/A	N/A
Complete Response Rate (CR/CRi), n (%)	16 (6.6)	36 (15.1)	7 (6.4)
(95% CI)	(3.8, 10.6)	(10.8, 20.3)	(2.6, 12.7)
Odds ratio (95% CI)	0.400 (0.216, 0.743)	N/A	N/A
Partial Response or Higher Rate, n (%)	225 (93.4)	203 (85.3)	97 (88.2)
(95% CI)	(89.4, 96.2)	(80.1, 89.5)	(80.6, 93.6)
Odds ratio (95% CI)	2.526 (1.341, 4.757)	N/A	N/A
Time to Partial Response with Lymphocytosis or Higher [b] (months)			

	Cohort 1 (without del(17p))		Cohort 2 (with del(17p))
	Zanubrutinib ARM A (N = 241)	B+R ARM B (N = 238)	Zanubrutinib ARM C (N = 110)
N	228	203	99
Mean (SD)	3.37 (1.514)	3.11 (0.944)	3.76 (2.737)
Median	2.87	2.89	2.86
Q1, Q3	2.79, 3.09	2.76, 3.09	2.79, 3.02
Min, Max	1.8, 14.2	1.9, 11.1	1.9, 19.4
Time to Partial Response or Higher [b] (months)			
N	225	203	97
Mean (SD)	3.38 (1.523)	3.11 (0.944)	3.61 (2.254)
Median	2.89	2.89	2.86
Q1, Q3	2.79, 3.09	2.76, 3.09	2.79, 3.02
Min, Max	1.8, 14.2	1.9, 11.1	1.9, 13.9

Source: Table 8 and Table 13 in Module 2.7.3.
Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADRSIRC, ADTTEIRC

Abbreviation: B+R, bendamustine and rituximab; CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; N/A, not applicable; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis or higher; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Percentages are based on N.
[a] Overall response is defined as achieving a best overall response of CR, CRi, nPR, PR, or PR-L.
[b] Time to response is summarized for responders only.

The FDA's Assessment:

To clarify, there were no reported cases of CRi in Study BGB-3111-304, and the p-value for the ORR odds ratio above is nominal.

FDA does not agree with the Applicant's definition of ORR, which included PR-L. Since lymphocytosis can be associated with disease persistence, progression, or lymphocyte mobilization following BTKi therapy, PR-L, although not considered as disease progression in the setting of BTKi therapy, is not considered in the definition of objective response for regulatory purposes. Therefore, FDA conducted an additional analysis for ORR per IRC by excluding PR-L from the definition of overall response. This resulted in three fewer responders in the zanubrutinib arm of Cohort 1, and two fewer responders in Cohort 2 as detailed in the table below. Similar to the assessment of ORR by including PR-L in Cohort 1, ORR was higher for patients in the zanubrutinib arm compared with the BR Arm in Cohort 1, with an odds ratio of 2.526.

Table 11: IRC-Assessed Overall Response Rate Excluding Partial Response with Lymphocytosis in Study BGB-3111-304

	Cohort 1 (without del(17p))		Cohort 2 (with del(17p))
	Zanubrutinib ARM A (N = 241)	B+R ARM B (N = 238)	Zanubrutinib ARM C (N = 110)
Best Overall Response, n (%)			
Complete Response	16 (6.6)	36 (15.1)	7 (6.4)
Nodular Partial Response	3 (1.2)	14 (5.9)	2 (1.8)
Partial Response	206 (85.5)	153 (64.3)	88 (80.0)
Overall Response Rate, n (%)	225 (93.4)	203 (85.2)	97 (88.2)
(95% CI)	(89.4, 96.2)	(80.1, 89.5)	(80.6, 93.6)
Odds Ratio (95% CI)	2.526 (1.341, 4.757)		

Source: FDA analysis based on Applicant's response to IR on October 6, 2022 and verified with ADRSIRC dataset. CCOD, May 7, 2021

Overall Response Rate by Investigator

Similar to the assessment by the independent central review in Cohort 1, investigator-assessed overall response rate was higher for patients in the zanubrutinib arm (97.5% [95% CI: 94.7, 99.1]) compared with the B+R Arm B (88.7% [95% CI: 83.9, 92.4]) in Cohort 1. The odds ratio was 5.220 (95% CI: 2.084, 13.076), and p-value = 0.0001.

The CR/CRi rate was 9.1% in the zanubrutinib arm and 18.5% in the B+R arm. The PR or higher rate was higher in the zanubrutinib arm (95.9% [95% CI: 92.5, 98.0] compared with the B+R arm (88.7% [95% CI: 83.9, 92.4]). The odds ratio was 3.054 (95% CI: 1.429, 6.524).

In Cohort 2, the overall response rate by investigator assessment was 96.4% (95% CI: 91.0, 99.0). The CR/CRi rate was 9.1% (95% CI: 4.4, 16.1), and the proportion of patients with best overall response of PR or higher was 95.5% (95% CI: 89.7, 98.5).

Progression-Free Survival Assessed by Investigator

As of data cutoff date, the investigator assessed median PFS in Cohort 1 was reached in the B+R arm but not in the zanubrutinib arm. The hazard ratio for investigator-assessed PFS in Cohort 1 was 0.42 (95% CI: 0.27, 0.66) in the zanubrutinib arm compared with the B+R arm in the ITT analysis set. Overall, the event-free rates for patients in the zanubrutinib arm and the B+R arm at 12 months were 95.8% and 91.2%, respectively; at 24 months were 87.7% versus 76.5%.

In Cohort 2, the median PFS determined by the investigator was not reached as of the data cutoff date. The event-free rates at 12, 24, and 36 months were 94.5%, 87.0%, and 82.6%, respectively.

These results support that PFS was consistent when assessed by the independent review committee or by the investigator, with improved response for zanubrutinib compared with B+R in Cohort 1 and high event-free rates among patients with del(17p) disease.

Duration of Response

In Cohort 1, 228 of 241 (94.6%) patients were responders as assessed by the independent central review in the zanubrutinib arm, and 203 of 238 (85.3%) patients were responders in the B+R arm. Of these responders, 27 patients reported progressive disease (21 patients) or death (6 patients) in the zanubrutinib arm. Fifty-eight patients reported progressive disease (53 patients) or death (5 patients) in the B+R arm. The event-free rates for patients in the zanubrutinib arm and in the B+R arm at 12-months were 96.0% and 90.8%, respectively, and at 24-months were 87.5% and 70.3%, respectively. Median follow up time was 22.1 months in both arms.

Duration of response as assessed by independent central review was also calculated for patients who achieved PR or better. In Cohort 1, the event-free rates for patients in the zanubrutinib arm and in the B+R arm at 12-months were 96.0% and 90.8%, respectively, and at 24-months were 87.5% and 70.3%, respectively.

The duration of response as assessed by the investigator in Cohort 1 was consistent with results as assessed by independent central review. Of the 235 responders in the zanubrutinib arm and 211 responders in the B+R arm, 24 patients reported progressive disease (15 patients) or death (9 patients) in the zanubrutinib arm, and 48 patients reported progressive disease (41 patients) or death (7 patients) in the B+R arm. The 12-month event-free rate was 94.9% (95% CI: 91.1, 97.0) in the zanubrutinib arm and 93.1% (95% CI: 88.7, 95.9) in the B+R arm. The median follow-up time was 19.8 months in both arms in the investigator assessment. The event-free rates for patients by investigator assessment in the zanubrutinib arm and in the B+R arm at 12-months were 95.0% and 93.1%, respectively, and at 24-months were 87.2% and 75.2%, respectively.

The FDA's Assessment:
The Agency considers DOR to be an exploratory endpoint for Cohort 1. Caution should be used in interpreting the DOR comparison because the analysis is conditioned on subjects having a response and thus is not based on the ITT population.

For Cohort 2, DOR was analyzed based on the FDA's revised ORR definition excluding PR-L. With an estimated median DOR follow-up of 25.1 months, the median DOR was not reached (Table 12).

Table 12: Duration of Response per IRC for Cohort 2

Parameter[a]	**del(17p) CLL/SLL N=110**
Responders[b], n (%)	97 (88)
Duration of response	
Median DOR (95% CI),[c] months	NE (NE, NE)
Range, months	(5.6 to 35.9+)
Rate at 12 months, % (95% CI)[c]	96 (89, 98)
Rate at 18 months, % (95% CI)[c]	95 (88, 98)

Source: FDA analysis

A + sign indicates a censored observation.
[a] Efficacy was assessed using the 2008 iwCLL guidelines and Lugano criteria for SLL.
[b] Defined as CR, CRi, PR and nPR. No patients had CRi as best response.
[c] Kaplan-Meier estimate. Estimated median follow-up for DOR was 25.1 months.

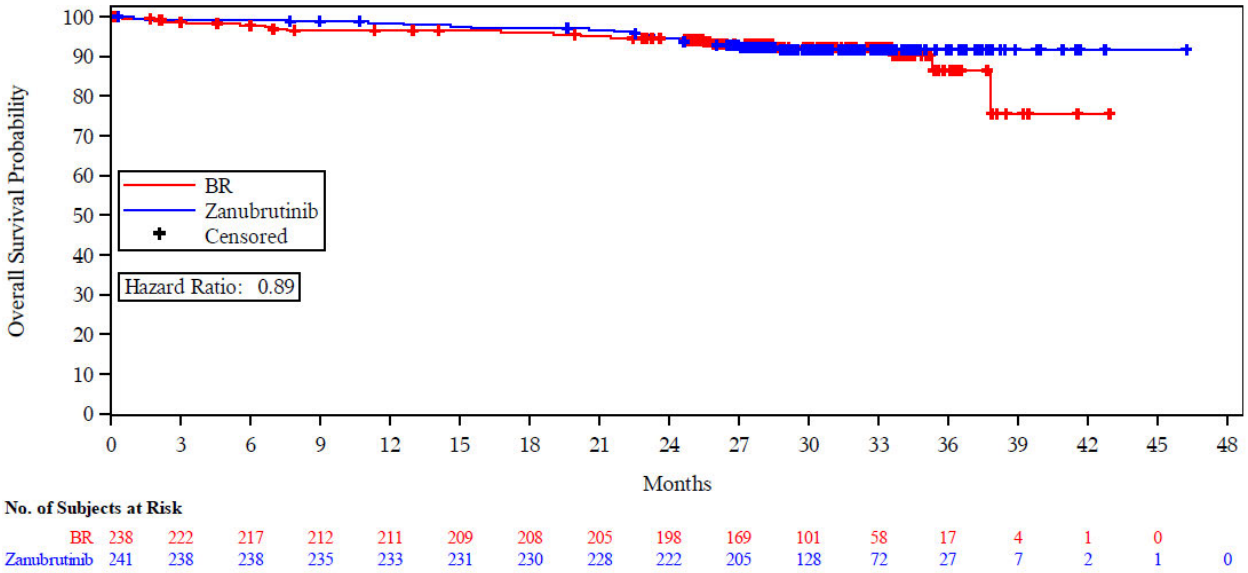
Overall Survival

Results presented in this submission include data from the 07May2021 data cutoff and an additional OS analysis from the 07 September 2021 data cutoff date. It was not expected that a statistically significant difference in overall survival would be detected between the treatment arms in Cohort 1, as the study was not powered to detect differences in overall survival.

For the 07 May 2021 data cutoff for Cohort 1, with comparable duration of follow-up between treatment arms (26.5 months in the zanubrutinib arm and 25.1 months in the B+R arm), there were 16 (6.6%) deaths reported in the zanubrutinib arm and 14 (5.9%) deaths reported in the B+R arm. Median estimated overall survival was not reached in the zanubrutinib arm and was 37.8 months in the B+R arm. Most patients were alive and censored at the data cutoff date.

For the 07 September 2021 data cutoff for Cohort 1, with 30.4 months follow-up in the zanubrutinib arm and 28.6 months follow-up in the B+R arm, there were 19 (7.9%) deaths reported in the zanubrutinib arm and 19 (8.0%) deaths reported in the B+R arm with a HR of 0.89 (95% CI: 0.47, 1.68). The additional survival data continued to show largely overlapping overall survival curves between study arms (Figure 4).

Figure 4: Kaplan-Meier Plot of Overall Survival in Cohort 1 (Intent-to-Treat Analysis Set)



Data cut-off: 07Sep2021; Data extraction: 30Nov2021; Data Source: ADTTE
Abbreviation: BR, Bendamustine and Rituximab.

Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_os_20211130/dev/pgm/tlfs/f_ef_km.sas
Output: f-14-2-1-2-4-1-a-ef-km-os-c1-itt.pdf (Date Generated: 01DEC2021:23:19)

It should be noted that assessment of treatment differences in overall survival in Cohort 1 may be confounded by many factors including the crossover study design, the numerically higher number of patients not ever initiating B+R treatment (who were censored at the date of randomization), the numerically higher number of patients in the B+R arm who discontinued study without a PFS event, and the extreme imbalance in patient exposure to SARS-CoV-2 during immunosuppression between the zanubrutinib arm versus the B+R arm. Regarding the last point, all B+R patients in Cohort 1 completed the fixed study drug treatment period by December 2019, and most of those patients achieved full or partial immune reconstitution prior to the onset of the global COVID-19 pandemic in February 2020. Conversely, the majority of patients randomized to receive zanubrutinib continued to receive therapy throughout the pandemic.

To account for the effect of COVID-19 on Study BGB-3111-304, an exploratory analysis was conducted to censor subjects who died due to COVID-19. In Cohort 1, with 4 additional months of follow-up, fewer deaths due to COVID-19 were observed in the B+R arm (n = 2) compared with the zanubrutinib arm (n = 6). Based on the 07Sep2021 data cutoff, censoring subjects who died due to known COVID-19 infection resulted in 13 deaths on the zanubrutinib arm and 17 deaths on the B+R arm, with a hazard ratio of 0.68 (95% CI: 0.33, 1.40). The estimated 18-month OS was 97.5% (95% CI: 94.5, 98.9) versus 96.0% (95% CI: 92.4, 97.9) for zanubrutinib versus B+R respectively. To adjust for the administration of second-line therapy that might have diluted the treatment effect on OS, patients who received subsequent therapy were censored at the time of initiation of the second line therapy. This analysis resulted in 15 deaths in the

zanubrutinib arm and 17 deaths in the B+R arm, with a hazard ratio of 0.75 (95% CI: 0.38, 1.51). The estimated 18-month OS was 97.9% (95% CI: 95.0, 99.1) versus 95.9% (95% CI: 92.3, 97.9) for zanubrutinib versus B+R, respectively.

In Cohort 2, overall survival was an exploratory endpoint. There were 8 (7.3%) deaths reported. Median overall survival was not reached, with median follow-up time of 30.4 months. The event-free rates were 96.4%, 93.6%, and 90.7% at 12-months, 24-months, and 36-months, respectively. Most patients were alive and censored at the data cutoff date.

The Applicant's Position:

Overall response rate, duration of response and PFS assessed by the investigator strongly support the clinical benefit of zanubrutinib as demonstrated by the PFS by independent central review.

Overall survival: Based on the data cutoff date of 07 May 2021, with only 30 deaths out of 479 patients enrolled into Cohort 1, the OS analysis showed largely overlapping Kaplan-Meyer curves for Cohort 1 Arm A and Arm B. Based on a subsequent data cutoff date of 07 September 2021, as reported in the BGB-3111-304 Clinical Study Report Addendum for OS, the number of deaths in Cohort 1 was 38, 19 in Arm A and 19 in Arm B, with a HR of 0.89 (95% CI: 0.47, 1.68). The additional survival data continued to show largely overlapping overall survival curves between study arms.

Patients with del(17p) mutation: Of note, patients with del(17p) mutation had similar efficacy outcomes as those with unmutated del(17p); with a median study follow-up of 30.5 months, the median PFS for Cohort 2 as determined by independent central review was not reached and the 24-month PFS was 88.9%. Additionally, the overall response rate of 90.0% (95% CI: 82.8, 94.9) in Cohort 2 was similar to the rate observed in Cohort 1.

The FDA's Assessment:

The FDA generally agreed with the description of the analysis results for the secondary and other study endpoints. The FDA notes that the analyses described by the Applicant were based on a cutoff date of May 07, 2021, when 107 PFS events were observed in zanubrutinib and BR arms.

In addition, as noted in FDA's assessment of the SAP, no inferential testing was to be done for secondary endpoints other than OS and a PRO endpoint, including ORR; the comparison between treatment groups for the ORR in Cohort 1 was descriptive only. For the ORR endpoint, the p-value 0.0006 for ORR per IRC and p-value 0.0001 for ORR per investigator presented as above were nominal p-values and not suitable for inferential purposes.

Based on the OS results with a data cutoff date of May 07, 2021, the Agency noted that there were 16 (6.6%) deaths reported in the zanubrutinib arm and 14 (5.9%) deaths reported in the B+R arm with a HR of 1.07 (95% CI: 0.51, 2.22). Based on this data cut, there were concerns that the PFS advantage with zanubrutinib study BGB-3111-304 may not translate into an OS advantage and a detriment compared to the BR control arm could not be excluded.

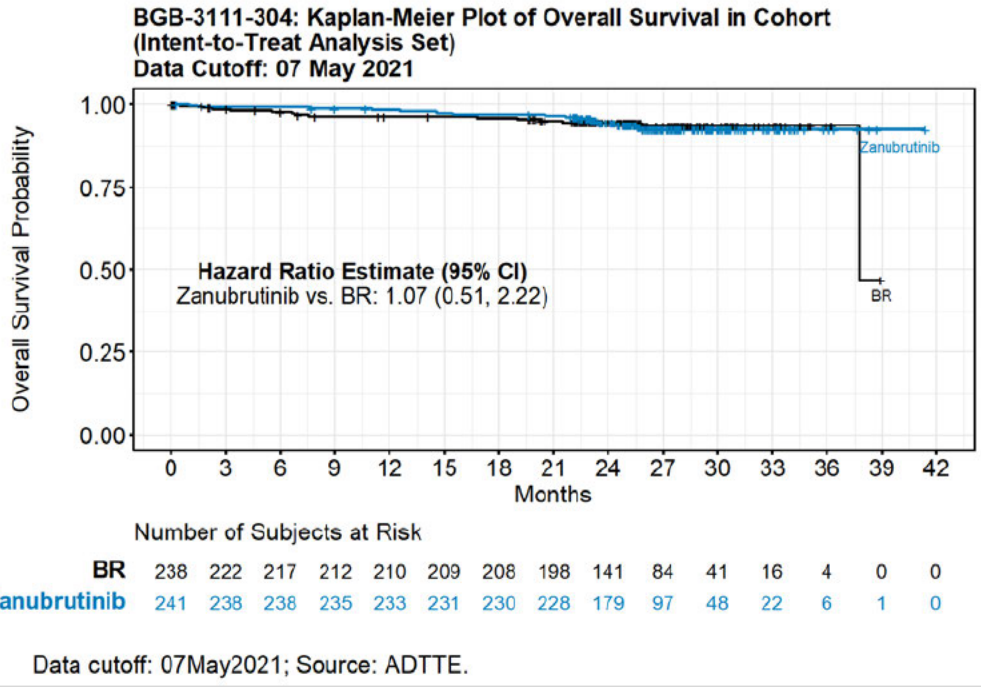
The Applicant provided further OS results with a data cutoff date of September 7th, 2021 and a data cutoff date of March 7, 2022. For the September 07, 2021 data cutoff for Cohort 1, there were 19 (7.9%) deaths reported in the zanubrutinib arm and 19 (8.0%) deaths reported in the B+R arm with a HR of 0.89 (95% CI: 0.47, 1.68). For the March 07 2022 data cutoff for Cohort 1, there were 23 (9.5%) deaths reported in the zanubrutinib arm and 22 (9.2%) deaths reported in the B+R arm with a HR of 0.93 (95% CI: 0.52, 1.67). The point estimates of HR at these two data cutoff dates (September 7, 2021 and March 7, 2022) were both observed to be less than 1.0 (Table 13). In addition, the FDA sent an information request to the Applicant to obtain additional simulated OS results, with different data cut-off dates (Appendix, Table 121). The updated OS data did not demonstrate a worsening trend with regards to safety in the zanubrutinib arm.

Table 13: OS Analyses in Study BGB-3111-304 by Different Cutoff Dates

	Data Cutoff: 05/07/2021		**Data Cutoff*: 09/07/2021**		**Data Cutoff*: 03/07/2022**	
	BR	**Zanubrutinib**	**BR**	**Zanubrutinib**	**BR**	**Zanubrutinib**
	(N=238)	(N=241)	(N=238)	(N=241)	(N=238)	(N=241)
Number of Events, n (%)	14 (5.9)	16 (6.6)	19 (8.0)	19 (7.9)	22 (9.2)	23 (9.5)
Number of Censored, n (%)	224 (94.1)	225 (93.4)	219 (92.0)	222 (92.1)	216 (90.8)	218 (90.5)
OS (Months)						
Median (95% CI)	37.8 (37.8, NE)	NE (NE, NE)	NE (37.8, NE)	NE (NE, NE)	35.4 (34.1, 35.8)	36.1 (35.8, 36.5)
Min, Max	0.0, 38.9	0.3, 41.4	0.0, 42.9	0.0, 46.3	0.0, 48.8	0.3, 52.2
HR, (95% CI)	1.07 (0.51, 2.22)		0.89 (0.47, 1.68)		0.93 (0.52, 1.67)	
OS Rate (%) with 95% CI						
12 Months	96.4 (93.0, 98.2)	98.3 (95.6, 99.4)	96.4 (93.0, 98.2)	98.3 (95.6, 99.4)	96.4 (93.0, 98.2)	98.3 (95.6, 99.4)
24 Months	94.6 (90.6, 96.9)	94.3 (90.4, 96.7)	94.6 (90.7, 96.9)	94.5 (90.7, 96.8)	94.6 (90.7, 96.9)	94.5 (90.7, 96.8)
36 Months	93.6 (88.9, 96.3)	92.3 (87.6, 95.3)	86.4 (74.2, 93.1)	91.8 (87.4, 94.7)	89.5 (84.2, 93.1)	90.9 (86.3, 94.0)

Source: FDA analysis generated from ADTTE datasets

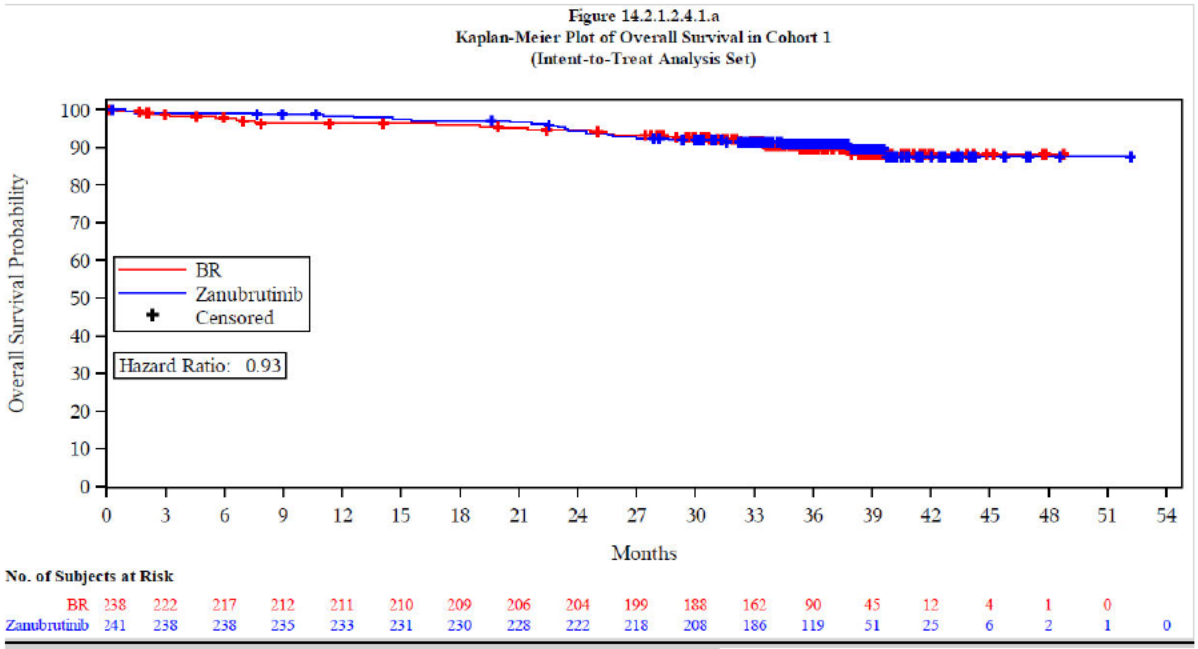
Figure 5: Kaplan-Meier Plot of OS in Cohort 1 (ITT) with CCOD of May 07, 2021



Data cutoff: 07May2021; Source: ADTTE.

Source: FDA analysis. Data cutoff date: May 07, 2021

Figure 6: Kaplan-Meier Plot of OS in Cohort 1 (ITT) with CCOD of March 07, 2022



Source: FDA analysis. Data cutoff date: March 07, 2022

Dose/Dose Response

Data:
See the Clinical Pharmacology Sections 6.2.1 and 6.2.2.

The Applicant's Position:
Dose response was evaluated using pop pk and expose-response analyses.

The FDA's Assessment:
Refer to Section 6.

Durability of Response

The Applicant's Position:

See "Duration of Responses" under "Efficacy Results – Secondary and Other Related Endpoints"

The FDA's Assessment:
Refer to discussion of DOR for Cohorts 1 and 2 under Efficacy Results-Secondary and Other Related Endpoints.

9 Persistence of Effect

10 The Applicant's Position:

The Study BGB-3111-304 is still ongoing. With the median follow-up of approximately 26 months at the planned interim analysis, zanubrutinib treatment at 160 mg BID demonstrated statistical superiority in PFS compared to the B+R treatment. These data are supported by ORR, DOR and preliminary OS, as presented in the efficacy results above. The results suggest zanubrutinib, at the proposed dosing regimen has persistence of effects on the treatment of patients with naïve CLL/SLL.

The FDA's Assessment:
Persistence of effect is not evaluable in this study, because this refers to persistence of the treatment effect after study drug discontinuation, and zanubrutinib was administered continuously.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

As indicated by the LS mean difference (SE) at 95% CI from baseline to Week 24, patients in the zanubrutinib arm experienced a clinically greater improvements in the PRO endpoints compared with the B+R arm, with GHS/QoL (4.9 [95% CI: 0.9, 9.0]) and physical function (3.5 [95% CI: 0.6, 6.5]), role functioning (4.1 [95% CI: -0.7, 9.0]), fatigue (-4.4 [95% CI: -8.9, 0.1]), nausea/vomiting (-4.0 [95% CI: -6.4, -1.5]) and diarrhea (-5.7 [95% CI: -9.5, -2.0]).

The Applicant's Position:

The zanubrutinib arm had better overall health related quality of life outcomes compared with the B+R arm as indicated in the mean changes from baseline of the key patient-reported outcome endpoints of General Health Status (GHS), physical, and role functions scales, and decreased symptoms of fatigue and nausea/vomiting and diarrhea. The score for pain was similar in both arms.

The FDA's Assessment:
The Applicant included results from the EORTC QLQ-C30 questionnaire from patients in Cohort 1. The Applicant included results assessing the endpoints of General Health Score (GHS)/Quality of Life (QoL), physical function, role function, pain, fatigue, nausea and vomiting and diarrhea from week 12 and week 24 of therapy. The Agency does not agree with the Applicant's claim that the zanubrutinib arm had better overall health-related quality of life outcomes compared with the BR arm since these results are considered descriptive, are subject to bias given the open-label trial design, and were not analyzed based on a prespecified hypothesis or formal testing plan.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

See the additional analyses on OS in the above section "Efficacy Results – Secondary and Other Relevant Endpoints". No other analyses were conducted for the BGB-3111-304 Study.

The FDA's Assessment:
Refer to the discussion of additional OS analyses in the section on secondary endpoints. The Agency requested additional OS data with additional follow-up from the Applicant to further investigate a potential safety finding of increased fatal TEAEs observed in the zanubrutinib arm compared to the BR arm at the time of the primary PFS analysis (CCOD of May7, 2021) and with additional follow-up (CCOD of September 7, 2021) that was included in the original application. The Applicant provided additional OS data during the review cycle with a CCOD of March 7, 2022. In addition, the Applicant provided estimations of OS events and information that would be available at future timepoints to adequately inform of the risk for harm with zanubrutinib compared to BR in patients with TN CLL. Refer to section 12 for a discussion of postmarketing

requirements.

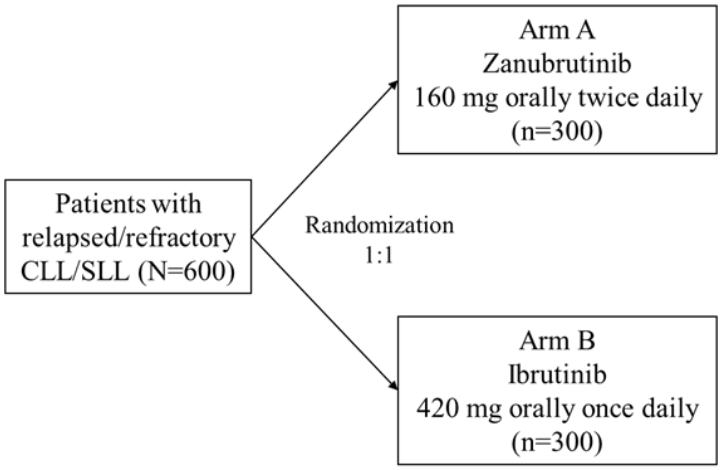
8.1.2 BGB-3111-305

The Applicant's Description

8.1.2.1 Trial Design

Study BGB-3111-305 is an ongoing, international Phase 3, open-label, randomized study of zanubrutinib versus ibrutinib in 652 patients (600 planned) with R/R CLL/SLL (refer to BGB-3111-305 Protocol and CSR Body). The schema for this study is presented in Figure 7.

Figure 7: Study Schema



Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present versus absent).

The efficacy data presented in this submission are based on the planned interim analysis which occurred 12 months after 415 patients had been randomized. The final analysis will occur approximately 12 months after 600 patients have been randomized.

Trial location
The study was conducted at 117 study centers in 15 countries (Australia, Belgium, China, Czech Republic, France, Germany, Italy, Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, United Kingdom, and United States).

Choice of Control Groups
This Phase 3, randomized study was designed to compare the efficacy and safety of zanubrutinib with ibrutinib in patients with R/R CLL/SLL. Ibrutinib is a first generation BTK inhibitor and has been approved for the treatment of adult patients with R/R CLL/SLL in many

countries, including the US. With a well-characterized efficacy and safety profile in the treatment of CLL/SLL, ibrutinib is considered the most appropriate active comparator for zanubrutinib to establish efficacy and safety evidence for the proposed indication.

Selection of Study Population

Key Inclusion/Exclusion Criteria

Patients who met all of the following criteria were eligible to participate in the study:

- Age 18 years or older
- Confirmed diagnosis of CLL or SLL
- CLL/SLL requiring treatment
- Relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL.
- Measurable disease by computed tomography (CT)/magnetic resonance imaging (MRI).
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Life expectancy ≥ 6 months
- Adequate bone marrow function
- Adequate organ function

Patients who met any of the following criteria were excluded from the study:

- Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation (biopsy based on clinical suspicion may be needed to rule out transformation)
- Clinically significant cardiovascular disease
- Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast
- History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention.
- History of stroke or intracranial hemorrhage within 180 days before first dose of study drug.
- Severe or debilitating pulmonary disease
- Active fungal, bacterial, and/or viral infection requiring systemic therapy
- Known central nervous system involvement by leukemia or lymphoma

- Known infection with HIV, or serologic status reflecting active hepatitis B or hepatitis C infection
- Moderate or severe hepatic impairment, i.e., Child-Pugh class B or C
- Major surgery within 4 weeks of the first dose of study drug
- Prior treatment with a BTK inhibitor
- Last dose of prior therapy for CLL/SLL ≤ 14 days before randomization
- Ongoing need for corticosteroid used during the trial. NOTE: systemic corticosteroids must be fully tapered off/stopped at least 5 days before the first dose of study drug
- Patient requires treatment with warfarin or other vitamin K antagonists
- Requires ongoing treatment with a strong CYP3A inhibitor or inducer
- Concurrent treatment for CLL/SLL outside of this clinical trial (includes the screening period)
- Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (e.g., idiopathic thrombocytopenia purpura) requiring treatment

A complete list of inclusion and exclusion criteria are presented in Section 4 of the BGB-3111-305 protocol under Appendix 16.1.1 of the CSR.

Zanubrutinib Dose Modifications for Hematologic Toxicity

Dosing was held for individual patients under any of the following conditions, based on investigator assessment (using Hallek et al 2008) of study drug relatedness:

- Grade 4 neutropenia (that was persistent for at least 10 consecutive days)
- Grade 4 thrombocytopenia (that was persistent for at least 10 consecutive days)
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

For the first occurrence of hematologic toxicity, zanubrutinib treatment could restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

Dose modification for patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention were discussed with the medical monitor.

Asymptomatic treatment-related lymphocytosis was not considered an AE. Patients with treatment-related lymphocytosis remained on study treatment and continued with all study-related procedures.

Zanubrutinib Dose Modifications for Nonhematologic Toxicity

For dose reductions, investigators were instructed to follow the guidance described in Table 14. Guidelines for nonhematologic toxicities are given in

Table 15.

For patients experiencing symptomatic and/or incompletely controlled atrial fibrillation, the study drug could be restarted at either the original dose or dose level -1, per discretion of the treating investigator, after the atrial fibrillation was adequately controlled. Zanubrutinib was permanently discontinued for any intracranial hemorrhage.

If the HCV RNA was ≥ 15 IU/mL, the HBV DNA by polymerase chain reaction (PCR) was ≥ 100 IU/mL, or a rechecked detectable copy number was recorded during monthly monitoring, then study drug was stopped, and antiviral therapy initiated.

Table 14: Zanubrutinib and Ibrutinib Dose Reductions

Toxicity Occurrence	Dose Level	Zanubrutinib Dose (Arms A) (Starting dose = 160 mg twice a day)	Ibrutinib Dose (Arm B) (Starting dose = 420 mg once a day)
First	0 = starting dose	Restart at 160 mg twice a day	Restart at 420 mg once a day
Second	-1 dose level	Restart at 80 mg twice a day	Restart at 280 mg once a day
Third	-2 dose level	Restart at 80 mg once a day	Restart at 140 mg once a day
Fourth	Discontinue study drug	Discontinued zanubrutinib	Discontinued ibrutinib

Source: Table 2 and Table 5 of the study protocol in Appendix 16.1.1

Table 15: Zanubrutinib Dose Reduction Steps for Nonhematologic Toxicity

Toxicity	Action for Zanubrutinib	Re-start Dose
≥ Grade 3 bleeding not considered related to study drug	Held until recovery to less than or equal to Grade 1	Restarted at either the original dose or dose level (-1), at the discretion of the treating investigator
≥ Grade 3 bleeding considered related to study drug	Held until underlying condition had fully resolved. If underlying condition cannot be treated to full resolution, permanently discontinued zanubrutinib.	Restarted at dose level (-1)

Toxicity	Action for Zanubrutinib	Re-start Dose
Any grade intracranial hemorrhage	Permanently discontinued zanubrutinib.	Not Applicable
Atrial fibrillation (AF) that was symptomatic and/or incompletely controlled	Held until AF was clinically controlled	Restarted at either the original dose or dose level (-1), at the discretion of the treating investigator
Other ≥ Grade 3 toxicity considered related to study drug, including inadequately controlled hypertension (HTN) and/or liver or renal laboratory value abnormalities	Held until recovery to less than or equal to baseline (BL) if BL was greater than Grade 1; held until less than or equal to Grade 1 if BL was less than or equal to Grade 1.	Restarted at either the original dose level or dose level (-1), at the discretion of the treating investigator

Administrative Structure

The Sponsor of the trial is BeiGene USA, Inc and the trial was conducted under sponsor IND. Study management and monitoring was performed by (b) (4) An independent Data Monitoring Committee (DMC) was established to monitor safety data periodically throughout the study and review the interim analysis of efficacy. An independent review committee (IRC) was established to provide an independent and blinded review of imaging and clinical data necessary to assess tumor response. Review was conducted by qualified, board-certified radiologists and hematologists at (b) (4) (formerly known as (b) (4)

Concomitant Medications

Medications that were prohibited and restricted, as well as medications whose use was to be considered cautionary while participating in the trial, are summarized Section 9.4.7 of the CSR.

Treatment Compliance

Compliance was assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian, including patient's diary and pill count on returned study drug containers.

Subject Completion, Discontinuation, or Withdrawal

Zanubrutinib or ibrutinib was taken as prescribed from Cycle 1 Day 1 until disease progression, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or termination of the study by the sponsor. Patients who continued to receive benefit from zanubrutinib after disease progression may have remained in the study upon discussion with the medical monitor

or designee. Patients could voluntarily withdraw consent from treatment at any time and continue into the follow-up phase if the patient withdrew consent from the treatment phase.

The FDA's Assessment:
The Agency agrees with the Applicant's description of the BGB-3111-305 study design. Per protocol, participants received either zanubrutinib 160mg twice daily or ibrutinib 420mg once daily continuously until disease progression, unacceptable toxicity, or withdrawal from the study.

Study Endpoints

The Applicant's Description

Primary Endpoint:

The primary endpoint was overall response rate (PR or higher, defined as CR/CRi + nodular PR + PR) determined by investigator assessment using the "modified" 2008 iwCLL guidelines (Hallek et al 2008Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL and per the Lugano Classification for NHL (Cheson et al 2014) for patients with SLL. While the primary efficacy endpoint was per investigator assessment, overall response rate per independent central review was also analyzed to support the primary analysis. In the United States and China, overall response rate assessed by independent central review will be the primary endpoint for regulatory decisions. According to FDA guidance on endpoints for oncology drugs (2018), ORR rather than PFS (time-to-event) is the most appropriate endpoint for non-inferiority study designs.

Secondary Endpoints:

Key Secondary Endpoints:

The key secondary endpoints were PFS and incidence of atrial fibrillation/flutter.

The key secondary endpoint of PFS was defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurred first, as determined by the investigator. While the key secondary efficacy endpoint was PFS per investigator assessment, PFS per independent central review was also analyzed to support the key secondary endpoint analysis. In the United States and China, PFS assessed by independent central review will be the key secondary endpoint used to support regulatory decisions.

The key secondary endpoint of incidence of atrial fibrillation/flutter was defined as the incidence of treatment-emergent AEs of either "atrial fibrillation" or "atrial flutter."

Other Secondary Endpoints:

- Duration of response, defined as the time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurs first, determined by independent central review

- Duration of response by investigator assessment
- Time to treatment failure, defined as the time from randomization to discontinuation of study drug due to any reason
- Rate of PR-L or higher, defined as the proportion of patients who achieved a CR/CRi + PR + nodular PR + PR-L determined by independent central review
- Rate of PR-L or higher determined by investigator assessment
- Overall survival, defined as the time from randomization to the date of death due to any cause
- PROs measuring HRQoL via the EORTC QLQ-C30 and EQ-5D-5L questionnaires
- Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical exams, and vital signs

The FDA's Assessment:
The FDA generally agreed with description of the primary endpoint. For U.S. regulatory purposes, the primary endpoint was considered to be ORR by IRC, rather than ORR by investigator. The key secondary endpoint was PFS per IRC, rather than PFS per investigator.

Statistical Analysis Plan and Amendments

The Applicant's Description

The SAP was finalized on 12 March 2021 prior to the interim analysis database lock and was based on the protocol version 3.0 dated 31 January 2020.

Analysis sets

- The Intent-to-Treat (ITT) Analysis Set included all randomized patients. The ITT Analysis Set was the primary analysis set for efficacy analyses except for the interim analysis of response endpoints including overall response rate, duration of response, and rate of PR-L or higher, which were based on the first 415 randomized patients as prespecified for the interim analysis.
- The Safety Analysis Set includes all patients who received any dose of study drug. Patient were included in the treatment group corresponding to the actual treatment received. The Safety Analysis Set was used for all safety analyses except for the interim analysis of atrial fibrillation/flutter incidence, which was based on those patients who received any dose of study drug amongst the first 415 patients randomized as prespecified for the interim analysis.
- The Per-Protocol Analysis Set included patients who received any dose of study drug and had no critical protocol deviations. Criteria for exclusion from the Per-Protocol Analysis Set were determined and documented before the database lock for the primary analysis. The noninferiority of overall response rate was also analyzed using the Per-

Protocol Analysis Set and for the interim analysis, this included patients in the Per-Protocol Analysis Set that were among the first 415 patients randomized.

Primary Efficacy Analysis

The primary hypothesis testing for the primary endpoint of overall response rate by investigator assessment (for the United States and China, by independent central review) was to demonstrate the noninferiority of zanubrutinib to ibrutinib. The null and alternative hypotheses for the noninferiority test are as follows:

H_{0NI}: Response Ratio (zanubrutinib/ibrutinib) ≤ 0.8558

H_{aNI}: Response Ratio (zanubrutinib/ibrutinib) > 0.8558

One interim analysis occurred approximately 12 months after 415 patients had been randomized. The final analysis will occur approximately 12 months after 600 patients have been randomized.

A stratified Wald test for the response ratio adjusting for the 4 randomization stratification factors (age [< 65 years versus ≥ 65 years], geographic region [China versus non-China], refractory status [yes or no], and del17p/*TP53* mutation status [present versus absent]) was performed for the noninferiority test against a null response ratio of 0.8558. The treatment effect in overall response rate and its 95% Wald confidence interval (CI) were estimated, and the Clopper-Pearson 95% CIs were calculated for overall response rate for each treatment group. Please refer to the SAP (Appendix 16.1.9 of the BGB-3111-305 CSR) for detailed information on the form of the stratified Wald test and the justification of the noninferiority margin.

If noninferiority is demonstrated either at the interim or the final analysis, further testing for the superiority of zanubrutinib to ibrutinib will be performed using a stratified Cochran-Mantel-Haenszel test (Brannath et al 2003).Brannath et al 2003). The null and alternative hypotheses for the superiority test are as follows:

$H_{0\,SUP}$: Response Ratio (zanubrutinib/ibrutinib) ≤ 1

$H_{a\,SUP}$: Response Ratio (zanubrutinib/ibrutinib) > 1

The monitoring boundaries for the noninferiority and superiority tests were based on the O'Brien-Fleming boundary approximated by the Lan-DeMets spending function and are listed in Table 16 and Table 17. The monitoring boundaries were adjusted based on the actual information fraction (number of patients for overall response rate at the interim and final analysis, which are 415 and 652, respectively). Superiority testing with a 1-sided significance level of 0.005 at the interim analysis and 0.0235 at the final analysis of overall response rate correspond to chi-squared p-value cutoffs of 0.0099 and 0.0469, respectively. Refer to Section 6.4.1 of the SAP for the detail of boundaries and primary efficacy analysis.

A sensitivity analysis of overall response rate using an alternative set of response confirmation rules was performed that counted assessments of PR-L followed by PR or higher as responses.

Table 16: Monitoring Boundaries for the Overall Response Rate Noninferiority Testing

	Number of patients evaluated	Information fraction	1-sided p-value boundary	Approximate response ratio boundary
Interim	415	64%	0.005	1.01
Final	652	100%	0.0235	0.952

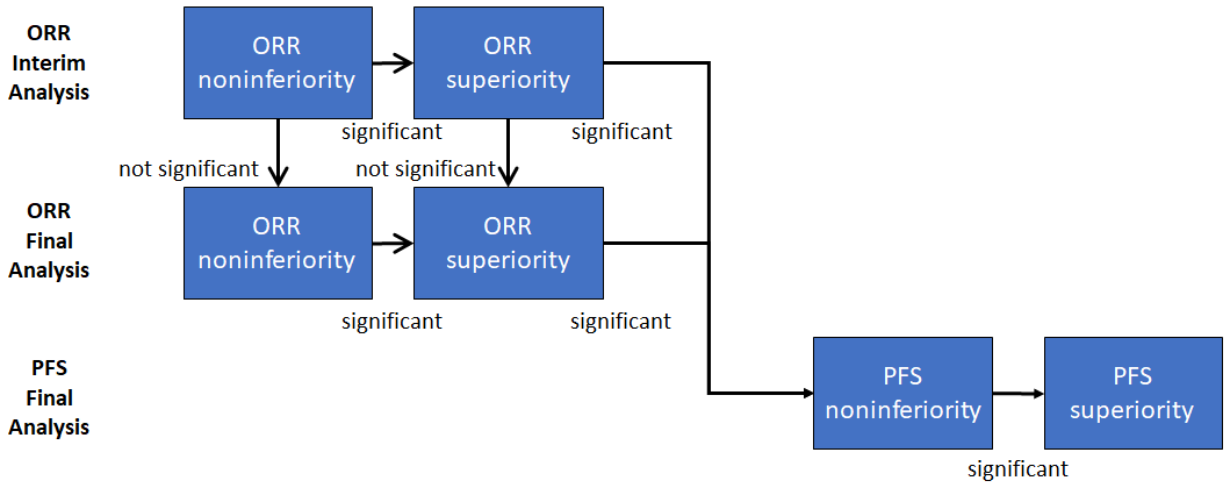
Table 17: Monitoring Boundaries for the Overall Response Rate Superiority Testing

	Number of patients evaluated	Information fraction	1-sided p-value boundary	Approximate response ratio boundary
Interim	415	64%	0.005	1.176
Final	652	100%	0.0235	1.105

Secondary Efficacy Analysis

If the noninferiority and superiority of zanubrutinib to ibrutinib in overall response rate by investigator assessment (for the United States and China, by independent central review) were statistically significant, the treatment effect of the key secondary efficacy endpoint of PFS by investigator assessment (for the United States and China, by independent central review) would be tested for noninferiority under hierarchical testing to control the study-wise type I error. If noninferiority was demonstrated for the key secondary efficacy endpoint of PFS, further testing of superiority would be performed for the endpoint. The multiplicity adjustment approach is presented in Figure 8.

Figure 8: Multiplicity Adjustment for Study BGB-3111-305



If the noninferiority in overall response rate were statistically significant, the key secondary endpoint of atrial fibrillation/flutter incidence would be tested with the same 1-sided significance levels as for overall response rate but would be tested separately from the fixed sequence hierarchical testing of overall response rate and PFS.

Treatment arm comparison for the other secondary efficacy endpoints were descriptive, and no hypothesis testing was performed.

The FDA's Assessment:

The FDA generally agrees with the description of Primary and Secondary Efficacy Analysis plan. As stated by the Applicant, ORR per IRC was considered the primary endpoint for U.S. regulatory purposes. The Agency notes that the Applicant's description represents the interim analysis of ORR. The Agency requested additional data for the final ORR analysis conducted on the entire study population which was submitted during the review cycle. Results of the final ORR analysis are discussed in the sections that follow, and these data, supported by duration of response, are the basis for the regulatory decision and labeling.

To clarify,

- For the primary endpoint ORR by IRC, one interim analysis was to occur approximately 12 months after 415 patients had been randomized and the final analysis of ORR per IRC was to occur approximately 12 months after 600 patients had been randomized. For the key secondary endpoint PFS per IRC, the final analysis was to be conducted when 205 PFS per IRC events occurred
- At the interim analysis of ORR by IRC, noninferiority of ORR per IRC was to be tested at a 1-sided significance level of 0.005. If the noninferiority of ORR per IRC was statistically significant, the superiority of ORR per IRC was to be tested at a 1-sided significance level of 0.005. If the noninferiority of ORR per IRC was statistically significant but the superiority of ORR per IRC was not statistically significant, the superiority of ORR by IRC was to be tested at a 1-sided significance level of 0.0235 at the time of the final analysis of ORR.
- At the final analysis of ORR by IRC, if superiority of ORR by IRC was statistically significant, PFS per IRC was to be compared between the two treatment arms for descriptive purposes only, but not for statistical inference purposes.
- If the superiority of ORR per IRC was statistically significant at either the interim or final analysis of ORR per IRC, PFS per IRC was to be followed further until 205 PFS events per IRC had occurred for the final PFS analysis. Noninferiority of PFS per IRC was to be first tested at a 1-sided significance level of 0.02498; if noninferiority of PFS per IRC was statistically significant, the superiority of PFS per IRC was to be tested at a 1-sided significance level of 0.02498. There was to be a single analysis of PFS per IRC for the purpose of statistical inference when approximately 205 PFS events per IRC occurred.

Protocol Amendments

The Applicant's Description

A summary of global changes to the protocol is provided below by amendment.

Amendment 1 (04 August 2018)

No patients were enrolled before Amendment 1 of the protocol, and a total of 396 patients were enrolled in the study under Amendment 1. The main purpose of this amendment was to revise Inclusion Criterion 9c: increased the upper limit of serum bilirubin to 3.0, revise Exclusion Criterion 11a of HBV reactivation monitoring, and include initial confirmation of progressive disease assessed by CT was sufficient for patients with SLL.

Amendment 2 (29 August 2019)

A total of 39 patients enrolled under Amendment 2 of the study protocol. The main purpose of this amendment was to update study design (including use of local or central laboratories) and study duration (from 7 years to 60 months), allow patients who benefit from zanubrutinib or ibrutinib to enroll in Zanubrutinib Long-Term Extension Study, to add dose modifications and discontinuation guidelines for ibrutinib and zanubrutinib, revise inclusion and exclusion criteria, update information for serious adverse events for reporting and record, revised efficacy assessments including primary endpoint, and to provide clarity and consistency with the rest of protocol.

Amendment 3 (31 January 2020)

A total of 217 patients enrolled under Amendment 3 of the study protocol. The main purpose of this amendment was to:

- Increase the sample size from 400 patients to approximately 600 patients based on recently published ORR results for ibrutinib (Byrd et al. 2019)
- Update the statistical analyses for the primary (overall response rate) and key secondary (progression-free survival) objectives to state that overall response rate was assessed by investigator, with assessment performed by independent central review to support the primary analysis and as the basis of regulatory decisions (in the United States)
- Update the noninferiority and superiority testing analysis summary for the primary endpoint (overall response rate)
- Update analysis summary for key secondary endpoint (PFS) to remove the interim analysis and state that a single analysis would be performed
- Delete summary of planned sensitivity analyses for the primary efficacy endpoint (overall response rate) and the key secondary endpoint (PFS)
- Update study duration to approximately 51 months
- Adde information on warnings and precautions for zanubrutinib.
- Revised zanubrutinib dose reduction for nonhematologic toxicity.

The FDA's Assessment:

The Agency agrees with the Applicant's description of the protocol amendments.

8.1.2.2 Study Results

Compliance with Good Clinical Practices

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor or designee conducted quality assurance audit. The protocol, any amendments, and informed consent form were reviewed and approved by the Institutional Review Board/Independent Ethics Committee in conformance with Good Clinical Practice (GCP) and applicable regulatory requirements.

The Applicant's Position:

A total of 2 sites were audited by BeiGene 2 times during the study. No significant findings were observed. This study was conducted in accordance with sponsor procedures, which comply with the principles of GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

The FDA's Assessment:
The Agency agrees that a statement detailing the methods used to evaluate compliance with Good Clinical Practices and audit certificates were included in the application. In additional, concerns were not identified during the clinical site inspection or inspection of the Applicant.

Financial Disclosure
Data:

Per 21 CFR Part 54, all disclosable financial interests and arrangements with the clinical investigators in Study BGB-3111-305 was tracked and evaluated by Applicant. The submission reports Financial Disclosures for 25 investigators out of total of 1519 in Study BGB-3111-305.

The Applicant's Position:

The Applicant minimized the potential for bias that could be associated with reported Financial Disclosures. The design of the studies aimed to mitigate the potential for investigator bias. Study BGB-3111-305 was a randomized controlled study with primary endpoint ORR assessed by Independent Review Committees (IRCs). The IRC members were completely blinded to treatment arm. Safety and efficacy data were reviewed by an independent data monitoring committee (DMC). In addition, sensitivity analyses taking into account the Financial Disclosures demonstrated that the efficacy and safety data are robust, and patient data from these investigators are consistent with the conclusions drawn from the study results. The applicant concludes that the Financial Disclosures have no impact on the overall benefit/risk analysis for this NDA.

The FDA's Assessment:

The Agency agrees that the financial disclosure information was provided for the 25 investigators and a statement of measures that were undertaken to mitigate potential for bias. The information submitted does not indicate a conflict of interest and it appears that reasonable measures were undertaken to mitigate potential for investigator bias.

The Applicant's Description:

Patient Disposition

Data

Patient disposition for Study BGB-3111-305 (ITT Analysis Set and the first 415 randomized patients) are summarized in Table 18 and Table 19.

The most common reasons for study discontinuation were death and withdrawal by subject. For the first 415 randomized patients, the median follow-up times for zanubrutinib Arm A and ibrutinib Arm B were 15.31 and 15.43 months, respectively. For the ITT Analysis Set, the median follow-up times for zanubrutinib Arm A and ibrutinib Arm B were 13.60 and 13.47 months, respectively. The most common reasons for discontinuing study treatment were adverse event and progressive disease.

Table 18: Patient Disposition and Reasons for Discontinuation (BGB-3111-305 Patients, ITT Analysis Set)

	Zanubrutinib (N = 327)	**Ibrutinib (N = 325)**
Number of patients randomized, n (%)	327 (100.0)	325 (100.0)
Number of patients randomized, but not treated	3 (0.9)	1 (0.3)
Number of patients treated	324 (99.1)	324 (99.7)
Number of patients discontinued from treatment	31 (9.5)	61 (18.8)
Reason for discontinuation		
Adverse Event	23 (7.0)	35 (10.8)
Related to COVID-19	3 (0.9)	4 (1.2)
Progressive Disease	5 (1.5)	16 (4.9)
Withdrawal by Subject	3 (0.9)	7 (2.2)
Physician Decision	0 (0.0)	2 (0.6)
Lost to Follow-up	0 (0.0)	1 (0.3)
Number of patients remained on treatment	293 (89.6)	263 (80.9)
Number of patients discontinued from study	22 (6.7)	35 (10.8)
Reason for discontinuation		
Death	15 (4.6)	23 (7.1)
Related to COVID-19	3 (0.9)	6 (1.8)
Withdrawal by Subject	5 (1.5)	8 (2.5)
Lost to Follow-up	1 (0.3)	1 (0.3)
Other	1 (0.3)	1 (0.3)
Physician Decision	0 (0.0)	2 (0.6)
Number of patients remained in study	305 (93.3)	290 (89.2)

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Study Follow-up Time (Months)		
n	327	325
Mean (SD)	11.49 (6.182)	11.19 (6.249)
Median	13.60	13.47
Q1, Q3	5.36, 16.46	4.83, 16.39
Min, Max	0.1, 23.1	0.1, 26.0

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Note: Study follow-up time is defined as the time from the randomization date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ds-i.sas 23AUG2021 02:31 t-1-ds-i.rtf

Table 19: Patient Disposition and Reasons for Discontinuation (BGB-3111-305 Patients, First 415 Randomized)

	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Number of patients randomized, n (%)	207 (100.0)	208 (100.0)
Number of patients randomized, but not treated	3 (1.4)	1 (0.5)
Number of patients treated	204 (98.6)	207 (99.5)
Number of patients discontinued from treatment	23 (11.1)	50 (24.0)
Reason for discontinuation		
Adverse Event	16 (7.7)	27 (13.0)
Related to COVID-19	1 (0.5)	2 (1.0)
Progressive Disease	4 (1.9)	14 (6.7)
Withdrawal by Subject	3 (1.4)	6 (2.9)
Physician Decision	0 (0.0)	2 (1.0)
Lost to Follow-up	0 (0.0)	1 (0.5)
Number of patients remained on treatment	181 (87.4)	157 (75.5)
Number of patients discontinued from study	18 (8.7)	28 (13.5)
Reason for discontinuation		
Death	11 (5.3)	19 (9.1)
Related to COVID-19	1 (0.5)	4 (1.9)
Withdrawal by Subject	5 (2.4)	6 (2.9)
Lost to Follow-up	1 (0.5)	1 (0.5)
Physician Decision	0 (0.0)	2 (1.0)
Other	1 (0.5)	0 (0.0)
Number of patients remained in study	189 (91.3)	180 (86.5)
Study Follow-up Time (Months)		
n	207	208
Mean (SD)	15.53 (3.601)	15.00 (4.224)
Median	15.31	15.43

	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Q1, Q3	13.86, 17.61	13.60, 17.48
Min, Max	0.1, 23.1	0.1, 26.0

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Note: Study follow-up time is defined as the time from the randomization date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ds-i.sas 23AUG2021 02:31 t-2-ds-fst-i.rtf

The Applicant's Position:
The zanubrutinib arm had a lower percentage of patients discontinuing from treatment compared with the ibrutinib arm both for the first 415 randomized patients (11.1% versus 24.0%, respectively) and for the ITT Analysis Set (9.5% versus 18.8%, respectively), mainly due to lower percentages of patients discontinuing zanubrutinib versus ibrutinib for adverse events and for progressive disease.

The zanubrutinib arm also had a lower percentage of patients discontinuing from the study compared with the ibrutinib arm both for the first 415 patients randomized and for the ITT Analysis Set, primarily due to the lower percentage of deaths in the zanubrutinib arm.

The FDA's Assessment:
The Agency agrees with the Applicant's description of patient disposition based on the original data submitted reflecting the first 415 patients treated. The Applicant submitted additional efficacy data at the Agency's request that included the total ITT population and the final analysis of the primary endpoint (ORR). The topline data and datasets were received on 19 April 2022 with a follow-up CSR received on 30 June 2022 resulting in a major amendment.

The patient disposition for the total ITT population is displayed in the table below and generally, was similar to the interim analysis population. As of the CCOD of 1 Dec 2022, the median time on study was 24.3 months in the zanubrutinib arm and 24.8 months in the ibrutinib arm. The most common reason for treatment discontinuation was an adverse event occurring in 14% in the zanubrutinib arm vs. 18% in the ibrutinib arm.

Table 20: Updated Patient Disposition and Reasons for Discontinuation (BGB-3111-305 Patients, total population N = 652, CCOD December 1, 2021)

	Zanubrutinib (N = 327)	Ibrutinib (N = 325)
Number of patients randomized, n (%)	327 (100.0)	325 (100.0)
Number of patients randomized, but not treated	3 (0.9)	1 (0.3)
Number of patients treated	324 (99.1)	324 (99.7)
Number of patients discontinued from treatment	63 (19)	108 (33)
Reason for discontinuation		
Adverse Event	45 (14)	59 (18)
Progressive Disease	13 (4)	32 (10)
Withdrawal by Subject	4 (1.2)	13 (4)
Physician Decision	0 (0.0)	3 (0.9)
Lost to Follow-up	1 (0.3)	1 (0.3)
Number of patients remained on treatment	261 (80)	216 (67)
Number of patients discontinued from study	47 (14)	68 (21)
Reason for discontinuation		
Death	33 (10)	40 (12)
Withdrawal by Subject	10 (3.1)	17 (5)
Lost to Follow-up	2 (0.6)	1 (0.3)
Other	1 (0.3)	2 (0.6)
Physician Decision	0 (0.0)	8 (2.5)
Number of patients remained in study	280 (86)	257 (79)
Study Follow-up Time (Months)		
Median	24.3	23.8
Q1, Q3	15.2, 27.2	14.4, 26.9
Min, Max	0.1, 34.1	0.1, 37.0

Source: FDA reviewer, ADSL dataset submitted on April 19, 2022

Reviewer comment: Analysis of patient disposition at the final ORR analysis (CCOD of 1 Dec 2022) compared to the primary analysis (CCOD of 20 Dec 2022) did not demonstrate significant differences in trends in reasons for discontinuations and lower rates of discontinuation of therapy due to adverse events.

Protocol Violations/Deviations

The Applicant's Description:

Study conduct was monitored by the CRO and the sponsor's medical monitor (BeiGene). In China, these activities were conducted by BeiGene. Protocol deviations were assessed as either minor or important and reviewed by the CRO or BeiGene's clinical operations team (China) in consultation with the medical monitor before a final determination was made. Important protocol deviations were defined as those that were likely to have had a major impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis. The final determination of important protocol deviations was made by the medical monitor, using the

criteria that define important protocol deviation in the ICH E3 guidelines as follows: eligibility criteria not satisfied, received of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications.

Critical protocol deviations are a subset of important protocol deviations that have the potential to affect the results of analyses of the primary or secondary objectives of the study. Critical protocol deviations were identified and used to define the Per-Protocol Analysis Set.

Important protocol deviations were reported in 5 (1.5%) patients in the zanubrutinib arm and 2 (0.6%) patients in the ibrutinib arm. One patient (b) (6)) had a critical protocol deviation (prohibitive medication or treatment) in the zanubrutinib arm (Table 14.1.1.4.1 and Listing 16.2.2.1). There were no important or critical protocol deviations related to COVID-19 (Table 14.1.1.4.2).

Important protocol deviations are summarized below. Each deviation listed occurred in 1 patient.

- Did not hold the study drug (zanubrutinib) before surgical procedure.
- Missed several monthly HBV DNA PCR monitoring tests. The patient started study treatment (ibrutinib).
- Met protocol Exclusion Criterion 8, which excluded patients who had active fungal, bacteria, and/or viral infection requiring systemic therapy.
- Met Exclusion Criterion 9, patients who had central nervous system involvement by leukemia or lymphoma.
- Given a prohibited medication *(Critical IPD – removed from per-protocol analysis)*.
- Had monthly HBV DNA PCR monitoring test results >100 IU/mL on Cycle 3 and Cycle 4, but the study drug (zanubrutinib) was not interrupted.
- Had a monthly HBV DNA PCR monitoring test result >100 IU/mL on 28 May 2019, but the study drug (ibrutinib) was not interrupted.

The Applicant's Position:
None of the protocol deviations identified were considered to have the potential to impact the overall interpretation of efficacy or safety conclusions from the study.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment that the reported protocol violations were not considered to significantly impact the overall efficacy and safety conclusions for the study.

Table of Demographic Characteristics
Data:

Patient demographics and baseline characteristics in Study BGB-3111-305 (ITT Analysis Set and first 415 randomized patients) are summarized in Table 21.

Table 21: Demographics, Baseline Characteristics and Disease History (Study BGB-3111-305 Patients)

	First 415 patients randomized		ITT Analysis Set	
	Zanubrutinib (N = 207) n (%)	Ibrutinib (N = 208) n (%)	Zanubrutinib (N = 327) n (%)	Ibrutinib (N = 325) n (%)
Sex, n (%)				
Male	142 (68.6)	156 (75.0)	213 (65.1)	232 (71.4)
Female	65 (31.4)	52 (25.0)	114 (34.9)	93 (28.6)
Age (years)				
n	207	208	327	325
Mean (SD)	66.2 (9.98)	67.1 (9.13)	66.7 (10.18)	67.1 (9.18)
Median	67.0	67.0	67.0	68.0
Q1, Q3	60.0, 73.0	61.0, 73.0	60.0, 74.0	61.0, 73.0
Min, Max	35, 90	36, 89	35, 90	35, 89
Age Group, n (%)				
< 65 years	78 (37.7)	80 (38.5)	126 (38.5)	125 (38.5)
≥ 65 and <75 years	88 (42.5)	85 (40.9)	127 (38.8)	131 (40.3)
≥ 75 years	41 (19.8)	43 (20.7)	74 (22.6)	69 (21.2)
Geographic Region, n (%)				
Asia	26 (12.6)	26 (12.5)	49 (15.0)	45 (13.8)
Australia/New Zealand	20 (9.7)	16 (7.7)	28 (8.6)	30 (9.2)
Europe	130 (62.8)	124 (59.6)	198 (60.6)	191 (58.8)
North America	31 (15.0)	42 (20.2)	52 (15.9)	59 (18.2)
Race, n (%) [a]				
Asian	25 (12.1)	25 (12.0)	47 (14.4)	44 (13.5)
White	168 (81.2)	177 (85.1)	261 (79.8)	270 (83.1)
Other	9 (4.3)	1 (0.5)	10 (3.1)	4 (1.2)
Unknown	5 (2.4)	5 (2.4)	9 (2.8)	7 (2.2)
ECOG Performance Status, n (%)				
0-1	203 (98.1)	199 (95.7)	320 (97.9)	312 (96.0)
2	4 (1.9)	9 (4.3)	7 (2.1)	13 (4.0)
Patients with positive HBcAb, n (%) [b]	23 (11.1)	23 (11.1)	37 (11.3)	43 (13.2)
Time from Initial Diagnosis to Randomization (months)				
n	207	208	327	325
Mean (SD)	91.3 (51.91)	93.7 (63.34)	89.5 (55.21)	94.1 (60.43)
Median	87.3	81.3	83.3	82.0
Q1, Q3	49.2, 124.6	49.1, 119.6	47.8, 122.0	50.5, 125.7
Min, Max	6, 302	1, 326	1, 346	1, 326
Disease Type, n (%)				
CLL	200 (96.6)	199 (95.7)	314 (96.0)	309 (95.1)
SLL	7 (3.4)	9 (4.3)	13 (4.0)	16 (4.9)

	First 415 patients randomized		ITT Analysis Set	
	Zanubrutinib (N = 207) n (%)	Ibrutinib (N = 208) n (%)	Zanubrutinib (N = 327) n (%)	Ibrutinib (N = 325) n (%)
Disease Stage, n (%)				
Binet stage A/B or Ann Arbor stage I/II bulky	122 (58.9)	124 (59.6)	181 (55.4)	189 (58.2)
Binet stage C or Ann Arbor stage III/IV	85 (41.1)	84 (40.4)	146 (44.6)	135 (41.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bulky Disease, n (%)				
Any target lesion longest diameter ≥ 5 cm	106 (51.2)	105 (50.5)	145 (44.3)	149 (45.8)
Any target lesion longest diameter ≥ 10 cm	23 (11.1)	23 (11.1)	31 (9.5)	29 (8.9)
Del 17p status, n (%)				
Deleted / Abnormal	24 (11.6)	26 (12.5)	45 (13.8)	50 (15.4)
Not deleted / Normal	183 (88.4)	182 (87.5)	282 (86.2)	275 (84.6)
Del 11q status, n (%)				
Deleted / Abnormal	61 (29.5)	55 (26.4)	91 (27.8)	88 (27.1)
Not deleted / Normal	146 (70.5)	153 (73.6)	236 (72.2)	236 (72.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
TP53 mutation status, n (%)				
Mutated	29 (14.0)	24 (11.5)	50 (15.3)	45 (13.8)
Unmutated	176 (85.0)	184 (88.5)	275 (84.1)	280 (86.2)
Missing	2 (1.0)	0 (0.0)	2 (0.6)	0 (0.0)
Del 17p and/or TP53 mutation status, n (%)				
Present	41 (19.8)	38 (18.3)	75 (22.9)	75 (23.1)
Absent	164 (79.2)	170 (81.7)	250 (76.5)	250 (76.9)
Missing	2 (1.0)	0 (0.0)	2 (0.6)	0 (0.0)
Beta 2 microglobulin, n (%)				
≤ 3.5 mg/L	71 (34.3)	63 (30.3)	104 (31.8)	92 (28.3)
> 3.5 mg/L	113 (54.6)	111 (53.4)	177 (54.1)	183 (56.3)
Missing	23 (11.1)	34 (16.3)	46 (14.1)	50 (15.4)
IGHV mutation status				
Mutated	43 (20.8)	46 (22.1)	77 (23.5)	69 (21.2)
Unmutated	147 (71.0)	148 (71.2)	229 (70.0)	234 (72.0)
Missing	17 (8.2)	14 (6.7)	21 (6.4)	22 (6.8)
Complex Karyotype[c]				
Yes	36 (17.4)	43 (20.7)	56 (17.1)	70 (21.5)
No	101 (48.8)	84 (40.4)	153 (46.8)	130 (40.0)
Missing	70 (33.8)	81 (38.9)	118 (36.1)	125 (38.5)

Source: ADSL, ADBASE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: CLL, chronic lymphocytic leukemia ; SD, standard deviation ; SLL, small lymphocytic lymphoma. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group. HBcAb, Hepatitis B Core Antibody.

Note: Baseline value was the last non-missing result before first dose of study drug (or randomization date if not dosed).
[a] Unknown = Unknown or Not Reported. Other = Other, Multiple, Black or African American, or Native Hawaiian or Other Pacific Islander.
[b] Positive HBcAb = Reactive.
[c] Complex karyotype is defined as having 3 or more abnormalities.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-dm-dh-i.sas 09AUG2021 23:08
t-4-dm-dh-i.rtf

The Applicant's Position:
Demographics were generally balanced between the zanubrutinib and ibrutinib arms amongst the first 415 randomized patients. Most patients were male (zanubrutinib 68.6%; ibrutinib 75.0%). The median age was 67.0 years in both treatment arms. Approximately two-thirds of patients in the 2 arms were ≥ 65 years old. Most patients were white (zanubrutinib 81.2%; ibrutinib 85.1%) and randomized at sites in Europe (zanubrutinib 62.8%; ibrutinib 59.6%). Most patients in both arms had an ECOG PS of 0 or 1 (zanubrutinib 98.1%; ibrutinib 95.7%). Patient characteristics were similarly balanced in the ITT Analysis Set.

The FDA's Assessment:
The Agency agrees with the description of the study population. The Agency notes that racial and ethnic minorities were underrepresented in study BGB-3111-305 compared to a U.S. population. In study BGB-3111-305, 0.9% of patients were Black or African American, 14% were Asian, 0.9% were Black or African American and 0.4% were of Native American or Pacific Islander race. Of the total study population, 0.3% were of Hispanic or Latino ethnicity. The majority (60%) of patients were treated in Europe, with 17% treated in the United States and 14% treated in China. The baseline disease characteristics and prior therapies were similar to what would be expected for the general U.S. population of patients with CLL/SLL.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Data:

Disease history:

Disease history for patients in Study BGB-3111-305 (ITT Analysis Set and first 415 randomized patients) is summarized in Table 21.

Prior Anticancer Therapies:

The most frequently used anticancer therapies were alkylators (other than bendamustine), anti-CD20 antibodies and chemoimmunotherapy (each with prior usage in >75% of patients), and purine analogues (>50% of patients) (Table 22).

Table 22: Prior Systemic Anticancer Therapies (ITT Analysis Set)

	First 415 patients randomized		ITT Analysis Set	
	Zanubrutinib (N = 207) n (%)	Ibrutinib (N = 208) n (%)	Zanubrutinib (N = 327) n (%)	Ibrutinib (N = 325) n (%)
Number of Prior Lines of Systemic Therapy				
n	207	208	327	325
Mean (SD)	1.7 (1.01)	1.9 (1.25)	1.7 (1.00)	1.8 (1.15)
Median	1.0	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	1, 6	1, 8	1, 6	1, 8
Number of Prior Lines of Systemic Therapy, n (%)				
1	116 (56.0)	110 (52.9)	192 (58.7)	190 (58.5)
2	57 (27.5)	49 (23.6)	87 (26.6)	68 (20.9)
3	19 (9.2)	28 (13.5)	26 (8.0)	40 (12.3)
≥ 4	15 (7.2)	21 (10.1)	22 (6.7)	27 (8.3)
Patients with any prior use of following, n (%)				
Anti-CD20 antibody	176 (85.0)	172 (82.7)	274 (83.8)	268 (82.5)
Alkylators (other than bendamustine)	178 (86.0)	165 (79.3)	274 (83.8)	259 (79.7)
Purine analogue	118 (57.0)	105 (50.5)	178 (54.4)	168 (51.7)
Bendamustine	51 (24.6)	66 (31.7)	84 (25.7)	95 (29.2)
PI3K/SYK inhibitor	8 (3.9)	10 (4.8)	11 (3.4)	19 (5.8)
BCL2 inhibitor	2 (1.0)	3 (1.4)	7 (2.1)	8 (2.5)
iMiD	3 (1.4)	1 (0.5)	6 (1.8)	1 (0.3)
Alemtuzumab	0 (0.0)	1 (0.5)	2 (0.6)	1 (0.3)
Chemoimmunotherapy	166 (80.2)	158 (76.0)	260 (79.5)	246 (75.7)

Source: ADSL, ADCM, ADBASE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Notes: For patients with any prior systemic anticancer therapy, percentages were based on number of patients in the Intent-to-Treat Analysis Set; For others, percentages were based on the number of patients with any prior systemic anticancer therapy.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-prior-anticanc-i.sas 09AUG2021 23:09 t-5-prior-anticanc-i.rtf

The Applicant's Position:
Baseline disease characteristics showed the following trends:

- Disease history was generally comparable between the ibrutinib and zanubrutinib arms in the ITT Analysis Set and first 415 patients randomized. In the first 415 randomized patients, the median time from initial diagnosis to randomization was 87.3 months in the zanubrutinib arm and 81.3 months in the ibrutinib arm.
- All patients in the ITT Analysis Set received prior systemic anticancer therapy. The proportion of patients who had received these anticancer agents was comparable between

the zanubrutinib arm and the ibrutinib arm. The median number of prior lines of systemic therapy was 1.0 in both arms. The majority of the patients had received prior chemoimmunotherapy in any prior line of therapy (79.5% in the zanubrutinib arm and 75.7% in the ibrutinib arm)

The FDA's Assessment:
The Agency agrees with the Applicant's assessment of baseline characteristics of the study population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Data:
Compliance with study drug administration was measured using review of patient diaries and tablet counts at each study visit.

Concomitant Medications

Almost all patients received ≥ 1 concomitant medication (94.8% in the zanubrutinib arm; 96% in the ibrutinib arm).

The most common concomitant medications in both arms were antibacterials for systemic use (185 [57.1%] patients in the zanubrutinib arm and 197 [60.8%] patients in the ibrutinib arm), antigout preparations (159 [49.1%] patients in the zanubrutinib arm and 184 [56.8%] patients in the ibrutinib arm), and antivirals for systemic use (145 [44.8%] patients in the zanubrutinib arm and 157 [48.5%] patients in the ibrutinib arm).

The percentage of patients who received analgesics was higher for patients in the ibrutinib arm (117 [36.1%] patients) compared with those in the zanubrutinib arm (90 [27.8%] patients).

Use of psycholeptics was more common in the ibrutinib-treated patients (76 [23.5%] patients) compared with the zanubrutinib-treated patients (47 [14.5%] patients).

The percentage of patients who received any concomitant growth factor or transfusion use was comparable between the zanubrutinib arm (59 [18.2%] patients) and the ibrutinib arm (57 [17.6%] patients). Of these, 36 (11.1%) patients in the zanubrutinib arm and 36 (11.1%) patients in the ibrutinib arm received colony stimulating factors. Red blood cell transfusions were received by 24 (7.4%) patients in the zanubrutinib arm and 28 (8.6%) patients in the ibrutinib arm. Platelet transfusions were received by 7 (2.2%) patients in the zanubrutinib arm and 7 (2.2%) patients in the ibrutinib arm

The Applicant's Position:
Overall, the concomitant treatments administered were balanced on medications and were representative of those commonly prescribed for patients of the target population. They were not considered to have impacted the study results.

The FDA's Assessment:
The Agency agrees with the Applicant's position regarding concomitant medication use.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Overall Response Rate Assessed by Independent Central Review

Efficacy results for the primary endpoint of overall response rate by independent central review are based on the first 415 patients randomized. With a median follow-up of 15 months on the first 415 patients enrolled into the study, the study met its primary endpoint. Overall response rate was higher for patients in the zanubrutinib arm (76.3% [95% CI: 69.9, 81.9]) compared with the ibrutinib arm (64.4% [95% CI: 57.5, 70.9]). The response ratio was 1.17 (95% CI: 1.04, 1.33). In this assessment, noninferiority to ibrutinib was demonstrated with a statistically significant 1-sided p-value < 0.0001 versus the prespecified 1-sided alpha of 0.005. Zanubrutinib fell short of demonstrating superiority by 0.0022 with a 2-sided p-value of 0.0121 versus the prespecified 2-sided alpha of 0.0099.

Table 23: Interim Analysis of Disease Response by Independent Central Review (ITT Analysis Set, First 415 Randomized Patients)

Response Category	**Zanubrutinib (N = 207)**	**Ibrutinib (N = 208)**
Best Overall Response, n (%)		
Complete response	3 (1.4)	2 (1.0)
Complete response w/incomplete bone marrow recovery	0 (0.0)	0 (0.0)
Nodular partial response	1 (0.5)	0 (0.0)
Partial response	154 (74.4)	132 (63.5)
Partial response w/lymphocytosis	19 (9.2)	36 (17.3)
Stable disease	21 (10.1)	25 (12.0)
Non-progressive disease	1 (0.5)	0 (0.0)
Progressive disease	1 (0.5)	4 (1.9)
Not evaluable	1 (0.5)	1 (0.5)
Discontinued prior to first assessment	6 (2.9)	7 (3.4)
Not assessed	0 (0.0)	1 (0.5)
Overall Response Rate[a], n (%)	158 (76.3)	134 (64.4)
(95% CI)[d]	(69.9, 81.9)	(57.5, 70.9)
Response ratio[b] (95% CI)		1.17 (1.04, 1.33)
	Noninferiority 1-sided p-value[c] = <0.0001	
	Superiority 2-sided p-value[c] = 0.0121	
Time to Response (Months)		
n	158	134
Mean (SD)	5.48 (2.710)	6.30 (3.154)
Median	5.55	5.63
Q1, Q3	2.92, 8.28	3.12, 8.34
Min, Max	2.7, 14.0	2.7, 16.7

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Rate of CR/CRi, n (%)	3 (1.4)	2 (1.0)
(95% CI)[d]	(0.3, 4.2)	(0.1, 3.4)
Rate of PR-L or Higher, n (%)	177 (85.5)	170 (81.7)
(95% CI)[d]	(80.0, 90.0)	(75.8, 86.7)

Source: ADSL, ADTTEIRC, ADRSIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CR, complete response; CRi, complete response w/incomplete bone marrow recovery; PR-L, partial response w/lymphocytosis.
[a] Responders are defined as patients with a best overall response of partial response or higher.
[b] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.
[c] P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.
[d] Clopper-Pearson confidence interval.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-orrirc-i.sas 09AUG2021 23:11 t-7-eff-orrirc-i.rtf

Sensitivity and Subgroup Analyses of Overall Response Rate Assessed by Independent Central Review

Several sensitivity analyses of the overall response rate were prespecified in the SAP. Among these were an analysis of the Per-protocol Analysis Set, an analysis that counted assessments of PR-L that were subsequently followed by PR or higher responses as confirmed best overall responses of PR for CLL patients, an analysis that accounted for disease progression due to study drug interruption, and an analysis that accounted for the impact of deaths due to COVID-19. Results in each of these sensitivity analyses were consistent with the overall response rate as assessed by independent central review for the first 415 randomized patients in the ITT Analysis Set.

Further, in prespecified analyses, a higher overall response rate per independent central review was observed in the zanubrutinib arm in all analyzed demographic or disease subgroups, notably including the more difficult to treat subgroups of patients harboring either del17p and/or *TP53* mutations (risk difference: 25.2% [95% CI: 5.3, 45.2]).

Overall Response Rate by Investigator Assessment: Protocol Specified Primary Endpoint

The overall response rate was higher for patients in the zanubrutinib arm (78.3% [95% CI: 72.0, 83.7]) compared with the ibrutinib arm (62.5% [95% CI: 55.5, 69.1]) as assessed by the investigator. Zanubrutinib demonstrated noninferiority (NI margin: 0.8558) to ibrutinib with a response ratio of 1.25 (95% CI: 1.10, 1.41), with a statistically significant 1-sided p-value < 0.0001 versus the prespecified 1-sided alpha of 0.005. Furthermore, zanubrutinib demonstrated superiority to ibrutinib with a statistically significant 2-sided p-value of 0.0006 versus the prespecified 2-sided alpha of 0.0099.

<u>The Applicant's Position:</u>

Zanubrutinib demonstrated non-inferiority to ibrutinib in overall response rate per independent central review with an observed response rate of 11.9% that was higher than that for ibrutinib (95% CI for rate difference: 3.2, 20.6). Results for investigator-assessed overall response rate were consistent with those assessed by independent central review and demonstrated not only the noninferiority of zanubrutinib to ibrutinib but superiority as well. A higher overall response rate was observed in the zanubrutinib arm compared with the ibrutinib arm across all analyzed subgroups, including the more difficult to treat subgroup of patients harboring either del17p and/or *TP53* mutations.

Overall response rate is a direct measure of drug antitumor activity, not attributable to natural history, and in certain cancers, it has been used as a direct measure of clinical benefit and utilized as a regulatory endpoint to support cancer drug approvals (FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [2018]).

The FDA's Assessment:

FDA notes that the description by the Applicant above represents a prespecified interim analysis for ORR which included the first 415 patients enrolled with a CCOD of 30 Dec 2020. At the Agency's request, the Applicant provided results from the prespecified final analysis of ORR which included all patients enrolled N = 652 with a CCOD of 1 Dec 2021 and are detailed below. This data was submitted during the review cycle resulting in a major amendment. The results from the final analysis of ORR per IRC, supported by durability, were the Agency's primary determinants of efficacy for study BGB-3111-305.

FDA disagrees that ORR non-inferiority and superiority were demonstrated based on risk difference. The difference in response rate (risk difference) was not planned to be estimated or tested in the SAP, was not discussed in the CSR, and there was no alpha allocation for testing difference in response rate prespecified in the SAP or protocol; therefore, no inference should be drawn based on the estimation of difference in response rate. Instead, the prespecified measure to demonstrate efficacy of zanubrutinib was response rate ratio (risk ratio), and the sample size determination and testing plan were designed based on response rate ratio as well. Thus, to demonstrate the efficacy of zanubrutinib vs Ibrutinib, the estimates of the prespecified measure, response rate ratio, should be evaluated.

In the final analysis (Table 24 and

Table 25), the study met the primary endpoint in assessment of ORR per IRC. ORR per IRC was higher for patients in the zanubrutinib arm compared with the ibrutinib arm (80.4% vs 72.9%). The response rate ratio per IRC was 1.10 (95% CI: 1.01, 1.20). In this assessment, superiority to ibrutinib was demonstrated with a statistically significant 2-sided p-value = 0.0264 versus the prespecified 2-sided alpha of 0.047. ORR by investigator in zanubrutinib was numerically higher compared with ibrutinib arm (79.5% vs 71.1%) with a response rate ratio of 1.12 (95% CI: 1.02, 1.22), which was supportive to the ORR per IRC results.

Duration of response at the time of final ORR analysis is summarized in Table 26.

Table 24: Final Analysis of ORR per IRC in Study BGB-3111-305

Outcome	Zanubrutinib (N=327)	Ibrutinib (N=325)
Overall response rate[a]		
ORR, n (%)	263 (80)	237 (73)
(95% CI, %)	(76, 85)	(68, 78)
CR, n (%)	13 (4.0)	8 (2.5)
nPR, n (%)	1 (0.3)	0 (0)
PR, n (%)	249 (76)	229 (70)
Response Rate Ratio (95% CI)[c]	1.10 (1.01, 1.20)	
2-sided p-value[b]	0.0264 [b]	
Time to response		
Median (range), months	5.5 (2.6 to 22.1)	5.6 (2.3 to 19.8)

Source: FDA analysis. Data Cutoff Date: December 01, 2021.
[a] Defined as CR + CRi + nPR + PR. No patients had CRi as best response.
[b] 2-sided significance level of 0.0469 was allocated for ORR superiority testing.

Table 25: Final Analysis of ORR per IRC and Investigator Assessment in Study BGB-3111-305

Final Analysis	Zanubrutinib (n=327) Event/Total (%)	Ibrutinib (n=325) Event/Total (%)	Response Rate Ratio (95% CI)[a]
ORR by IRC: n (%) events	263/327 (80.4%)	237/325 (72.9%)	1.10 (1.01, 1.20); Superiority: p=0.0264 (2-sided)[b]
ORR by Investigator: n (%) events	260/327 (79.5%)	231/325 (71.1%)	1.12 (1.02, 1.22)[c]

Source: FDA analysis. Data Cutoff Date: December 01, 2021.
[a] Response rate ratio was calculated for ORR by IRC.
[b] Prespecified significance level of 0.0469
[c] ORR by Investigator was the secondary endpoint and had no alpha allocation in the testing plan; therefore, the p-value was not reported.

Data Quality and Integrity

Data:
The applicant submitted this sNDA including the data to the FDA CDER Electronic Document Room (EDR). The data in this submission are in electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submission. The data sets are well documented and included definition files.

The Applicant's Position:
No issues were identified with the data quality or integrity from BGB-3111-305 which could affect the efficacy results.

The FDA's Assessment:
The Agency agrees.

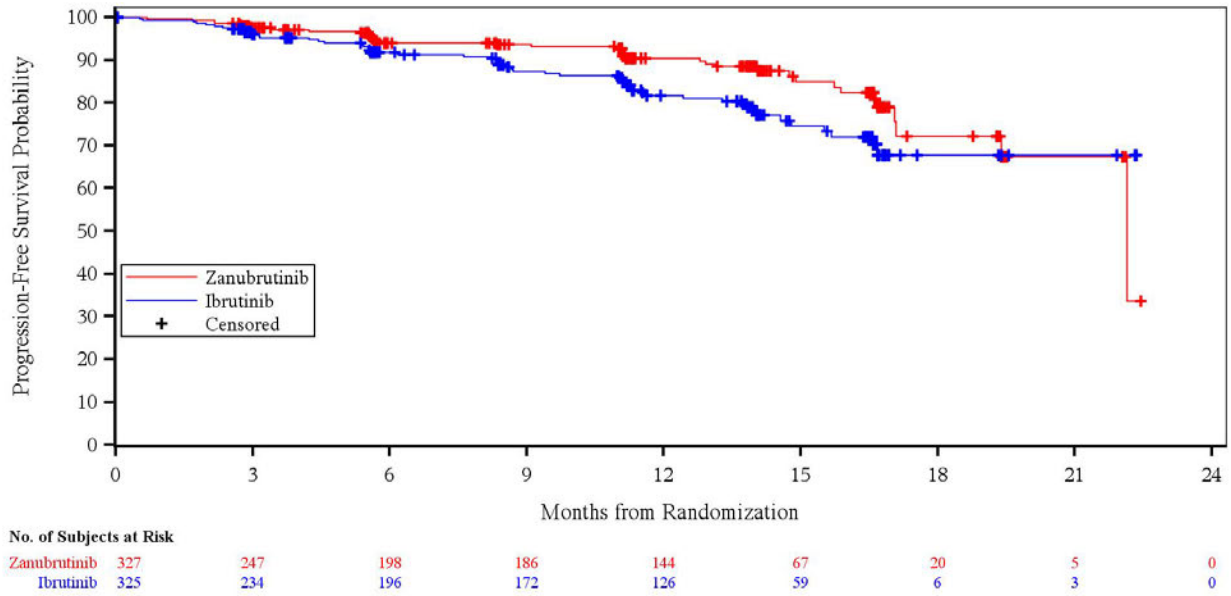
Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Progression-Free Survival

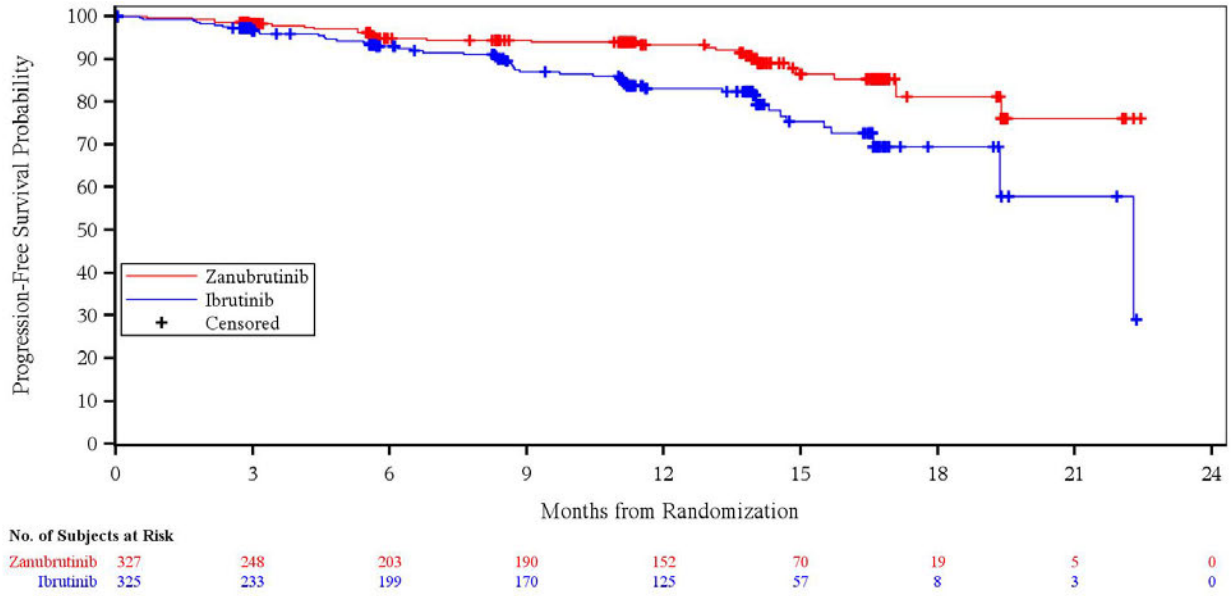
The hazard ratio for PFS in the ITT Analysis Set assessed by IRC was 0.61 (95% CI: 0.39, 0.95) for the zanubrutinib arm compared with the ibrutinib arm. The 12-month event-free rate was 90.4% in the zanubrutinib arm and 81.7% in the ibrutinib arm in the ITT Analysis Set. PFS events as assessed by IRC were observed in 36 (11.0%) patients in the zanubrutinib arm and 52 (16.0%) patients in the ibrutinib arm. The median follow-up time was 11.3 months in both arms.

Figure 9: Kaplan-Meier Curve of Progression-Free Survival by Independent Central Review (Intent-to Treat Analysis Set)



Results for PFS as assessed by investigator were consistent with those as assessed by independent central review. In the ITT Analysis Set, the hazard ratio for investigator-assessed PFS was 0.47 (95% CI: 0.29, 0.76) favoring the zanubrutinib arm compared with the ibrutinib arm. The 12-month event-free rate was 93.3% in the zanubrutinib arm and 83.1 % in the ibrutinib arm in the ITT Analysis Set. PFS events were observed in 27 (8.3%) patients in the zanubrutinib arm and 50 (15.4%) patients in the ibrutinib arm. The median follow-up time was 11.6 months in the zanubrutinib arm and 11.3 months in the ibrutinib arm.

Figure 10：Kaplan-Meier Curve of Progression-Free Survival by Investigator Assessment (Intent-to Treat Analysis Set)



Amongst the first 415 patients randomized, PFS assessed by independent central review was prolonged with a hazard ratio of 0.55 (95% CI: 0.34, 0.90) favoring the zanubrutinib arm compared with the ibrutinib arm. For PFS by investigator assessment, the hazard ratio was 0.40 (95% CI: 0.23, 0.69) favoring the zanubrutinib arm compared with the ibrutinib arm.

Duration of Response

Based on investigator-assessed duration of response in the first 415 randomized patients, 162 of 207 (78.3%) patients were responders in the zanubrutinib arm, and 130 of 208 (62.5%) patients were responders in the ibrutinib arm. At 12 months, 89.8% of responders treated with zanubrutinib remain event-free, and 77.9% of responders treated with ibrutinib remain event-free.

Duration of response as assessed by independent central review yielded similar results with the 12-month event-free rates of 90.3% in the zanubrutinib arm and 78.0% in the ibrutinib arm.

The FDA's Assessment:

The Applicant provided updated data reflecting the final ORR analysis of the ITT population (CCOD 1 Dec 2021). In general results regarding durability of response were consistent with those at the time of interim ORR analysis. With an estimated median follow-up of 14.1 months, the median DOR was not reached for either arm. The estimated 1-year DOR rate was 92% for the zanubrutinib arm and 86% for the ibrutinib arm. This comparison is descriptive. The PFS results are discussed in the FDA section below.

Table 26: Duration of Response per IRC in Study BGB-3111-305 (CCOD 1 Dec 2021)

Outcome per IRC	**Zanubrutinib (N=327)**	**Ibrutinib (N=325)**
Objective response, n (%)	263 (80)	237 (73)
(95% CI, %)	(76, 85)	(68, 78)
Duration of response		
Median DOR (95% CI) [a]	NE (NE, NE)	NE (NE, NE)
Range, months	(1.4 to 30.4+)	(1.9+ to 30.8+)
Rate at 12 months, % (95% CI) [a]	92 (87, 95)	86 (80, 91)

Source: FDA analysis

[a] Based on Kaplan-Meier estimate. Estimated median follow-up for DOR was 14.1 months.

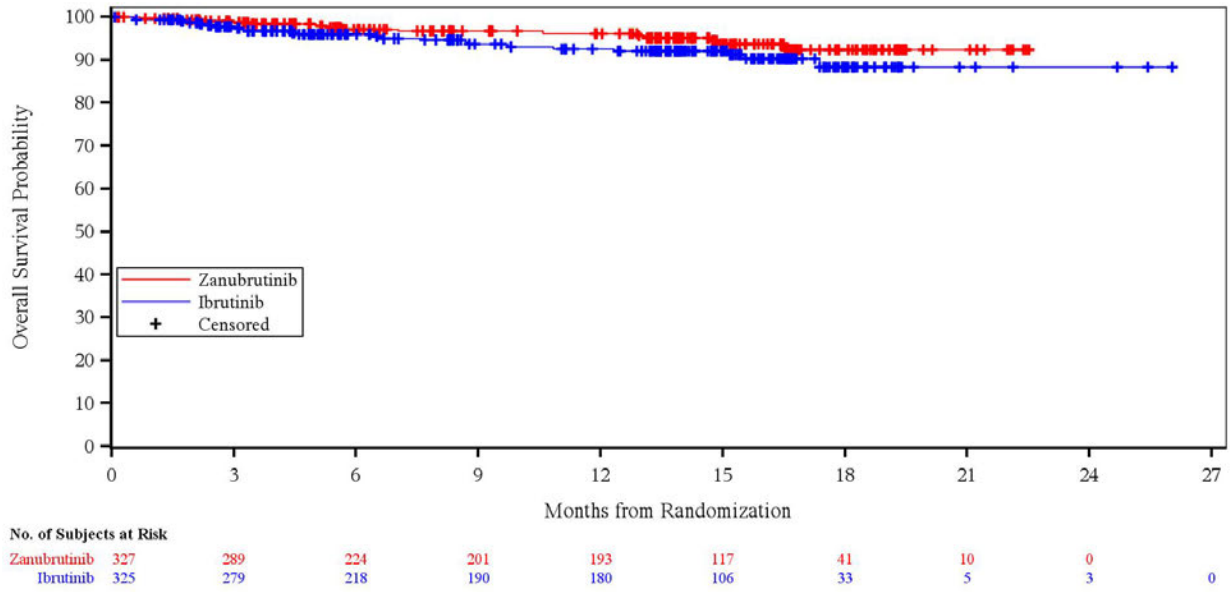
Overall Survival

Data

As of the data cutoff date, the 12-month event-free rate for overall survival in the first 415 randomized patients was 97.0% in the zanubrutinib arm and 92.7% in the ibrutinib arm.

In the larger ITT Analysis Set (N = 652 patients), there were 15 (4.6%) deaths reported in the zanubrutinib arm and 23 (7.1%) deaths reported in the ibrutinib arm, with median follow-up time of 13.8 months in the zanubrutinib arm and 13.6 months in the ibrutinib arm. Although few deaths had occurred at the time of data cutoff, the initial Kaplan-Meier estimate trends for overall survival appear to favor zanubrutinib over ibrutinib. The 12-month event-free rate was 96.2% in the zanubrutinib arm and 92.6% in the ibrutinib arm. Thus, survival was consistent when evaluated over a larger set of patients from the study.

Figure 11： Kaplan-Meier Curve of Overall Survival (ITT Analysis Set)



Atrial fibrillation/flutter

Atrial fibrillation/atrial flutter rate, a key secondary endpoint as prespecified in the SAP, was analyzed for dosed patients among the first 415 randomized and is summarized in Table 27. Patients in the zanubrutinib arm (5 [2.5%] patients) had a statistically significant lower frequency of atrial fibrillation/flutter compared with patients in the ibrutinib arm (21 [10.1%] patients). The rate difference between the 2 arms was -7.7% (95% CI: -12.3, -3.1) and met statistical significance with a 2-sided p-value of 0.0014.

Table 27: Analysis of Atrial Fibrillation/Flutter (Safety Analysis Set, Among the First 415 Patients Randomized)

Response Category	Zanubrutinib (N = 204)	Ibrutinib (N = 207)
Rate of Atrial Fibrillation/Flutter[a], n(%)	5 (2.5)	21 (10.1)
(95% CI)	(0.8, 5.6)	(6.4, 15.1)
Rate difference[b], % (95% CI)		-7.7 (-12.3, -3.1)
		2-sided p-value = 0.0014

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
[a] Patients reported a treatment-emergent adverse event with a preferred term of atrial fibrillation or atrial flutter.
[b] Rate difference is the zanubrutinib rate minus the ibrutinib rate.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-afib-i.sas 09AUG2021 23:13 t-9-afib-i.rtf

Patient-Reported Outcomes

Patients in the zanubrutinib arm experienced a greater improvement in health-related quality of life in comparison to the patients in the ibrutinib arm as observed in clinically meaningful improvements from baseline to key clinical Cycle 7, indicated by estimated mean treatment difference at Cycle 7 (95% CI) in the PRO endpoints of GHS/QoL (3.45 [95% CI: 0.29, 6.61]), fatigue (-2.95 [95% CI: -6.07, 0.17]) and physical functioning (2.63 [95% CI: 0.19, 5.08]), as well as at Cycle 13 in diarrhoea (-2.50 [95% CI: -5.24, 0.23]).

The Applicant's Position:

Progression-free survival assessed by independent central review and by investigator were both prolonged with zanubrutinib compared with ibrutinib as evidenced by higher landmark event-free rates. In addition, a favorable trend in overall survival was noted, so overall response rate, progression-free survival and overall survival all showed consistent benefit with zanubrutinib.

The rate of atrial fibrillation/flutter was shown to be significantly lower for zanubrutinib than for ibrutinib with a four-fold lower incidence (2.5% versus 10.1%).

PRO endpoints showed consistent pattens of improvement with zanubrutinib as observed for other secondary endpoints.

The FDA's Assessment:

Efficacy

The Applicant's description of PFS per IRC above reflects the PFS at the interim analysis timepoint (CCOD of December 30, 2020). In the interim analysis of ORR, the ORR superiority endpoint was met per investigator but not met per IRC. No further PFS analysis was suggested at this time point.

The data below reflects the outcomes at the time of the final analysis for ORR with a CCOD of December 1, 2021. In the final analysis of ORR, the ORR superiority endpoint per IRC was met, thus the analysis of PFS per IRC was conducted although this was descriptive only, not for inferential purposes.

At the time of the final ORR analysis (CCOD December 1, 2021), the hazard ratio for PFS per IRC (ITT) was 0.61 (95% CI: 0.44, 0.86) for the zanubrutinib arm compared with the ibrutinib arm (Table 28 and Figure 12). IRC-assessed PFS events occurred in 60/327 (18.3%) patients in the zanubrutinib arm and 87/325 (26.8%) patients in the ibrutinib arm. The Kaplan-Meier plot is shown in Figure 12.

Results for PFS per investigator and PFS per IRC were consistent. In the ITT Analysis Set, the HR for investigator-assessed PFS was 0.55 (95% CI: 0.39, 0.76) favoring the zanubrutinib arm.

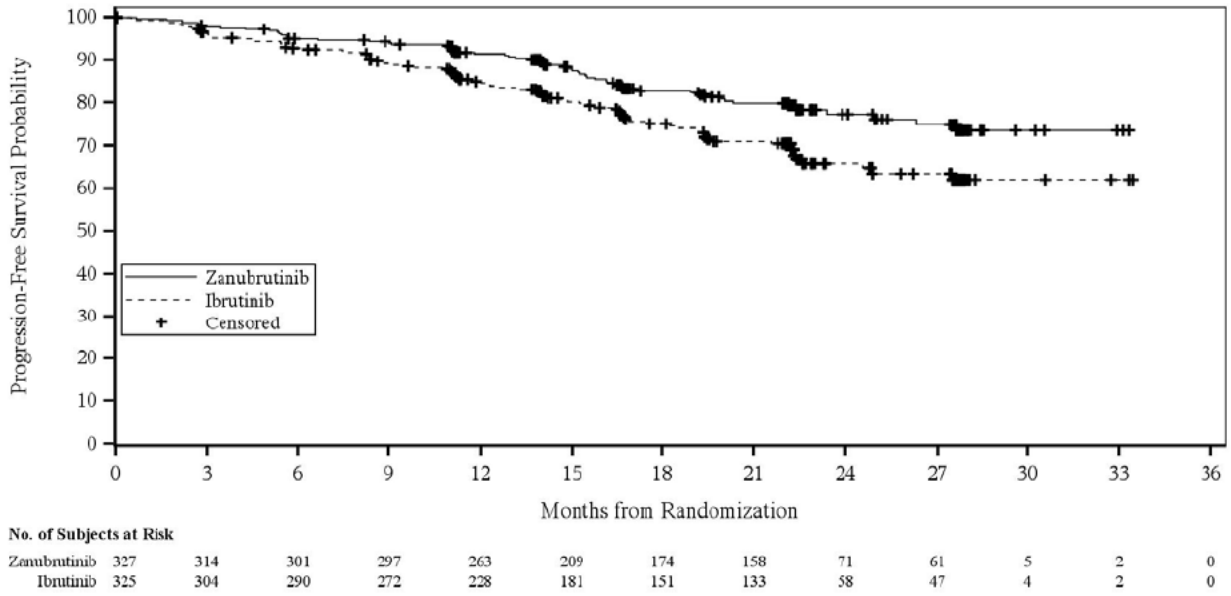
OS data were immature. In the ITT Analysis Set, deaths were reported in 10.1% of the zanubrutinib arm and 12.3% of the ibrutinib arm; the OS HR was 0.80 (95% CI: 0.50, 1.28) with ibrutinib as the reference group.

Table 28: Analyses of PFS and OS at the Time of Final ORR Analysis in Study BGB-3111-305

Final Analysis	Zanubrutinib N=327	Ibrutinib N=325	Hazard Ratio (95% CI)[a]
PFS by IRC: Event/N (%)	60/327 (18.3)	87/325 (26.8)	0.61 (0.44, 0.86)[b]
PFS by Investigator: Event/N (%)	58/327 (17.7)	91/325 (28.0)	0.55 (0.39, 0.76)[c]
OS: Event/N (%)	33/327 (10.1)	40/325 (12.3)	0.80 (0.50, 1.28)[c]

Source: FDA analysis. CCOD: December 01, 2021.
[a] Hazard Ratio was calculated for PFS per IRC and OS.
[b] PFS per IRC analysis was considered as descriptive analysis at the timepoint of final analysis of ORR.
[c] As the secondary endpoint, PFS by investigator or OS analysis did not have alpha allocation prespecified in the SAP, thus the analyses were descriptive only.

Figure 12: Kaplan-Meier Plot of PFS per IRC at the Time of Final ORR Analysis in Study BGB-3111-305



Source: Applicant's analysis; CCOD, December 01, 2021

Comparative safety and PRO-related claims

The Agency does not agree with the Applicant's position regarding the significance of the findings of the secondary endpoint of atrial fibrillation. While the difference in the rates of atrial fibrillation (all grades) met the Applicant's prespecified criteria for significance favoring zanubrutinib, the Agency cannot conclude that the results represent a clinically meaningful

difference in the rates of atrial fibrillation. (b) (4)
(b) (4)
(b) (4) See section 8.2.5.2 for additional discussion of atrial fibrillation.

The Agency does not agree with the Applicant's claims of improved PRO-related metrics in the zanubrutinib arm given the descriptive nature of the PRO endpoints, with lack of prespecified hypothesis testing or multiplicity control.

Dose/Dose Response

Data:
See Section 6.2.1 and Section 6.2.2.

The Applicant's Position:
Dose response was evaluated using population PK and expose-response analyses.

The FDA's Assessment:
Refer to section 6.2 regarding PK and exposure-response analyses.

Persistence of Effect

The Applicant's Position:

Study BGB-3111-305 is still ongoing. With the median follow-up duration of approximately 15 months, persistence of effects of zanubrutinib have been demonstrated by the results of ORR, DOR, PFS and OS on the treatment of patients with R/R CLL/SLL, as presented in the above Efficacy Results.

The FDA's Assessment:
Persistence of effect is not evaluable in this study, because this refers to persistence of the treatment effect after study drug discontinuation, and zanubrutinib was administered continuously.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

See "Patient-Reported Outcomes" under "Efficacy Results – Secondary and other relevant endpoints"

The FDA's Assessment:
Refer to above-referenced section.

8.1.3 Supportive Studies

Study BGB-3111-AU-003

Study BGB-3111-AU-003 was a Phase 1/2, open-label, multiple-dose, multicenter, international dose-escalation (Part 1), and expansion (Part 2) study designed to investigate the safety and PK of zanubrutinib in patients with B-cell malignancies. This first in human study for zanubrutinib has been completed. A total of 125 patients with CLL/SLL were enrolled in the study with a median duration of treatment of 37.13 months (range: 0.8 to 71.5 months) for patients with R/R CLL/SLL, and 49.17 months (range: 3.6 to 65.3 months) for patients with TN CLL/SLL. Data for these patients are presented in Module 2.7.3 and briefly below.

The study was conducted at sites in Australia, New Zealand, Italy, South Korea, the UK, and the USA. The study was conducted in two parts and included patients with TN (N = 22) and R/R CLL/SLL (n = 103) who received ≥ 1 dose of study drug. This dose-finding and expansion study was the first in human study for zanubrutinib and has a median follow-up time of 50.87 months (range: 11.1 to 65.3 months) for patients with TN CLL/SLL and a median follow-up time of 40.44 months (range: 5.3 to 71.5 months) for patients with R/R CLL/SLL. These extensive data help to support high overall response rates, long duration of response, and long PFS in patients with CLL/SLL treated with zanubrutinib. Results from Study BGB-3111-AU-003 demonstrate that zanubrutinib is safe and effective in patients with CLL/SLL.

Efficacy results for Study BGB-3111-AU-003 are briefly described here. In patients with R/R CLL/SLL, the overall response rate (PR with lymphocytosis or better) was high at 94.2% (97 of 103 patients; 95% CI: 87.8, 97.8). The overall response rate was similar in patients with del(17p) mutation (92.3% [12 of 13 patients; 95% CI: 64.0, 99.8]). The PR or better rate overall was 90.3%, with a lower rate in patients with del(17p) mutations (84.6%). The CR/CRi rate was 15.5% overall, with a rate of 7.7% (1 patient) in patients with del(17p)+ disease. The overall response rate (PR-L or better) and the PR or better rate in patients with TN CLL/SLL was 100.0% (22 patients; 95% CI: 84.9, 100.0 for both), with no difference in either rate according to del(17p) mutation status. The CR/CRi rate overall was 22.7%; none of the patients with del(17p) achieved a CR.

In patients with R/R CLL/SLL, the median PFS was 61.4 months (95% CI: 50.4 months, not evaluable) with a median follow-up of 39.4 months. Twenty-four (23.3%) events were observed, including 23 events of disease progression and 1 death. The median PFS was lower in patients with del(17p) (50.2 months) than in patients without del(17p) (61.4 months). Overall, PFS rates at 12, 24, and 36 months were 96.0%, 90.6%, and 82.8%, respectively. Lower rates were observed in patients with del(17p) disease (92.3%, 75.5%, and 75.5% at 12, 24, and 36 months, respectively).

Among patients with TN CLL/SLL, the median PFS was not evaluable (95% CI: 41.4 months, not evaluable) with a median follow-up of 49.4 months. Events were observed in 5 patients (22.7%), including 4 disease progression events and 1 death. Progression-free survival rates overall at 12, 24, 36, and 48 months were 95.2%, 90.5%, 81.0%, and 74.4%, respectively.

The median overall survival for patients with CLL/SLL was not reached after a median follow-up time of 48.9 months (range: 5.3 to 71.5 months). Overall survival rates for patients with CLL/SLL on the study were 98.4%, 95.8%, 91.1%, and 86.2% at 12, 24, 36, and 48 months, respectively.

Rates were similar for patients with TN disease (100.0%, 95.2%, 90.5%, and 90.5% at 12, 24, 36, and 48 months, respectively) and R/R disease (98.0%, 95.9%, 91.2%, and 84.6% at 12, 24, 36, and 48 months, respectively).

In patients with R/R CLL/SLL, overall survival was also similar in patients with del(17p)+ and del(17p)- CLL/SLL. The median overall survival was not reached after a median follow-up time of 44.5 months (range: 9.4 to 62.6 months) for patients with del(17p)+ and 49.3 months (range: 5.8 to 71.5 months) for patients with del(17p)- CLL.

Study BGB-3111-205

Study BGB-3111-205 was a single-arm, multicenter Phase 2 study designed to evaluate the efficacy and safety of zanubrutinib in patients with CLL/SLL who had relapsed or refractory disease after ≥ 1 prior treatment regimen(s). The study was conducted at sites in China. Ninety-one patients were enrolled and treated with zanubrutinib and received zanubrutinib 160 mg orally twice daily continuously in repeated 28-day cycles. Study BGB-3111-205 demonstrates that zanubrutinib is safe and effective in a population of mostly high-risk patients from China with CLL/SLL.

Patients enrolled on BGB-3111-205 were of poor prognosis. At study entry, most patients had advanced clinical stage disease (Binet Stage C CLL [67.1%], Rai Stage III or IV CLL [67.1%], or Stage IV SLL [77.8%]). Over one-half of all patients (56.0%) had unmutated IGHV, approximately one-quarter of all patients had disease with ≥ 1 poor prognostic cytogenetic feature including del(17p), del(11q), and/or *TP53* mutation. Approximately one-half of patients had received ≥ 2 prior lines of therapy. For most patients (79.1%), their disease was refractory to the most recent systemic therapy.

The overall response rate, defined as the proportion of patients with a best response of PR-L or better was 87.9% (95% CI: 79.40 to 93.81; $p < 0.0001$ with respect to the null hypothesis of 32% [based on the overall response rate in the historical control as of the study start]). The median PFS for this study, as assessed by investigator assessment, has not been reached. The estimated PFS event-free rates by investigator assessment at 24 and 36 months were 80.5% (95% CI: 70.52 to 87.42) and 68.1% (95% CI: 56.56 to 77.24), respectively. With a median follow-up time for PFS of 34.5 months (range: 0.8 to 41.4 months), as estimated by the reverse Kaplan-Meier method, the median PFS as assessed by independent central review, has not been reached. The estimated PFS event-free rates as assessed by independent central review at 24 and 36 months were 80.5% (95% CI: 70.52 to 87.42) and 68.1% (95% CI: 56.56 to 77.24), respectively.

Median overall survival (an exploratory study endpoint) has not been reached. The estimated overall survival rates at 24 and 36 months were 89.8% (95% CI: 81.27 to 94.55) and 86.5% (95% CI: 76.62 to 92.44), respectively, through a median follow up time of 35.1 months.

The Applicant's Position:

In Phase 2 Study BGB-3111-205, it is notable that response to zanubrutinib was observed in the CLL/SLL population predominantly with advanced clinical stage disease that was heavily pretreated and refractory to the most recent systemic therapy. The overall response rate in

patients with R/R CLL/SLL enrolled in Study BGB-3111-AU-003 was high and similar between the overall population (94.2% [95% CI: 87.8, 97.8]) and the subset (n = 13) of patients with del(17p) disease (92.3% [95% CI: 64.0, 99.8]). These results from the supportive efficacy studies further support the benefits of zanubrutinib among patients with high-risk R/R CLL/SLL.

Importantly, responses were durable in Study BGB-3111-AU-003 with an PFS event-free rate of nearly 82.8% at 36 months. In R/R disease, both PFS at 12 months (96%) and overall survival at 12 months (98%) were very near in Study BGB-3111-AU-003 those seen in Study BGB-3111-305 (95% and 97% respectively). By extrapolation zanubrutinib-treated patients in Study BGB-3111-305 would be expected to sustain similar benefit as those in Study BGB-3111-AU-003.

The FDA's Assessment:
The efficacy data in these supportive trials were not reviewed in detail as part of this submission. The results did not raise any concerns regarding efficacy. The PFS and OS outcomes are not interpretable in these single-arm trials and are considered exploratory.

8.1.4 Integrated Review of Effectiveness

The FDA's Assessment:
Two randomized studies BGB-3111-304 (SEQUOIA) and BGB-3111-305 (ALPINE) serve as the primary studies supporting the approval of a broad CLL/SLL indication, to include TN and R/R disease and patients with and without 17p del. The SEQUOIA study in TN CLL is the primary study supporting approval based on a statistically significant improvement in PFS in a randomized trial in patients with TN CLL/SLL without 17p del. The SEQUOIA study also demonstrates efficacy in TN CLL/CLL with 17p del, on the basis of ORR with durability in a separate single-arm cohort. The ALPINE trial is considered supportive and demonstrates clinically meaningful activity in patients with R/R CLL/SLL comparted to an active relevant comparator, ibrutinib. Efficacy was supported by an improvement in ORR, with durability, and a tendency towards a benefit in both PFS and OS at an early analysis. Taken in total, both trials support zanubrutinib monotherapy for patient with CLL/SLL.

8.1.5 Assessment of Efficacy Across Trials

Primary Endpoints

Data:

The two pivotal Phase 3 trials were conducted and submitted in this supplement for establishing substantial efficacy evidence to support the proposed CLL/SLL indication. Study BGB-3111-304 was conducted in patients with TN CLL/SLL and Study BGB-3111-305 was conducted in patients with R/R CLL/SLL.

The primary endpoint for Study BGB-3111-304 was PFS by IRC for superiority comparison between zanubrutinib and B+R in patients without del(17)p (Cohort 1 Arm A and Arm B,

respectively) and zanubrutinib single-arm in patients with del(17p) (Cohort 2, Arm C). ORR by IRC was one of major secondary endpoints.

In Study BGB-3111-305, ORR (CR/CRi + nPR + PR) assessed by the investigator was a primary endpoint for the noninferiority comparison between zanubrutinib and ibrutinib followed by prespecified superiority testing. The primary endpoint was supported by a prespecified key secondary endpoint, PFS by investigator and IRC.

The primary efficacy results across the two Phase 3 trials are summarized in Table 29 for PFS and

Table 30 for ORR. The data in this section are from Section 3 of the Summary of Clinical Efficacy, and differences in analysis population or censoring rules from the individual clinical study reports are described in Sections 1.4.3.6 and 1.4.4.6 of the Summary of Clinical Efficacy.

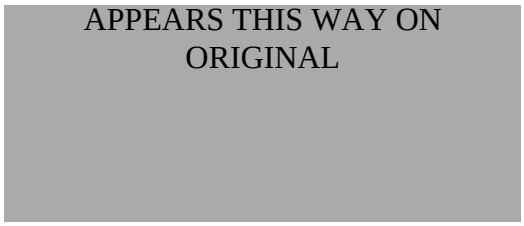


Table 29: Analysis of Progression-Free Survival by Independent Central Review (BGB-3111-304 and BGB-3111-305 Patients)

	BGB-3111-304			BGB-3111-305	
	Zanubrutinib Arm A (N = 241)	**Bendamustine + Rituximab Arm B (N = 238)**	**Zanubrutinib Arm C in del(17p)+ (N = 110)**	**Zanubrutinib Arm A (N = 207)**	**Ibrutinib Arm B (N = 208)**
Progression-free Survival					
Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)	28 (13.5)	45 (21.6)
Progressive Disease	27 (11.2)	59 (24.8)	14 (12.7)	21 (10.1)	33 (15.9)
Death	9 (3.7)	12 (5.0)	1 (0.9)	7 (3.4)	12 (5.8)
Censored, n (%)	205 (85.1)	167 (70.2)	95 (86.4)	179 (86.5)	163 (78.4)
No documented PD/death	195 (80.9)	140 (58.8)	93 (84.5)	168 (81.2)	150 (72.1)
No baseline/post-baseline assessment	2 (0.8)	16 (6.7)	0 (0.0)	6 (2.9)	1 (0.5)
PD/death after consecutive missed disease assessments	4 (1.7)	4 (1.7)	0 (0.0)	1 (0.5)	1 (0.5)
No documented PD/death: discontinued from study	3 (1.2)	6 (2.5)	1 (0.9)	2 (1.0)	8 (3.8)
New anticancer therapy	1 (0.4)	1 (0.4)	1 (0.9)	2 (1.0)	3 (1.4)
Follow-up Time (Months)					
Median (95% CI) [a]	25.1 (24.9, 25.4)	24.6 (22.8, 25.2)	27.9 (27.7, 29.2)	13.9 (13.9, 14.1)	14.0 (13.9, 14.1)
(Min, Max)	(0.0, 41.4)	(0.0, 36.2)	(1.0, 38.8)	(0.0, 22.4)	(0.0, 22.3)
Progression-free Survival (Months) [b]					
Median (95% CI)	NE (NE, NE)	33.7 (28.1, NE)	NE (NE, NE)	22.1 (22.1, NE)	NE (NE, NE)
Q1 (95% CI)	NE (27.5, NE)	22.1 (17.5, 25.2)	NE (NE, NE)	17.1 (16.7, NE)	14.8 (13.3, NE)
Q3 (95% CI)	NE (NE, NE)	NE (33.7, NE)	NE (NE, NE)	NE (22.1, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI) [c]					
12 Months	94.5 (90.8, 96.8)	90.2 (85.4, 93.5)	93.6 (87.0, 96.9)	92.2 (87.4, 95.2)	82.2 (75.9, 87.0)
18 Months	91.9 (87.7, 94.8)	80.5 (74.4, 85.2)	89.9 (82.5, 94.3)	74.7 (60.7, 84.3)	70.6 (61.5, 77.9)
24 Months	85.5 (80.1, 89.6)	69.5 (62.4, 75.5)	88.9 (81.3, 93.6)	NE (NE, NE)	NE (NE, NE)
36 Months	81.5 (74.6, 86.6)	40.8 (17.5, 63.1)	84.9 (76.0, 90.8)	NE (NE, NE)	NE (NE, NE)

Source: Table 37 in Module 2.7.3. Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia; NE, not evaluable; Q1, first quartile; Q3, third quartile; SLL, small lymphocytic lymphoma.
Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on arm c was not included in this summary.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles of progression-free survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-eff-itt.sas 08SEP2021 02:53 t-18-eff-pfsirc-itt-i.rtf

Table 30: Analysis of Disease Response per Independent Central Review (BGB-3111-304 and BGB-3111-305 Patients)

	BGB-3111-304			BGB-3111-305	
	Zanubrutinib Arm A (N = 241)	**Bendamustine + Rituximab Arm B (N = 238)**	**Zanubrutinib Arm C in del(17p)+ (N = 110)**	**Zanubrutinib Arm A (N = 207)**	**Ibrutinib Arm B (N = 208)**
Best Overall Response, n (%)					
Complete Response (CR)	16 (6.6)	36 (15.1)	7 (6.4)	3 (1.4)	2 (1.0)
Complete Response w/incomplete bone marrow recovery (CRi)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodular Partial Response (nPR)	3 (1.2)	14 (5.9)	2 (1.8)	1 (0.5)	0 (0.0)
Partial Response (PR)	206 (85.5)	153 (64.3)	88 (80.0)	154 (74.4)	132 (63.5)
Partial Response w/lymphocytosis (PR-L)	3 (1.2)	0 (0.0)	2 (1.8)	19 (9.2)	36 (17.3)
Stable Disease	7 (2.9)	14 (5.9)	11 (10.0)	21 (10.1)	25 (12.0)
Non-Progressive Disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Progressive Disease	2 (0.8)	1 (0.4)	0 (0.0)	1 (0.5)	4 (1.9)
Unknown [a]	4 (1.7)	20 (8.4)	0 (0.0)	7 (3.4)	9 (4.3)
Rate of PR or Higher (CR+CRi+nPR+PR), n (%)	225 (93.4)	203 (85.3)	97 (88.2)	158 (76.3)	134 (64.4)
(95% CI) [b]	(89.4, 96.2)	(80.1, 89.5)	(80.6, 93.6)	(69.9, 81.9)	(57.5, 70.9)

	BGB-3111-304			BGB-3111-305	
	Zanubrutinib Arm A (N = 241)	**Bendamustine + Rituximab Arm B (N = 238)**	**Zanubrutinib Arm C in del(17p)+ (N = 110)**	**Zanubrutinib Arm A (N = 207)**	**Ibrutinib Arm B (N = 208)**
Time to First PR or Higher (Months)					
n	225	203	97	158	134
Mean (SD)	3.379 (1.5232)	3.112 (0.9439)	3.607 (2.2544)	5.485 (2.7103)	6.297 (3.1543)
Median	2.891	2.891	2.858	5.552	5.634
Min, Max	1.77, 14.16	1.94, 11.14	1.91, 13.90	2.69, 14.03	2.66, 16.69
Rate of CR or CRi, n(%)	16 (6.6)	36 (15.1)	7 (6.4)	3 (1.4)	2 (1.0)
(95% CI) [b]	(3.8, 10.6)	(10.8, 20.3)	(2.6, 12.7)	(0.3, 4.2)	(0.1, 3.4)
Rate of PR-L or Higher (PR-L + PR or higher), n(%)	228 (94.6)	203 (85.3)	99 (90.0)	177 (85.5)	170 (81.7)
(95% CI) [b]	(91.0, 97.1)	(80.1, 89.5)	(82.8, 94.9)	(80.0, 90.0)	(75.8, 86.7)

Source: Table 30 in Module 2.7.3.

Abbreviations: CI, confidence interval; CR, complete response; CRi, complete response w/incomplete bone marrow recovery; Max, maximum; Min, minimum; nPR, nodular partial response; PR, partial response; PR-L, partial response w/lymphocytosis; SD, standard deviation.

Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on arm c was not included in this summary.

[a] Unknown includes a best overall response of Not Evaluable as well as patients with no assessments prior to the data cutoff date or new CLL/SLL therapy.

[b] Clopper-Pearson confidence interval.

The Applicant's Position:

Zanubrutinib at the proposed dosing regimen 160 mg BID has demonstrated clinically meaningful improvement in PFS and ORR in patients with treatment naïve and R/R CLL/SLL, including patients with del(17p) or TP53. The primary efficacy evidence is supported by results of secondary endpoints in both CLL/SLL populations as summarized below.

The FDA's Assessment:
The FDA disagrees with Applicant's position that the studies are similar and that it is appropriate to compare outcomes across studies in this manner.

The two randomized studies involved different treatment settings, different comparator regimens, and different primary endpoints. Both PFS (in randomized cohorts only) and ORR (with durability) support the efficacy of zanubrutinib in patients with CLL/SLL. PFS with zanubrutinib was only assessed as a primary endpoint in the BGB-3111-304 study and was demonstrated to be superior compared to BR in patients with TN CLL with 17p del. In the single-arm cohort of patients with 17p del (Cohort 2), PFS is considered descriptive.

A summary of endpoints and efficacy results for the two randomized studies is provided in the Appendix (Table 122).

Secondary and Other Endpoints

Data:

Duration of Response

In TN CLL/SLL patients (Study BGB-3111-304), with median follow-up of 19.4 months in zanubrutinib Arm A, 23.1 months in zanubrutinib Arm C, and 19.8 months in B+R Arm B, the median duration of response had not been reached in the zanubrutinib treatment (Arm A and Arm C) and was 30.6 months in the B+R treatment (Arm B). The event-free rates at 12 months were 95.0% and 92.2% in zanubrutinib Arm A and zanubrutinib Arm C, respectively, and 93.1% in B+R Arm B. The event-free rates at 24 months were 87.2% and 86.8% in zanubrutinib Arm A and zanubrutinib Arm C, respectively, and 75.2% in B+R Arm B. Duration of response by investigator (based on response of PR or better) is summarized in Table 31.

In the R/R CLL/SLL patients (Study BGB-3111-305), with median follow-up time of 10.1 months in the zanubrutinib arm and 8.3 months in the ibrutinib arm, the median duration of response was not reached in the zanubrutinib arm and was 16.6 months (95% CI: 13.7, NE) in the ibrutinib arm. At 12 months, 89.8% of responders treated with zanubrutinib remain event-free, and 77.9% of responders treated with ibrutinib remain event-free. Duration of response by investigator (based on response of PR or better) is summarized in Table 32.

Table 31: Duration of Response by Investigator Assessment (BGB-3111-304 and BGB-3111-305 Patients)

	BGB-3111-304			BGB-3111-305	
	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)	Zanubrutinib Arm A (N = 207)	Ibrutinib Arm B (N = 208)
Duration of Response (Partial Response or Higher)					
Number of Responders	231	211	105	162	130
Events, n (%)	23 (10.0)	48 (22.7)	15 (14.3)	9 (5.6)	16 (12.3)
Censored, n (%)	208 (90.0)	163 (77.3)	90 (85.7)	153 (94.4)	114 (87.7)
Follow-up Time (Months)					
Median (95% CI) [a]	19.4 (19.2, 19.6)	19.8 (19.6, 20.6)	23.1 (22.0, 24.9)	10.1 (8.3, 11.0)	8.3 (8.3, 9.5)
(Min, Max)	(0.0, 35.9)	(0.0, 31.7)	(0.0, 35.9)	(2.7, 19.2)	(2.4, 19.5)
Duration of Response (Months) [b]					
Median (95% CI)	NE (NE, NE)	30.6 (26.2, NE)	NE (NE, NE)	NE (14.0, NE)	16.6 (13.7, NE)
Q1 (95% CI)	NE (NE, NE)	24.4 (19.7, 25.3)	NE (25.1, NE)	NE (12.9, NE)	13.7 (10.7, 16.6)
Q3 (95% CI)	NE (NE, NE)	NE (30.6, NE)	NE (NE, NE)	NE (NE, NE)	NE (16.6, NE)
Event Free Rate at, % (95% CI) [c]					
12 Months	95.0 (91.2, 97.2)	93.1 (88.7, 95.9)	92.2 (85.0, 96.0)	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)
18 Months	92.5 (88.0, 95.3)	87.0 (81.5, 91.0)	86.8 (78.3, 92.1)	77.2 (49.8, 90.8)	34.1 (1.8, 74.9)
24 Months	87.2 (80.8, 91.6)	75.2 (66.9, 81.6)	86.8 (78.3, 92.1)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 07MAY2021(304), 31DEC2020(305). Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: CI, confidence interval, NE, not evaluable; Q1, first quartile; Q3, third quartile.
Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on arm c was not included in this summary.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles of duration of response were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-eff-itt.sas 08SEP2021 02:53 t-23-eff-dorinv-itt-i.rtf

Table 32: Duration of Response by Investigator Assessment (R/R CLL/SLL Zanubrutinib Patients)

	BGB-3111-305 Zanubrutinib Arm A (N = 207)	BGB-3111-AU-003 Zanubrutinib (N = 99)	BGB-3111-205 Zanubrutinib (N = 91)	R/R CLL/SLL Zanubrutinib (N = 397)
Duration of Response (Partial Response or Higher)				
Number of Responders	162	90	71	323
Events, n (%)	9 (5.6)	19 (21.1)	19 (26.8)	47 (14.6)
Censored, n (%)	153 (94.4)	71 (78.9)	52 (73.2)	276 (85.4)
Follow-up Time (Months)				
Median (95% CI) [a]	10.1 (8.3, 11.0)	31.5 (28.4, 36.9)	27.6 (24.9, 30.1)	13.9 (13.1, 16.5)
(Min, Max)	(2.7, 19.2)	(0.0, 65.1)	(0.0, 36.1)	(0.0, 65.1)
Duration of Response (Months) [b]				
Median (95% CI)	NE (14.0, NE)	54.1 (47.7, NE)	NE (NE, NE)	54.1 (44.0, NE)
Q1 (95% CI)	NE (12.9, NE)	43.0 (29.0, 53.1)	23.1 (11.4, NE)	35.1 (23.1, 44.0)
Q3 (95% CI)	NE (NE, NE)	NE (54.1, NE)	NE (NE, NE)	NE (54.1, NE)
Event Free Rate at, % (95% CI) [c]				
12 Months	89.8 (78.1, 95.4)	95.3 (87.9, 98.2)	85.4 (74.6, 91.9)	91.4 (87.0, 94.4)
18 Months	77.2 (49.8, 90.8)	92.6 (84.3, 96.6)	77.8 (65.8, 86.0)	85.6 (79.7, 89.9)
24 Months	NE (NE, NE)	88.2 (78.4, 93.7)	74.1 (61.6, 83.1)	81.6 (74.9, 86.7)
36 Months	NE (NE, NE)	79.7 (66.7, 88.0)	67.9 (53.1, 79.0)	73.1 (63.4, 80.6)

Source: ADSL, ADTTE. Data cutoff: 31MAR2021(AU-003), 11SEP2020(205), 31DEC2020(305). Data extraction: 03MAY2021(AU-003), 16OCT2020(205), 19MAR2021(305).

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia; NE, not evaluable; Q1, first quartile; Q3, third quartile; SLL, small lymphocityi lymphoma.

Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized.

[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.

[b] Medians and other quartiles of duration of response were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-eff-rrcs.sas 08SEP2021 02:54 t-24-eff-dorinv-rrcs-i.rtf

APPEARS THIS WAY ON ORIGINAL

Overall Survival

Overall survival, while premature in both studies, is summarized in Table 33 for pivotal Studies BGB-3111-304 and BGB-3111-305, and in Table 34 for R/R CLL/SLL patients treated with zanubrutinib.

Studies BGB-3111-304 and BGB-3111-305

TN CLL/SLL Patients

For the TN CLL/SLL population, the median follow-up times in BGB-3111-304 for Cohort 1 were 26.5 months in zanubrutinib Arm A and 25.1 months in B+R Arm B. For Cohort 2, the median follow-up time was 30.4 months (zanubrutinib Arm C).

The median overall survival had not been reached in the zanubrutinib treatment groups. In Cohort 1 B+R Arm B, the estimated overall survival was 37.8 months. Event-free rates at 12 and 24 months were 98.3% and 94.3%, respectively, in zanubrutinib Arm A; 96.4% and 94.6%, respectively, in B+R Arm B, and 96.4% and 93.6%, respectively, in zanubrutinib Arm C.

The Kaplan-Meier analysis of overall survival for Study BGB-3111-304 Cohort 1 shows largely overlapping curves. Based on an additional analysis of overall survival with four additional months of data (data cutoff date of 07 September 2021), as reported in the BGB-3111-304 CSR addendum for OS Analysis, 38 deaths had occurred in Cohort 1, 19 in Arm A and 19 in Arm B, with a HR of 0.89 (95% CI: 0.47, 1.68). The Kaplan-Meier curves for Cohort 1 overall survival were generally overlapping for each analysis.

The median overall survival had not been reached in Study BGB-3111-305. The median follow-up time in Study BGB-3111-305 was 15.6 months in zanubrutinib Arm A, and 15.4 months in ibrutinib Arm B.

Event-free rates at 12 months were 97.0% in zanubrutinib Arm A and 92.7% in ibrutinib Arm B.

R/R CLL/SLL Patients

In R/R patients, median follow-up times were 15.6 months in Study BGB-311-305, 43.8 months in Study BGB-3111-AU-003, and 35.1 months in Study BGB-3111-205. The median overall survival had not been reached in studies in R/R patients.

The event-free rate at 12 months in Study BGB-3111-305 was 97.0%. Event-free rates for 12 and 24 months were 97.9% and 95.8%, respectively, in Study BGB-3111-AU-003 and 95.6% and 89.8% respectively, in Study BGB-3111-205.

The Kaplan-Meier analysis of overall response in R/R CLL/SLL patients treated with zanubrutinib is provided in Figure 13.

Table 33: Analysis of Overall Survival (BGB-3111-304 and BGB-3111-305 Patients)

	BGB-3111-304			BGB-3111-305	
	Zanubrutinib Arm A (N = 241)	Bendamustine + Rituximab Arm B (N = 238)	Zanubrutinib Arm C in del(17p)+ (N = 110)	Zanubrutinib Arm A (N = 207)	Ibrutinib Arm B (N = 208)
Overall Survival					
Events, n (%)	16 (6.6)	14 (5.9)	8 (7.3)	11 (5.3)	19 (9.1)
Censored, n (%)	225 (93.4)	224 (94.1)	102 (92.7)	196 (94.7)	189 (90.9)
Follow-up Time (Months)					
Median (95% CI) [a]	26.5 (25.7, 27.0)	25.1 (24.9, 25.6)	30.4 (30.0, 31.4)	15.6 (15.2, 16.4)	15.4 (14.8, 16.0)
(Min, Max)	(0.3, 41.4)	(0.0, 38.9)	(5.0, 38.8)	(0.1, 22.5)	(0.1, 26.0)
Overall Survival (Months) [b]					
Median (95% CI)	NE (NE, NE)	37.8 (37.8, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI) [c]					
12 Months	98.3 (95.6, 99.4)	96.4 (93.0, 98.2)	96.4 (90.6, 98.6)	97.0 (93.5, 98.7)	92.7 (88.1, 95.5)
18 Months	97.1 (93.9, 98.6)	96.0 (92.4, 97.9)	95.4 (89.4, 98.1)	93.3 (87.7, 96.4)	88.4 (81.3, 92.9)
24 Months	94.3 (90.4, 96.7)	94.6 (90.6, 96.9)	93.6 (87.1, 96.9)	NE (NE, NE)	88.4 (81.3, 92.9)
36 Months	92.3 (87.6, 95.3)	93.6 (88.9, 96.3)	90.7 (80.3, 95.7)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 07MAY2021(304), 31DEC2020(305). Data extraction: 28JUN2021(304), 19MAR2021(305).
Abbreviations: CI, confidence interval, Min, minimum; Max, maximum; NE, not evaluable; PD, progressive disease; Q1, first quartile; Q3, third quartile.
Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized; +: one patient without del (17p) enrolled on arm c was not included in this summary.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians of overall survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-eff-itt.sas 08SEP2021 02:53 t-25-eff-os-itt-i.rtf

Table 34: Analysis of Overall Survival (R/R CLL/SLL Zanubrutinib Patients)

	BGB-3111-305 Zanubrutinib Arm A (N = 207)	BGB-3111-AU-003 Zanubrutinib (N = 99)	BGB-3111-205 Zanubrutinib (N = 91)	R/R CLL/SLL Zanubrutinib (N = 397)
Overall Survival				
Events, n (%)	11 (5.3)	13 (13.1)	11 (12.1)	35 (8.8)
Censored, n (%)	196 (94.7)	86 (86.9)	80 (87.9)	362 (91.2)
Follow-up Time (Months)				
Median (95% CI) [a]	15.6 (15.2, 16.4)	43.8 (39.3, 50.7)	35.1 (33.6, 35.7)	19.4 (18.5, 22.4)
(Min, Max)	(0.1, 22.5)	(5.3, 69.8)	(0.8, 41.4)	(0.1, 69.8)
Overall Survival (Months) [b]				
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI) [c]				
12 Months	97.0 (93.5, 98.7)	97.9 (91.9, 99.5)	95.6 (88.7, 98.3)	96.9 (94.7, 98.2)
18 Months	93.3 (87.7, 96.4)	96.9 (90.6, 99.0)	92.2 (84.3, 96.2)	93.9 (90.7, 96.0)
24 Months	NE (NE, NE)	95.8 (89.2, 98.4)	89.8 (81.3, 94.6)	92.3 (88.5, 94.9)
36 Months	NE (NE, NE)	90.8 (82.5, 95.3)	86.5 (76.6, 92.4)	88.4 (83.3, 92.0)

Source: ADSL, ADTTE. Data cutoff: 31MAR2021(AU-003), 11SEP2020(205), 31DEC2020(305). Data extraction: 03MAY2021(AU-003), 16OCT2020(205), 19MAR2021(305).

Abbreviations: CI, confidence interval, Min, minimum; Max, maximum; NE, not evaluable; PD, progressive disease; Q1, first quartile; Q3, third quartile.

Note: in this analysis, patients from the BGB-3111-305 study will be restricted to the first 415 patients randomized.

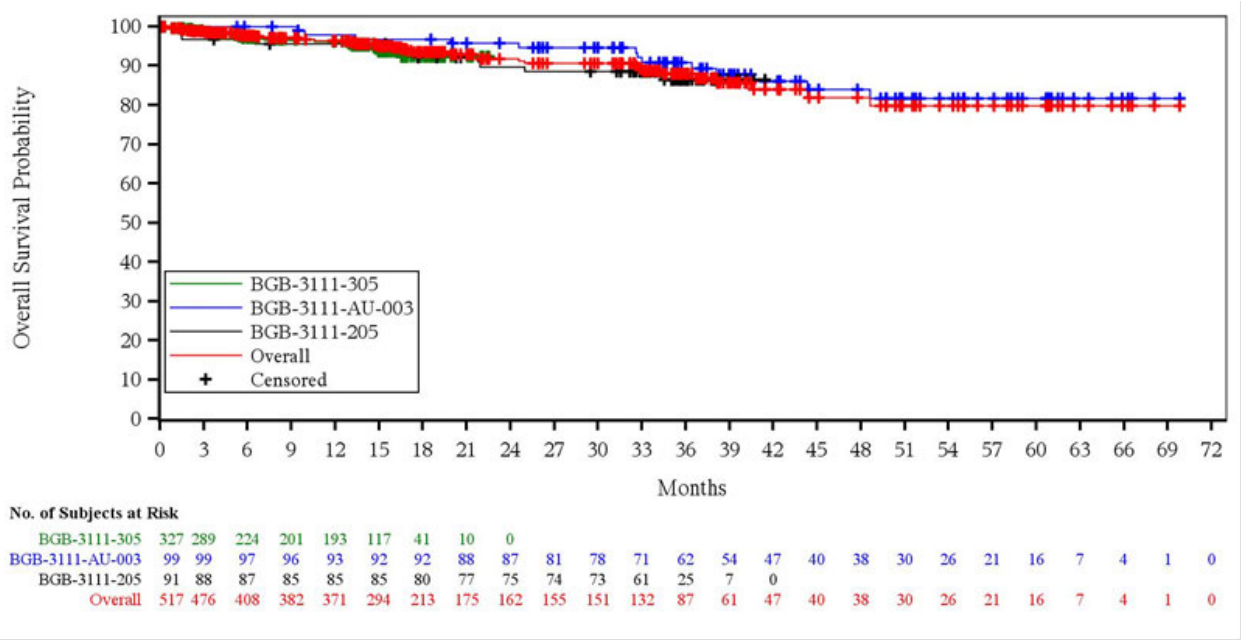
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.

[b] Medians of overall survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/t-eff-rrcs.sas 08SEP2021 02:54 t-26-eff-os-rrcs-i.rtf

Figure 13: Kaplan-Meier of Overall Survival: R/R CLL/SLL Patients Treated with Zanubrutinib (ITT Analysis Set)



Source: ADSL, ADTTE. Data cutoff: 31MAR2021(AU-003), 11SEP2020(205), 31DEC2020(305). Data extraction: 03MAY2021(AU-003), 16OCT2020(205), 19MAR2021(305).
Note: in this analysis, patients from the BGB-3111-305 study will be from all 652 patients randomized.
/bgb_3111/filing_cll_2021/ise/dev/pgm/tlfs/f-eff-km.sas 23AUG2021 01:00 f-2-7-3-4-39-eff-km-os-rrcs-all.rtf

The Applicant's Position:

Results from each of the 4 studies of zanubrutinib in patients with CLL/SLL show that zanubrutinib resulted in high overall response rates seen in all studies independent of line of therapy and independent of high risk del (17p) or TP53 mutational status. The availability of data from Study BGB-3111-AU-003 provides additional information on long-term exposure of zanubrutinib, particularly in patients with R/R disease.

High overall response was seen in both pivotal studies independent of line of therapy or disease characteristics. In Study BGB-3111-304, in patients with R/R CLL/SLL, the proportions of patients who achieved PR or higher were 93.4% in zanubrutinib Arm A and 88.2% in zanubrutinib Arm C (del(17p)+) versus 85.3% in the B+R Arm B. In Study BGB-3111-305, in patients with R/R CLL/SLL, the proportion of patients who achieved PR or higher was 76.3% in zanubrutinib Arm A versus 64.4% in the ibrutinib Arm B. The median time to PR or higher was consistent across arms in each study. In patients with R/R CLL/SLL, the incidence of CR was higher in studies with longer follow-up (BGB-3111-AU-003 and BGB-3111-205) compared with BGB-3111-305. This is expected given that responses to BTK inhibitors deepen over time. The

median time to PR or higher was 5.552 months (overall R/R), 5.585 months (BGB-3111-305), 5.536 months (BGB-3111-AU-003), and 5.520 months (BGB-3111-205).

Deep and durable responses to zanubrutinib also were seen in patients with high-risk features, including patients with del(17p) mutation alone and those with del(17p) or TP53 mutations (Section 3.3 in Module 2.7.3). This finding was apparent in both TN patients and in patients with R/R disease and was consistent with or without censoring for initiation of new anticancer therapy.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment regarding the consistency of high ORRs across trials which supports the activity of zanubrutinib in CLL/SLL. However, randomized studies evaluating clinically meaningful, time-to-event endpoints are required to fully inform benefit-risk.

Subpopulations

Data:

Patients with TN CLL/SLL in Study BGB-3111-304

For Cohort 1, a longer PFS by independent central review was observed in the zanubrutinib arm in all high-risk subgroups with sufficient number of patients for analyses, including the difficult to treat subgroups of patients harboring unmutated IGHV and patients harboring del11q (hazard ratios: 0.24 [95% CI: 0.13, 0.43] and 0.21 [95% CI: 0.09, 0.50], respectively).

For Cohort 2, the high risk del17p+ population, the PFS and overall response rate were similar to those of the Cohort 1 zanubrutinib arm, showing efficacy for zanubrutinib regardless of del17p status.

Patients with R/R CLL/SLL and del(17p) or *TP53* Mutations in Study BGB-3111-305

Mutation in del(17p) or TP53 was one of the strata for the randomization of patients in Study BGB-3111-305. The subgroup analysis of PFS-IRC by del(17p) or TP53 PFS is summarized in Table 35 with the Kaplan-Meier estimates in Figure 13.

With median follow-up of approximately 14 months for both treatment arms, the median PFS had not been reached. However, the PFS events rate was lower with zanubrutinib (12.2%) versus ibrutinib (34.2%). The 12 months event-free rates were higher in zanubrutinib treated patients (91.9%) versus ibrutinib treated patients (69.4%).

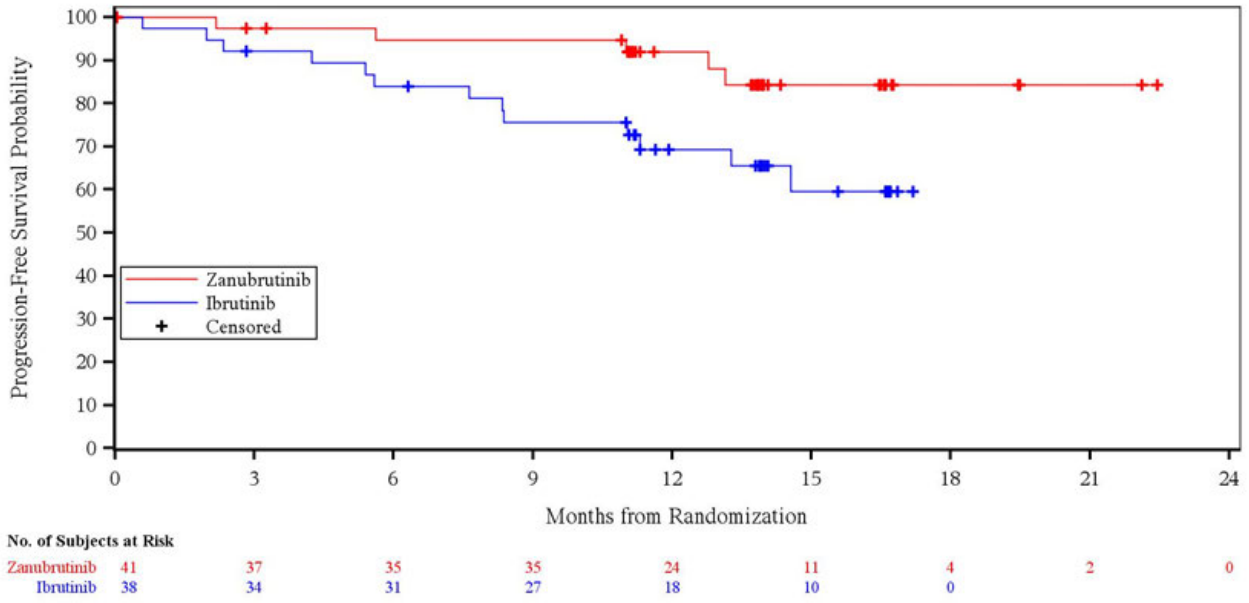
The Kaplan-Meier analysis of PFS assessed by IRC for the patients with del(17p) or TP53 is consistently separated over time in favor of zanubrutinib (Figure 14).

Table 35: Progression-Free Survival Assessed by Independent Central Review in Patients with del(17)p or TP53, Censored to New Anticancer Therapy (BGB-3111-305)

	Zanubrutinib (N = 41)	Ibrutinib (N = 38)	Total (N = 79)
Progression-free Survival			
Events, n (%)	5 (12.2)	13 (34.2)	18 (22.8)
Progressive disease	3 (7.3)	10 (26.3)	13 (16.5)
Death	2 (4.9)	3 (7.9)	5 (6.3)
Censored, n (%)	36 (87.8)	25 (65.8)	61 (77.2)
No documented PD/death	34 (82.9)	24 (63.2)	58 (73.4)
No baseline/post-baseline assessment	2 (4.9)	0 (0.0)	2 (2.5)
PD/death after >1 missing planned disease assessments	0 (0.0)	1 (2.6)	1 (1.3)
Follow-up Time (Months)			
Median (95% CI) [a]	13.8 (11.3, 14.3)	14.0 (11.9, 16.6)	13.9 (13.7, 14.3)
(Min, Max)	(0.0, 22.4)	(0.6, 17.2)	(0.0, 22.4)
Hazard Ratio [b] (95% CI)		0.37 (0.12, 1.19)	
Progression-free Survival (Months) [c]			
Median (95% CI)	NE (NE, NE)	NE (13.3, NE)	NE (NE, NE)
Q1 (95% CI)	NE (12.8, NE)	11.0 (4.2, NE)	13.3 (8.4, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Event-Free Rate at, % (95% CI) [d]			
6 Months	94.7 (80.5, 98.7)	84.0 (67.8, 92.5)	89.4 (79.9, 94.5)
12 Months	91.9 (77.0, 97.3)	69.4 (51.4, 81.8)	80.7 (69.5, 88.1)
18 Months	84.3 (65.7, 93.3)	NE (NE, NE)	71.6 (57.5, 81.6)
24 Months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTEIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CI, confidence interval, Min, minimum; Max, maximum; NE, not evaluable; PD, progressive disease; Q1, first quartile; Q3, third quartile.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Hazard ratio is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.
[c] Medians and other quartiles of progression-free survival are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[d] Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-pfsirc-1753.sas 09AUG2021 20:47 t-14-2-1-7-1-13-eff-pfssirc-1753-ia.rtf

Figure 14: Kaplan-Meier Plot of Progression-Free Survival (Censored to New Anticancer Therapy) Assessed by Independent Central Review for Patients with del(17p) or TP53: Study BGB-3111-305



Source: Figure 14.2.1.2.1.10 of BGB-3111-305 Clinical Study Report
Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/f-ef-km-1753.sas 10AUG2021 01:12 f-14-2-1-2-1-10-eff-km-pfssirc-1753-ia.rtf

Overall Response Rate and Duration of Response in Patients with R/R CLL/SLL del(17p) or TP53 in Study BGB-3111-305

Overall response rate assessed by IRC in patients with del(p17) or TP53 was 80.5% on zanubrutinib versus 55.3% on ibrutinib with risk difference of 25.2% (95% CI: 5.3, 45.2) favorable to zanubrutinib. With median follow-up of 8.4 months, the median duration of response had not been reached. The 12-month event-free rates were 92.1% in zanubrutinib patients and 81.6% in ibrutinib patients.

The Applicant's Position:

It is well known that the CLL/SLL patients with del(17p) and/or TP53 mutation respond poorly to otherwise effective standard purine analogue or alkylator-based chemoimmunotherapy and have a poor prognosis. In the R/R CLL/SLL study (Study BGB-3111-305), the subgroup analysis in patients with del(17p) and/or TP53 mutation demonstrated a favorable improvement in ORR and PFS with zanubrutinib compared to the first generation BTKi, ibrutinib. In Study BGB-3111-304, treatment naïve CLL/SLL patients in the del(17)p arm (Cohort 2, Arm C) showed similar efficacy outcomes with zanubrutinib as for patients without del17p. Taken together, these

results demonstrate efficacy for zanubrutinib in the broad CLL/SLL patient population and suggest zanubrutinib has an advantage over ibrutinib in the treatment of R/R CLL/SLL patients with del(17p) or TP53. See Section 8.1.2.

The FDA's Assessment:
The Agency agrees that data support that zanubrutinib is active in patients with CLL/SLL with 17p del or TP53 mutation.

Additional Efficacy Considerations

The FDA's Assessment:
The Agency considers OS a key endpoint in patients with TN CLL needed to fully inform benefit risk as it informs both efficacy and safety. Therefore, additional OS follow-up is warranted for study BGB-3111-304, as described in Section 12.

8.1.6 Integrated Assessment of Effectiveness

The Applicant's Position:

The benefit-risk assessment for zanubrutinib is based on a clinical development program that included 2 global pivotal Phase 3 studies in CLL/SLL, 2 additional studies that also evaluated efficacy in patients with CLL/SLL, and 5 additional studies in a variety of B-cell malignancies. Overall, these studies afforded an extensive efficacy database comprised of 1518 individual patients.

Study BGB-3111-304 demonstrated superiority of zanubrutinib over B+R in TN CLL/SLL for PFS by independent central review. The primary study endpoint (median PFS) for zanubrutinib was not reached versus 33.7 months for B+R; 1-sided p-value of < 0.0001. The hazard ratio for PFS in Cohort 1 assessed by independent central review was 0.42 (95% CI: 0.28, 0.63) in the ITT Analysis Set. PFS in Cohort 1 was also improved in the zanubrutinib arm compared with the B+R arm when assessed by investigator (HR: 0.42 [95% CI: 0.27, 0.66]). The overall response rate by independent central review also was improved for patients in the zanubrutinib arm (94.6% [95% CI: 91.0, 97.1]) compared with the B+R arm (85.3% [95% CI: 80.1, 89.5]). The odds ratio was 3.162 (95% CI: 1.608, 6.220); p-value = 0.0006. Similar findings were observed when overall response rates were as assessed by investigator. In Cohort 1, duration of response was longer for patients in the zanubrutinib arm compared with the B+R arm. The estimated median OS based on the 07May2021 data cutoff was not reached for the Cohort 1 zanubrutinib arm and was 37.8 months for the B+R arm. For the 07 September 2021 data cutoff with additional survival data, the estimated median OS was not reached for the Cohort 1 zanubrutinib arm or the B+R arm with a HR of 0.89 [95% CI : 0.47, 1.68]). The KM curves for Cohort 1 overall survival are generally overlapping for each OS analysis. Patients in Cohort 2, which enrolled patients with del(17p), a prognostic cytogenetic factor for poor outcomes, had similar efficacy outcomes as those without del(17p); the median PFS assessed by independent central review in Cohort 2

was not reached, and the 24-month PFS was 88.9%. The ORR in Cohort 2 was 90.0% (95% CI: 82.8, 94.9).

In Study BGB-3111-305, in the protocol-specified primary endpoint, the investigator-assessed overall response rate was higher for patients in the zanubrutinib arm (78.3% [95% CI: 72.0, 83.7]) compared with the ibrutinib arm (62.5% [95% CI: 55.5, 69.1]), demonstrating both noninferiority of zanubrutinib to ibrutinib (response ratio 1.25 [95% CI: 1.10, 1.41]; 1-sided p-value < 0.0001) as well as superiority of zanubrutinib to ibrutinib (2-sided p-value = 0.0006) in patients with R/R CLL/SLL. Consistent results were observed for the overall response rate assessed by independent central review. The hazard ratio for PFS assessed by independent central review was 0.61 (95% CI: 0.39, 0.95).

The overall response rate in patients with R/R CLL/SLL enrolled in Study BGB-3111-AU-003 was high and similar between the overall population (94.2% [95% CI: 87.8, 97.8]) and the subset (n = 13) of patients with del(17p) disease (92.3% [95% CI: 64.0, 99.8]). These results from the supportive efficacy studies further support the benefits of zanubrutinib among patients with high-risk R/R CLL/SLL. Importantly, responses were durable in Study BGB-3111-AU-003 with an event-free rate of nearly 82.8% at 36 months. In R/R disease, both PFS at 12 months (96%) and overall survival at 12 months (98%) in Study BGB-3111-AU-003 were very similar to those seen in Study BGB-3111-305 (95% and 97% respectively). By extrapolation zanubrutinib-treated patients in Study BGB-3111-305 would be expected to sustain similar benefit as observed in Study BGB-3111-AU-003. In Phase 2 Study BGB-3111-205, it is notable that response to zanubrutinib was observed in the CLL/SLL population predominantly with advanced clinical stage disease that was heavily pretreated and refractory to the most recent systemic therapy. The overall response rate was 87.9% (95% CI: 79.40, 93.81).

Of note, as observed with previously evaluated patient populations (i.e., WM in Phase 3 Study BGB-3111-302), patients who received zanubrutinib reported greater improvements in quality of life compared with those receiving ibrutinib in Study BGB-3111-305, including scores on the GHS/QoL, physical functioning, fatigue, and diarrhea subscales of EORTC QLQ-C30. These quality-of-life measures can be an important indicator of the ability to maintain stable and sustained administration in chronically administered anticancer therapies.

The FDA's Assessment:

The efficacy of zanubrutinib in patients with CLL/SLL is based on two randomized trials, one in TN CLL/SLL (Study BGB-3111-304; SEQUOIA) and one in relapsed or refractory CLL/CLL (Study BGB-3111-305; ALPINE).

Substantial evidence of efficacy in TN CLL/SLL is primarily based on PFS per IRC in SEQUOIA, a multicenter, randomized (1:1), open-label phase 3 trial comparing zanubrutinib monotherapy (160mg twice daily until disease progression or unacceptable toxicity) to BR for 6 cycles. The trial enrolled patients with previously untreated CLL without 17p del in Cohort 1. Of 479 patients total, 241 were assigned to zanubrutinib monotherapy, 238 to bendamustine + rituximab. Baseline characteristics were balanced. There was a statistically significant and clinically meaningful improvement in the primary endpoint of IRC-assessed PFS in the

zanubrutinib arm. On a prespecified interim analysis, with a median follow-up of 25.1 months, the HR for IRC-assessed PFS was 0.42 (95% CI: 0.28, 0.63) and p-value <0.0001, with a 1-sided significance level of 0.186 (p-value <0.0001 with 2-sided significance level of 0.372). The median PFS was not reached in the zanubrutinib arm (95% CI: NE, NE) and was 33.7 months (95% CI: 28.1, NE) in the BR arm. Results of sensitivity analyses were consistent with the primary endpoint, and there were no outlier subgroups identified. The superior PFS in the zanubrutinib arm is likely attributable, at least in part, to the substantially longer duration of exposure to zanubrutinib than to the BR regimen. The median duration of exposure was 2-fold longer to zanubrutinib (median 26 months) than to BR (median 5.5 months).

At the time of analysis, with 25.7 month median follow-up, median OS had not been reached in either arm with a limited number of events. With additional OS follow-up requested by the Agency, there was no signal for harm with regards to OS.

Efficacy in patients with TN CLL with 17p del was based on a single-arm cohort (Cohort 2) in SEQUOIA, which enrolled 110 patients with TN CLL/SLL with centrally confirmed 17p del who received zanubrutinib monotherapy 160mg twice daily until disease progression or unacceptable toxicity. The IRC-assessed ORR was 88% (95% CI: 81, 94) with durability; the median DOR was not reached (95% CI: NE, NE), and the DOR rate (Kaplan-Meier estimate) at 18 months was 95% (95% CI: 88, 98).

Efficacy in R/R CLL/SLL is primarily based on ORR per IRC with durability in ALPINE, a multicenter, randomized (1:1), open-label phase 3 trial comparing zanubrutinib monotherapy (160 mg twice daily) to ibrutinib 420mg twice daily until disease progression or unacceptable toxicity. The trial enrolled patients with R/R CLL/SLL after at least 1 prior line of therapy including those with 17p del. Of 652 patients total, 327 were assigned to zanubrutinib monotherapy and 325 to ibrutinib monotherapy. The median age overall was 67 years (range: 35 to 90 years), 14% of patient had 17p del and 73% had an unmutated IGHV; the median number of prior lines of therapy was 1 (range 1-8). On the final prespecified analysis of the ITT population, the ORR was 80% (95% CI: 76, 85) with zanubrutinib compared to 73% (95% CI: 68, 78) with ibrutinib; the response ratio was 1.10 (95% CI: 1.01, 1.20), p-value 0.026 (2-sided significance level, 0.0469). With an estimated median follow-up of 14.1 months, the median DOR was not reached for either arm (95% CI: NE, NE) and the 1-year rates of DOR were similar (92% and 86% respectively). A descriptive analysis of PFS per IRC at the time of the final ORR analysis tended to favor the zanubrutinib arm (HR 0.61; 95% CI: 0.44, 0.86). At the time of analysis, median OS had not been reached in either arm with a limited number of events and there was a tendency towards benefit in the zanubrutinib arm (HR 0.80; 95% CI: 0.50, 1.28).

The results of SEQUOIA, in isolation, support regular approval of zanubrutinib for the treatment of adult patients with previously untreated CLL/SLL. The results of the ALPINE trial coupled with the results of the SEQUOIA trial supports regular approval in patients with R/R CLL/SLL. The totality of data supports regular approval of zanubrutinib for the treatment of adult patients with CLL or SLL.

8.2 Review of Safety

The Applicant's Position:

The safety review of zanubrutinib for the proposed CLL/SLL indication in this sNDA is primarily based on the results from studies BGB-3111-304 and BGB-3111-305 studies, as presented below along with the supporting safety data derived from 7 additional clinical studies across CLL/SLL and other hematologic malignancy studies. The pooled safety analysis (N=1550) demonstrated the safety profile for zanubrutinib is consistent with that observed in the studies presented in the original NDA. No new safety concerns were observed with zanubrutinib in CLL/SLL.

The FDA's Assessment:

The Agency agrees that the safety review for the proposed CLL/SLL indication is primarily based on the results from studies BGB-3111-304 (SEQUOIA) and BGB-3111-305 (ASCEND) studies, supported by the pooled safety analysis from 1550 patients who received zanubrutinib at a dose of either 160mg BID or 320mg daily for B-cell malignancies. The overall safety profile in CLL/SLL was similar to that in the previously approved indications.

In the TN CLL/SLL population, a safety signal of increased deaths due to AEs in the zanubrutinib arm compared to the comparator arm, primarily driven by COVID-19 and other infections, and second primary malignancies was identified at the time of the primary PFS analysis. Given the limited OS events available at the CCOD for the primary PFS analysis, additional OS data from study BGB-3111-304 was requested and reviewed by the Agency. Although review of the additional follow-up data for OS was reassuring, limited information was available in this treatment naïve setting and additional follow-up is required to fully evaluate any potential for harm with zanubrutinib therapy in the treatment naïve setting. Refer to section 13 regarding post-marketing requirements.

8.2.1 Safety Review Approach

The Applicant's Position

Substantial evidence of safety for zanubrutinib to treat patients with naïve or R/R CLL/SLL was based on the primary safety data and supportive safety data:

Primary safety data: the safety data collected from the two pivotal phase 3 trials and reviewed individually.

- **Study BGB-3111-304**, comprising patients in the zanubrutinib monotherapy (n = 391 patients, including 240 patients treated with zanubrutinib in Cohort 1, 40 patients treated with zanubrutinib in Cohort 1a, and 111 patients treated with zanubrutinib in Cohort 2) treatment arm.
- **Study BGB-3111-305,** comprising patients in the zanubrutinib monotherapy (n = 324) treatment arm are presented.
- The **All R/R CLL/SLL** group (n = 525), comprising all patients with R/R CLL/SLL treated with zanubrutinib at 160 mg twice a day or 320 mg once a day from Studies BGB-3111-305 (n = 324), BGB-3111- AU-003 (CLL/SLL patients, n = 101), BGB-3111-205 (n = 91), and BGB-3111-1002 (CLL/SLL patients, n = 9).
- The **All CLL/SLL** group (n = 938), comprising all patients with CLL/SLL treated with zanubrutinib at 160 mg twice a day or 320 mg once a day from Studies BGB-3111-304 (n = 391), BGB-3111-305 (n = 324), BGB-3111-AU-003 (CLL/SLL patients, n = 123), BGB-3111-205 (n = 91), and BGB-3111-1002 (CLL patients, n = 9).
- The **All Zanubrutinib** group (n = 1550), comprising data from all patients who were initially treated with zanubrutinib monotherapy at 160 mg twice a day or 320 mg once a day from all 9 aforementioned studies. Crossover patients, defined as patients who crossed over from the comparator arm to the zanubrutinib arm, were not included in this analysis.

The FDA's Assessment:

The Agency agrees with the Applicant's position. The safety review in patients with TN CLL without 17p del was based primarily on the safety data from Cohort 1 of study BGB-3111-304. For patients with TN CLL with 17p del, a separate analysis of the safety data from Cohort 2 was performed and was generally consistent with the Cohort 1 population with the exception of second primary malignancies, which was higher in patients with 17p del. The safety review in patients with R/R CLL/SLL was primary based on the safety data from study BGB-3111-305. Additional data was requested by the Agency reflecting a clinical cutoff date of 1 December 2021, consistent with the final analysis for the primary endpoint of ORR. This was submitted by the Applicant after the original sNDA submission, which had included data with the CCOD of 30 Dec 2020. The updated safety data with a CCOD of 1 Dec 2021 was used for the safety analysis of study BGB-3111-305. For the integrated safety analysis, the safety population consisted of 1,550 patients with B-cell malignancies who received zanubrutinib monotherapy at either 160mg BID or 320mg per day.

FDA safety analysis considers all-causality treatment-emergent AEs in recipients of study therapy. Treatment-emergent adverse events (TEAEs) were defined as AEs that were new or worsened from baseline grade. Laboratory grading is based on CTCAE criteria rather than iwCLL (Hallek 2008) criteria. The primary safety window is 30 days after last study drug with censoring for subsequent anti-cancer therapy. For increased sensitivity, FDA used a combination of

individual MedDRA preferred terms (PTs) and custom groupings as defined in the Appendix (Table 124).

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Study BGB-3111-304:

In Cohort 1, the overall median treatment durations were 5.52 months, 5.59 months, and 26.07 months among patients treated with bendamustine, rituximab, and zanubrutinib, respectively.

Table 36: Summary of Treatment Exposure in Cohort 1 (Safety Analysis Set)

Treatment Summary	Bendamustine (N = 227)	Rituximab (N = 227)	Zanubrutinib (N = 240)
Duration of Exposure (months) [a]			
n	227	227	240
Mean (SD)	5.16 (1.418)	5.29 (1.360)	25.58 (6.557)
Median	5.52	5.59	26.07
Q1, Q3	5.45, 5.78	5.52, 5.91	23.38, 29.37
Min, Max	0.9, 7.4	0.9, 7.4	0.5, 42.2
<3 months	27 (11.9)	25 (11.0)	3 (1.3)
3 - <6 months	164 (72.2)	156 (68.7)	2 (0.8)
6 - <9 months	36 (15.9)	46 (20.3)	6 (2.5)
9 - <12 months	0 (0.0)	0 (0.0)	5 (2.1)
12 - <24 months	0 (0.0)	0 (0.0)	54 (22.5)
24+ months	0 (0.0)	0 (0.0)	170 (70.8)
Number of Cycles			
n	227	227	240
Mean (SD)	5.34 (1.435)	5.44 (1.360)	27.81 (7.127)
Median	6.00	6.00	28.34
Q1, Q3	6.00, 6.00	6.00, 6.00	25.41, 31.93
Min, Max	1.0, 6.0	1.0, 6.0	0.5, 45.8
Cumulative Dose Administered [b]			
n	227	227	240
Mean (SD)	1658.44 (548.771)	4813.75 (1425.459)	235642.67 (63105.179)
Median	1800.00	5121.00	241920.00

Treatment Summary	Bendamustine (N = 227)	Rituximab (N = 227)	Zanubrutinib (N = 240)
Q1, Q3	1438.00, 2028.00	4500.00, 5720.00	220320.00, 272160.00
Min, Max	270.0, 2800.0	360.0, 8050.0	4480.0, 392320.0
Relative Dose Intensity (%) [c]			
n	224	224	240
Mean (SD)	90.96 (11.295)	97.88 (5.983)	94.85 (9.288)
Median	96.46	98.74	98.00
Q1, Q3	85.64, 99.06	97.38, 100.24	95.15, 99.73
Min, Max	50.4, 102.8	23.9, 104.2	48.1, 104.8
Total Dose Received at Cycle 1 [b]			
n	226	226	238
Mean (SD)	334.74 (47.404)	690.08 (117.695)	8858.15 (722.027)
Median	330.00	686.13	8960.00
Q1, Q3	306.00, 360.00	637.50, 750.00	8800.00, 8960.00
Min, Max	158.0, 504.0	11.8, 1050.0	3680.0, 10400.0
Total Dose Received per Cycle Beyond Cycle 1 [b]			
n	216	218	238
Mean (SD)	1392.66 (446.957)	4297.08 (1126.745)	228764.71 (59657.170)
Median	1497.00	4500.00	232960.00
Q1, Q3	1211.25, 1698.00	4000.00, 5000.00	213120.00, 264000.00
Min, Max	135.0, 2296.0	100.0, 7000.0	14880.0, 383360.0

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADEXSUM
Abbreviations: B: Bendamustine; R: Rituximab.
a Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff
date is used as last dose date for ongoing patients.
b Unit mg/m2 is reported for Bendamustine and Rituximab, and unit mg is reported for Zanubrutinib.
c Relative dose intensity is defined as the ratio of the actual dose intensity and the planned dose intensity times 100,
where actual dose intensity is the actual cumulative dose divided by the actual duration of Bendamustine or

Rituximab or Zanubrutinib administration (cycles) . For Bendamustine, the planned dose intensity will be calculated
as 180 mg/m2 per cycle; For Rituximab, the planned dose intensity in first cycle is 375 mg/m2, and for all
subsequent cycles, it will be calculated as 500 mg/m2. For Zanubrutinib, the planned dose intensity is 320 mg/day or
8,960 mg per cycle.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_ex_c1.sas
Output: t-14-3-1-1-1-1-ex-c1-saf.rtf (Date Generated: 06SEP2021:05:35)

Table 37: Summary of Treatment Exposure in Zanubrutinib Arm Cohort 2 (Safety Analysis Set)

Treatment Summary	**Zanubrutinib (Arm C) (N = 111)**
Duration of Exposure (months) [a]	
n	111
Mean (SD)	28.28 (7.176)
Median	30.00
Q1, Q3	26.97, 32.49
Min, Max	1.6, 39.0
<3 months	1 (0.9)
3 - <6 months	3 (2.7)
6 - <9 months	1 (0.9)
9 - <12 months	1 (0.9)
12 - <24 months	10 (9.0)
24+ months	95 (85.6)
Number of Cycles	
n	111
Mean (SD)	30.75 (7.800)
Median	32.61
Q1, Q3	29.32, 35.32
Min, Max	1.8, 42.4

Treatment Summary	**Zanubrutinib (Arm C) (N = 111)**
Cumulative Dose Administered [b]	
n	111
Mean (SD)	263290.09 (71981.688)
Median	280960.00
Q1, Q3	256000.00, 305440.00
Min, Max	15040.0, 373440.0
Relative Dose Intensity (%) [c]	
n	111
Mean (SD)	95.16 (8.875)
Median	97.92
Q1, Q3	95.07, 99.27
Min, Max	39.4, 100.0
Total Dose Received at Cycle 1 [b]	
n	111
Mean (SD)	8871.35 (1015.164)
Median	8960.00
Q1, Q3	8960.00, 9280.00
Min, Max	960.0, 10240.0
Total Dose Received per Cycle Beyond Cycle 1 [b]	
n	111
Mean (SD)	254418.74 (71982.782)
Median	272000.00
Q1, Q3	245760.00, 296480.00
Min, Max	6080.0, 364480.0

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADEXSUM
Abbreviations: B: Bendamustine; R: Rituximab.
[a] Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.

[b] Unit mg/m^2 is reported for Bendamustine and Rituximab, and unit mg is reported for Zanubrutinib.

[c] Relative dose intensity is defined as the ratio of the actual dose intensity and the planned dose intensity times 100, where actual dose intensity is the actual cumulative dose divided by the actual duration of Zanubrutinib administration (cycles). For Zanubrutinib, the planned dose intensity is 320 mg/day or 8,960 mg per cycle.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_ex_c2_i.sas
Output: t-14-3-1-1-1-3-ex-csaf-i.rtf (Date Generated: 06SEP2021:06:18)
Source: Table 14.3.1.1.1.3

The FDA's Assessment:

The Agency agrees with the Applicant's description of the exposure data for Cohorts 1 and 2 of study BGB-3111-304. For patients with TN CLL/SLL the number of patients exposed and the duration of exposure were adequate for safety review.

Data:

Study BGB-3111-305:

The overall median treatment durations were 13.503 months in the zanubrutinib arm and 12.830 months in the ibrutinib arm.

Table 38: Summary of Treatment Exposure (Safety Analysis Set)

	Safety Analysis Set	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**
Treatment Duration (months) [a]		
n	324	324
Mean (SD)	11.291 (6.2267)	10.366 (6.1838)
Median	13.503	12.830
Q1, Q3	5.076, 16.361	4.172, 15.688
Min, Max	0.39, 23.03	0.10, 25.89
< 3 months	39 (12.0)	54 (16.7)
3 to < 6 months	59 (18.2)	62 (19.1)
6 to < 9 months	29 (9.0)	33 (10.2)
9 to < 12 months	7 (2.2)	8 (2.5)
12 to < 24 months	190 (58.6)	164 (50.6)
≥ 24 months	0 (0.0)	3 (0.9)
Cumulative Dose Received (g)		
n	324	324
Mean (SD)	104.689 (58.9399)	126.745 (77.1704)
Median	128.320	141.470
Q1, Q3	48.040, 153.760	51.870, 189.000
Min, Max	2.88, 224.00	1.26, 329.28

	Safety Analysis Set	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**
Actual Dose Intensity (mg/day) [b]		
n	324	324
Mean (SD)	307.138 (30.6969)	401.732 (40.8519)
Median	319.111	419.250
Q1, Q3	310.360, 320.000	403.162, 420.000
Min, Max	143.59, 321.35	70.00, 420.00
Relative Dose Intensity (%) [c]		
n	324	324
Mean (SD)	95.981 (9.5928)	95.650 (9.7266)
Median	99.722	99.821
Q1, Q3	96.988, 100.000	95.991, 100.000
Min, Max	44.87, 100.42	16.67, 100.00
Patients with Dose Reduction, n (%)	33 (10.2)	39 (12.0)
Reason for dose reduction [d]		
Held for Procedure	2 (0.6)	0 (0.0)
PI Decision	3 (0.9)	3 (0.9)
Adverse Event	25 (7.7)	34 (10.5)
Other	3 (0.9)	2 (0.6)
Number of Dose Reductions Per Patient		
n	324	324
Mean (SD)	0.1 (0.41)	0.1 (0.36)
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 3	0, 2
1	26 (8.0)	36 (11.1)
2	6 (1.9)	3 (0.9)
3	1 (0.3)	0 (0.0)
Patients with Dose Interruption, n (%)	109 (33.6)	127 (39.2)
Reason for dose interruption [d]		
Held for Procedure	31 (9.6)	29 (9.0)
PI Decision	6 (1.9)	4 (1.2)
Adverse Event	84 (25.9)	105 (32.4)
Other	4 (1.2)	13 (4.0)
Number of Dose Interruptions Per Patient		
n	324	324
Mean (SD)	0.5 (0.86)	0.6 (0.96)
Median	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 1.0
Min, Max	0, 4	0, 6
1	70 (21.6)	81 (25.0)
2	25 (7.7)	26 (8.0)
3	10 (3.1)	15 (4.6)
≥ 4	4 (1.2)	5 (1.5)
Duration of Dose Interruption (days) [e]		

	Safety Analysis Set	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**
n	109	127
Mean (SD)	20.7 (24.92)	23.8 (29.10)
Median	13.0	14.0
Q1, Q3	7.0, 22.0	7.0, 27.0
Min, Max	1, 154	1, 164

Source: ADSL, ADEXSUM. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
a Treatment duration (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.
b Actual dose intensity (mg/day) is defined as the total dose (in mg) received by a patient divided by the treatment duration (in days).
c Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).
d A patient may be counted in more than one row. Multiples of the same reason were counted once per patient in each row.
e Duration was calculated for patients with dose interruption only.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ex-i.sas 09AUG2021 23:23 t-19-ex-i.rtf

All zanubrutinib (N=1550) safety data:

The safety database contributed by the 9 clinical studies contains a total of 1550 patients with one of the B-cell malignancies, including 938 patients with CLL/SLL (Table 39). Of the CLL/SLL patient population, 42% (n=391) had treatment-naïve CLL/SLL and 56% (n=525) had R/R CLL/SLL. Approximately 93% patients (n=1445) received zanubrutinib at a dose of 160 mg twice a day (n = 1445) and the remaining 7% patients (n=105) were treated with 320 mg once a day

The median duration of treatment in patients with CLL/SLL was 23 months. Among the 1550 patients in this pooled dataset, 1141 (73.6%), 744 (48.0%) and 365 (23.5%) patients had over 12 months, 24 months and 36 months of treatment exposure respectively.

Table 39: Summary of Treatment Exposure (Safety Analysis Set)

	304 Zanubrutinib (N = 391*) n (%)	**305 Zanubrutinib (N = 324) n (%)**	**All R/R CLL/SLL Zanubrutinib (N = 525) n (%)**	**All CLL/SLL Zanubrutinib (N = 938) n (%)**	**All Zanubrutinib (N = 1550) n (%)**
Starting Dose Regimen, n (%)					
160 mg BID	391 (100.0)	324 (100.0)	500 (95.2)	894 (95.3)	1445 (93.2)
320 mg QD	0 (0.0)	0 (0.0)	25 (4.8)	44 (4.7)	105 (6.8)
Duration of Exposure (months) [a]					
n	391	324	525	938	1550

	304 Zanubrutinib (N = 391*) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Mean (SD)	24.76 (8.282)	11.29 (6.227)	20.95 (16.671)	23.15 (14.385)	23.88 (15.777)
Median	26.58	13.50	15.77	22.93	22.95
Q1, Q3	22.90, 30.06	5.08, 16.36	6.97, 35.29	13.34, 31.15	10.61, 35.38
Min, Max	0.5, 42.2	0.4, 23.0	0.2, 71.2	0.2, 71.2	0.1, 71.2
Total exposure (patient-months)	9681.94	3658.18	10999.72	21718.21	37019.66
Duration of Exposure, n (%)					
<3 months	5 (1.3)	39 (12.0)	48 (9.1)	53 (5.7)	134 (8.6)
3 - < 6 months	9 (2.3)	59 (18.2)	64 (12.2)	74 (7.9)	128 (8.3)
6 - < 9 months	23 (5.9)	29 (9.0)	36 (6.9)	59 (6.3)	94 (6.1)
9 - < 12 months	13 (3.3)	7 (2.2)	12 (2.3)	25 (2.7)	53 (3.4)
12 - < 18 months	22 (5.6)	150 (46.3)	158 (30.1)	181 (19.3)	236 (15.2)
18 - < 24 months	54 (13.8)	40 (12.3)	52 (9.9)	106 (11.3)	161 (10.4)
24 - < 30 months	162 (41.4)	0 (0.0)	9 (1.7)	173 (18.4)	203 (13.1)
30 - < 36 months	94 (24.0)	0 (0.0)	16 (3.0)	111 (11.8)	176 (11.4)
36 - < 48 months	9 (2.3)	0 (0.0)	94 (17.9)	104 (11.1)	261 (16.8)
48+ months	0 (0.0)	0 (0.0)	36 (6.9)	52 (5.5)	104 (6.7)
Cumulative Dose Administered (g)					
n	391	324	525	938	1550
Mean (SD)	228.81 (79.563)	104.69 (58.940)	192.80 (157.242)	213.82 (136.507)	220.46 (149.898)
Median	245.28	128.32	147.04	208.04	204.76
Q1, Q3	208.00, 284.00	48.04, 153.76	62.40, 295.44	116.72, 288.64	90.40, 321.92
Min, Max	4.5, 392.3	2.9, 224.0	1.1, 687.5	1.1, 687.5	1.0, 687.5
Actual Dose Intensity (mg/day) [b]					
n	391	324	525	938	1550
Mean (SD)	303.46 (29.086)	307.14 (30.697)	304.22 (39.495)	304.08 (35.046)	303.91 (35.670)
Median	313.54	319.11	318.44	316.27	316.56
Q1, Q3	303.54, 318.90	310.36, 320.00	310.32, 320.00	306.78, 320.00	306.75, 319.84
Min, Max	126.1, 335.3	143.6, 321.4	46.7, 330.9	46.7, 335.3	46.7, 335.3

	304 Zanubrutinib (N = 391*) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Relative Dose Intensity (%) [c]					
n	391	324	525	938	1550
Mean (SD)	94.83 (9.089)	95.98 (9.593)	95.07 (12.343)	95.03 (10.953)	94.97 (11.146)
Median	97.98	99.72	99.47	98.84	98.92
Q1, Q3	94.85, 99.66	96.99, 100.00	96.98, 100.00	95.88, 100.00	95.87, 99.95
Min, Max	39.4, 104.8	44.9, 100.4	14.6, 103.4	14.6, 104.8	14.6, 104.8
Patients with Dose Reduction, n (%)	55 (14.1)	33 (10.2)	59 (11.2)	114 (12.2)	166 (10.7)
Reason for dose reduction [d]					
Adverse Event	34 (8.7)	25 (7.7)	43 (8.2)	77 (8.2)	120 (7.7)
Number of Dose Reductions Per Patient					
n	55	33	59	114	166
Mean (SD)	1.2 (0.58)	1.2 (0.50)	1.4 (0.81)	1.3 (0.71)	1.3 (0.71)
Median	1.0	1.0	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 2.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 4	1, 3	1, 5	1, 5	1, 5
Number of Dose Reductions Per Patient, n (%)					
1	45 (11.5)	26 (8.0)	43 (8.2)	88 (9.4)	127 (8.2)
2	8 (2.0)	6 (1.9)	11 (2.1)	19 (2.0)	30 (1.9)
3	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	5 (0.3)
4	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)
5	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
≥ 6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients With Dose Interruptions due to Adverse Event, n (%) [e]	135 (34.5)	84 (25.9)	175 (33.3)	321 (34.2)	557 (35.9)
Patients With Dose Modification (Reduction or Interruption) due to Adverse Event, n (%)	150 (38.4)	91 (28.1)	184 (35.0)	345 (36.8)	584 (37.7)

Source: ADSL, ADEXSUM. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302),

24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; eCRF, electronic case report form; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
[a] Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.
[b] Actual dose intensity (mg/day) is defined as the cumulative dose administration (mg) received by a patient divided by the duration of exposure (days).
[c] Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).
[d] A patient may be counted in more than one row. Multiple dose reductions due to the same reasons were counted once per patient in each row.
[e] Derived as any interruption due to an adverse event with duration > 1 day from drug administration eCRF in BGB-3111-AU-003; from drug administration eCRF in BGB-3111-304, -305, -205, -206, -210(interruption due to AE), -214 and -302; from adverse event eCRF in BGB-3111-1002 (action taken = drug held).
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-ex-i.sas 11OCT2021 01:20 t-1-ex-i.rtf
*Includes 40 patients in Cohort 1a from Chinese sites,

The Applicant's Position:

The safety database established from two pivotal Phase 3 trials and seven supportive clinical studies has provided sufficient extent of exposure (total number of patients, dosing regimen of zanubrutinib and duration of treatment) for adequate safety assessments of zanubrutinib for the proposed indication.

The FDA's Assessment:
Updated data were requested by the Agency and provided in the review reflecting approximately one year of additional safety data for study BGB-3111-305. The updated exposure data for study BGB-3111-305 and the ISS is detailed in the tables below.

Table 40: Updated Summary of Treatment Exposure: Study BGB-3111-305

	Safety Analysis Set	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**
Treatment Duration (months) [a]		
n	324	324
Mean (SD)	20.7 (7.7)	18.5 (8.5)
Median	23.8	17.7
Min, Max	0.39, 33.4	0.10, 36.9
≥ 12 months	292 (90.1)	261 (80.5)
≥ 24 months	161 (49.7)	129 (39.8)
Relative Dose Intensity (%) [b]		

	Safety Analysis Set	
	Zanubrutinib (N = 324)	**Ibrutinib (N = 324)**
n	324	324
Mean (SD)	94.981 (11.0)	94.4 (10.7)
Median	99.2	98.9
Min, Max	40.4, 100.42	16.67, 100.00
Patients with Dose Reduction, n (%)	40 (12.3)	56 (17.3)
Reason for dose reduction [c]		
Held for Procedure	2 (0.6)	0 (0.0)
PI Decision	3 (0.9)	3 (0.9)
Adverse Event	34 (10.5)	48 (14.8)
Other	3 (0.9)	3 (0.9)
Number of Dose Reductions Per Patient		
n	324	324
Mean (SD)	0.2 (0.46)	0.1 (0.36)
Min, Max	0, 3	0, 2
1	31 (9.6)	50 (15.4)
2	7 (2.2)	6 (1.9)
3	2 (0.6)	0 (0.0)
Patients with Dose Interruption, n (%)	155 (47.8)	188 (58.0)
Reason for dose interruption[c]		
Held for Procedure	52 (16.0)	55 (17.0)
PI Decision	5 (1.5)	6 (1.9)
Adverse Event	118 (36.4)	156 (48.1)
Other	10 (3.1)	16 (4.9)
Number of Dose Interruptions Per Patient		
n	324	324
Mean (SD)	0.9 (1.42)	1.1 (1.45)
Min, Max	0, 11	0, 11
1	85 (26.2)	95 (29.3)
2	37 (11.4)	47 (14.5)
3	18 (5.6)	26 (8.0)
≥ 4	15 (4.6)	20 (6.2)
Duration of Dose Interruption (days) [d]		
n	155	111
Mean (SD)	27.0 (29.2)	30.9 (34.9)
Median	18.0	19.0
Q1, Q3	8.0, 34.0	9.5, 39.5
Min, Max	1, 199	1, 211

Source: Applicant updated CSR, CCOD 1 Dec 2021, Table 20, verified by FDA review analysis of updated ADEXSUM dataset submitted 4/19/2022

[a] Treatment duration (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.

[b] Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).

[c] A patient may be counted in more than one row. Multiples of the same reason were counted once per patient in each row.
[d] Duration was calculated for patients with dose interruption only

Table 41: Updated Summary of Treatment Exposure: ISS Population

	All Zanubrutinib (N = 1550) n (%)
Starting Dose Regimen, n (%)	
160 mg BID	1445 (93.2)
320 mg QD	105 (6.8)
Duration of Exposure (months) [a]	
Mean (SD)	25.85 (14. 78)
Median	26.20
Q1, Q3	14.85, 35.38
Min, Max	0.1, 71.2
Total exposure (patient-months)	40062.03
Duration of Exposure, n (%)	
< 6 months	183 (11.8)
12 - < 18 months	124 (8.0)
18 - < 24 months	151 (9.7)
≥ 24 months	905 (58.3)

Source: Reviewer generated from Applicant's updated ISS tables submitted 9/20/2022, confirmed by reviewer analysis of ISS ADEXSUM datasets and updated 305 ADEXSUM dataset submitted 4-19-2022.
[a] Duration of exposure (months) was calculated as (last dose date – first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients

The updated exposure data reflecting the BGB-3111-305 CCOD of December 1, 2021 reflect a median duration of exposure of 26.2 months for the ISS population and provide an adequate number of patients and duration of exposure to perform an adequate safety analysis.

Relevant characteristics of the safety population:

Data:

The demographics and baseline characteristics of patients included the Safety Analysis Set are similar to the ITT population as summarized in Table 7 and Table 8 for Study BGB-3111-304; Table 21 and Table 22 for BGB-3111-305.

For All zanubrutinib safety data, the demographic and baseline characteristics were generally similar across the 5 analysis populations (Table 42).

Table 42: Demographics and Baseline Characteristics (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Age (years)					
n	391	324	525	938	1550
Mean (SD)	69.1 (8.34)	66.7 (10.21)	65.0 (10.60)	66.8 (9.87)	66.2 (10.71)
Median	70.0	67.0	66.0	68.0	67.0
Q1, Q3	66.0, 74.0	60.0, 74.0	58.0, 73.0	61.0, 73.0	60.0, 73.0
Min, Max	32, 86	35, 90	24, 90	24, 90	20, 95
Age Group, n (%)					
< 65 years	77 (19.7)	126 (38.9)	239 (45.5)	322 (34.3)	600 (38.7)
≥ 65 years	314 (80.3)	198 (61.1)	286 (54.5)	616 (65.7)	950 (61.3)
Sex, n (%)					
Male	260 (66.5)	212 (65.4)	345 (65.7)	623 (66.4)	1027 (66.3)
Female	131 (33.5)	112 (34.6)	180 (34.3)	315 (33.6)	523 (33.7)
Race, n (%)					
Asian	45 (11.5)	45 (13.9)	149 (28.4)	194 (20.7)	424 (27.4)
White	325 (83.1)	261 (80.6)	349 (66.5)	696 (74.2)	1033 (66.6)
Black or African American	4 (1.0)	4 (1.2)	7 (1.3)	11 (1.2)	13 (0.8)
Native Hawaiian or Other Pacific Islander	1 (0.3)	3 (0.9)	4 (0.8)	5 (0.5)	6 (0.4)
Multiple [a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Other	0 (0.0)	2 (0.6)	7 (1.3)	7 (0.7)	23 (1.5)
Not Reported	13 (3.3)	6 (1.9)	6 (1.1)	19 (2.0)	39 (2.5)
Unknown	3 (0.8)	3 (0.9)	3 (0.6)	6 (0.6)	8 (0.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Geographic Region, n (%) [b]					
Asia	44 (11.3)	45 (13.9)	148 (28.2)	192 (20.5)	406 (26.2)
European Union	225 (57.5)	199 (61.4)	201 (38.3)	426 (45.4)	551 (35.5)
North America	46 (11.8)	52 (16.0)	70 (13.3)	117 (12.5)	179 (11.5)
Oceania	76 (19.4)	28 (8.6)	106 (20.2)	203 (21.6)	414 (26.7)
HBcAb, n (%) [c]					
Positive	51 (13.0)	37 (11.4)	77 (14.7)	128 (13.6)	244 (15.7)
Negative	340 (87.0)	285 (88.0)	435 (82.9)	794 (84.6)	1273 (82.1)
Equivocal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Missing	0 (0.0)	2 (0.6)	13 (2.5)	16 (1.7)	31 (2.0)
HCV antibody, n (%) [c]					
Positive	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	5 (0.3)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Negative	389 (99.5)	323 (99.7)	523 (99.6)	934 (99.6)	1544 (99.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
ECOG Performance Status, n (%)					
0	168 (43.0)	126 (38.9)	222 (42.3)	399 (42.5)	690 (44.5)
1	188 (48.1)	191 (59.0)	290 (55.2)	489 (52.1)	765 (49.4)
2	35 (9.0)	7 (2.2)	13 (2.5)	50 (5.3)	95 (6.1)
Height (cm)					
n	383	320	519	924	1533
Mean (SD)	169.16 (8.772)	169.21 (10.095)	169.32 (9.793)	169.34 (9.402)	169.00 (9.525)
Median	170.00	169.25	170.00	170.00	170.00
Q1, Q3	163.00, 175.00	162.00, 177.00	162.00, 176.00	162.00, 176.00	162.00, 176.00
Min, Max	147.0, 191.0	140.0, 197.0	140.0, 197.0	140.0, 197.0	140.0, 197.0
Weight (kg)					
n	391	323	524	937	1549
Mean (SD)	76.53 (16.393)	78.35 (17.670)	77.05 (17.942)	76.96 (17.265)	75.25 (16.998)
Median	74.60	76.30	75.00	75.00	73.00
Q1, Q3	65.00, 86.00	66.00, 89.00	65.00, 87.80	65.00, 87.00	63.00, 85.00
Min, Max	42.5, 147.0	42.5, 149.0	42.5, 149.0	42.5, 149.0	36.0, 149.0
BMI (kg/m^2)					
n	383	319	518	923	1532
Mean (SD)	26.73 (5.169)	27.24 (4.946)	26.74 (5.135)	26.75 (5.158)	26.23 (4.970)
Median	25.86	26.72	25.92	25.92	25.46
Q1, Q3	23.26, 29.36	23.56, 30.56	23.15, 29.72	23.22, 29.48	22.79, 28.91
Min, Max	16.5, 50.6	15.9, 53.1	15.9, 54.6	15.9, 54.6	15.2, 54.6

Source: ADSL, ADBASE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; R/R, Relapsed/Refractory; HBcAb, Hepatitis B core antibody; HCV, Hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BMI, Body Mass Index.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.

[a] Patient BGB-3111-AU-003-(b) (6), BGB-3111-214-(b) (6) and BGB-3111-214-(b) (6) reported two races: American Indian or Alaska Native and White.

[b] Asia includes China (Mainland and Taiwan) and South Korea; European Union includes Austria,

Belgium, Czech, France, Germany, Greece, Italy, Netherlands, Russian Federation, Poland, Spain, Sweden, Turkey and United Kingdom; North America includes United States; Oceania includes Australia and New Zealand.
[c] For 305 study, central lab data was used with 'Non-Reactive' mapped to 'Negative' and 'Reactive' mapped to 'Positive'.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-dm-bsl-i.sas 24AUG2021 01:20 t-3-dm-bsl-i.rtf

The Applicant's Position:

The demographics and baseline characteristics of the safety population in both Phase 3 trials and the pooled safety database were consistent with the target patients with CLL/SLL. The demographics and baseline characteristics of the safety population are comparable between zanubrutinib and its active comparators in the Phase 3 trials.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment regarding the demographics and baseline characteristics of the safety population. In general, there is an underrepresentation of patients of Black or African American race (0.8%). In addition, in studies BGB-3111-304 and BGB-3111-305 there is an underrepresentation of patients with Hispanic or Latino ethnicity (Table 43).

Table 43: Ethnicity in the Patient Populations for Studies BGB-3111-304 and BGB-3111-305

	BGB-3111-304 Cohort 1		BGB-3111-304 Cohort 2	BGB-3111-305	
	Zanubrutinib (N = 240) n (%)	BR N = 227 n (%)	Zanubrutinib N = 111 n (%)	Zanubrutinib (N = 324) n (%)	Ibrutinib N = 324 n (%)
Ethnicity, n (%)					
Hispanic or Latino	5 (2.0)	4 (1.8)	1 (0.9)	7 (2.2)	13 (4.0)
Not Hispanic or Latino	217 (90.4)	203 (89.4)	99 (89.1)	306 (94.4)	302 (93.2)
Not Reported	11 (4.5)	16 (7.0)	11 (9.9)	7 (2.2)	6 (1.9%)
Unknown	7 (2.9)	4 (1.7)	--	4 (1.2)	3 (0.9%)

Source: Reviewer generated from ADSL datasets from study BGB-3111-304 and BGB-3111-305

Adequacy of the Safety Database:

Data:

The safety database comprises 1550 patients treated with zanubrutinib from 9 clinical studies in patients with B-cell malignancies, including 938 CLL/SLL patients (Table 39). The median duration of treatment was approximately 23 months with 320 mg daily zanubrutinib. The primary safety data were contributed by the two randomized, active-controlled phase 3 trials in patients with native CLL/SLL (Study BGB-3111-304) and R/R CLL/SLL (Study BGB-3111-305).

Demographics and baseline characteristics of patients with CLL/SLL are generally consistent with the target patient population in the U.S.

The Applicant's Position:

The safety database of zanubrutinib is considered adequate to assess the safety of the proposed dosing regimen, 160 mg BID or 320 mg daily for the treatment of patients naïve or R/R CLL/SLL.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

There are no issues regarding the data integrity and submission quality.

The FDA's Assessment:
The Agency did not identify issues with data integrity or submission quality.

Categorization of Adverse Event

Data:

A Treatment Emergent Adverse Event (TEAE) is defined as an adverse event with an onset date or increase in severity either on or after the first dose of study drug until 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever is earlier. Worsening of an event to Grade 5 beyond Day 30 after the last dose of study treatment is also considered a TEAE (if it is before initiation of a new anticancer therapy). Only those adverse events that were treatment-emergent are included in the summary tables.

All adverse events were graded for severity using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, with the exception of the LTE1 study (which graded using NCI-CTCAE Version 5.0) and hematologic adverse event of BGB-3111-304 and BGB-3111-305, which were graded according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Grading Scale (Hallek et al 2008).Hallek et al 2008). Adverse event verbatim descriptions were coded to the most similar Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 lower level term. The linked Preferred Term and primary System Organ Class were also captured in the database. Safety results are described per MedDRA preferred term and system organ class.

Summaries of the following categories of safety data are presented:

- Adverse events of all grades
- ≥ Grade 3 adverse events

- Serious adverse events
- Adverse events leading to treatment discontinuation
- Adverse events leading to reduction of study drug dose
- Adverse events leading to treatment interruption
- Adverse events leading to Deaths
- Treatment-related adverse events
- Adverse events of special interest
- Adverse events intrinsic to selected MedDRA system organ classes
- Laboratory assessments of interest
- Vital signs (systolic blood pressure and diastolic blood pressure) and electrocardiograms

Adverse events of special interest are those that are known to be associated with the class of BTK inhibitors. The categories of adverse events of special interest include hemorrhage (including minor bleeding such as contusion and petechiae, major hemorrhage (serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade), atrial fibrillation and flutter, hypertension, second primary malignancies and skin cancers, tumor lysis syndrome, Infections and opportunistic infections, cytopenia, neutropenia, thrombocytopenia, and anemia.

The exposure adjusted incidence rate (EAIR) was calculated as the number of patients experiencing the event of interest divided by the total exposure time, which was calculated as the total time of all patients from the first dose date to the first event date, or from first dose date to the treatment-emergent adverse event period end date if there was no event. EAIRs (no. of persons/100 person-months) for selected AESIs are reported to compare the incidence rates across patient groups after adjusting for exposure differences.

The Grouped Preferred Term that FDA recommended for WM and MZL indications (Link to ADR Addendum) were used for comparative safety analyses between zanubrutinib and BR (Study BGB-3111-304) and between zanubrutinib and ibrutinib (Study BGB-3111-305) to support the determination of the rates of adverse drug reactions in the draft USPI.

The Applicant's Position:
Definition and categorization of adverse events have followed a typical clinical study for safety evaluation of a BTK inhibitor to treat hematologic malignancies.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment; refer to the Appendix (Table 124) for additional grouping of PT performed by the Agency which was adopted for labeling.

Routine Clinical Tests

Data:

Routine clinical tests for safety assessments included routine clinical laboratory tests (hematology, chemistry), ECGs, vital sign assessments, and pregnancy tests as specified in the BGB-3111-304 and BGB-3111-305 protocols.

The Applicant's Position:

The routine clinical tests are consistent with a typical clinical study for hematologic malignancies.

The FDA's Assessment:
The Agency agrees with the Applicant's position.

8.2.4 Safety Results

8.2.4.1 Summary of Treatment Emergent Adverse Events

Data:

Study BGB-3111-304:

For the treatment-emergent adverse event data in Cohort 1, adverse events leading to dose modifications and treatment discontinuation, treatment-related adverse events, treatment-related Grade 3 or higher adverse events, treatment-related serious adverse events, and treatment-related serious adverse events leading to dose modifications and treatment discontinuation were higher in the B+R arm compared with the zanubrutinib arm.

Table 44: Overall Summary of Treatment-Emergent Adverse Events in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
	B+R (N = 227)	Zanubrutinib (N = 240)	Zanubrutinib (N = 111)
	Treatment-Emergent n (%)	Treatment-Emergent n (%)	Treatment-Emergent n (%)
Patients With at Least One AE	214 (94.3)	224 (93.3)	109 (98.2)
Grade 3 or Higher AE	169 (74.4)	126 (52.5)	61 (55.0)
Serious AE	93 (41.0)	87 (36.3)	45 (40.5)
TEAE Leading to Dose Modification	159 (70.0)	115 (47.9)	57 (51.4)
TEAE Leading to Dose Interruption	NA	111 (46.3)	56 (50.5)
TEAE Leading to Dose Delay/Held	154 (67.8)	NA	NA
TEAE Leading to Dose Reduction	84 (37.0)	18 (7.5)	6 (5.4)
TEAE Leading to Treatment Discontinuation	31 (13.7)	20 (8.3)	6 (5.4)
Treatment Related TEAE	202 (89.0)	168 (70.0)	79 (71.2)
Treatment Related Grade 3 or Higher TEAE	148 (65.2)	58 (24.2)	25 (22.5)
Treatment Related Serious TEAE	66 (29.1)	23 (9.6)	10 (9.0)
Treatment Related TEAE Leading to Dose Modification	152 (67.0)	59 (24.6)	25 (22.5)
Treatment Related TEAE Leading to Dose Interruption	NA	54 (22.5)	25 (22.5)
Treatment Related TEAE Leading to Dose Delay/Held	146 (64.3)	NA	NA
Treatment Related TEAE Leading to Dose Reduction	82 (36.1)	15 (6.3)	3 (2.7)
Treatment Related TEAE Leading to Treatment Discontinuation	26 (11.5)	7 (2.9)	3 (2.7)
Treatment Related TEAE Leading to Death	4 (1.8)	2 (0.8)	1 (0.9)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; B+R, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arm A and 90 days after the last dose of B or R (Arm B) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first.
AEs leading to treatment modifications or treatment discontinuation refer to either B or R in Arm B, and zanubrutinib in Arm A.
Treatment-related AEs included AEs related to either B or R in Arm B, and zanubrutinib in Arm A.
Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_ae_sum_saf_ab.sas
Output: t-14-3-1-2-1-1-ae-sum-c1-saf.rtf (Date Generated: 06SEP2021:05:35)

The FDA's Assessment:
The Agency agrees with the Applicant's summary of adverse events in study BGB-3111-304 (SEQUOIA). The Applicant's summary table does not include the number and percentage of fatal TEAEs (regardless of perceived relatedness) in Cohort 1. This breakdown is displayed in the table below and demonstrates an imbalance in fatal treatment-emergent AEs occurring in the zanubrutinib arm compared to the BR arm. While this may be attributed to the significantly longer exposure of continuous, indefinite zanubrutinib therapy compared to the fixed duration BR therapy, the increase in fatal TEAEs observed in the zanubrutinib arm, primarily driven by infections and second primary malignancy raise a concern for potential harm, particularly in a patient population with TN CLL who may have indolent disease and alternative effective therapies. See the section below for further discussion of fatal adverse events occurring in Cohort 1 of study BGB-3111-304.

Table 45: Fatal TEAEs in Study BGB-3111-304 at Primary Analysis (CCOD May 7, 2021) and with Additional Follow-up (CCOD March 7, 2022)

	Cohort 1		**Cohort 2**	**Cohort 1**		**Cohort 2**
	CCOD May 7, 2021			**CCOD March 7, 2022**		
	BR N = 227	**Zanubrutinib N = 240**	**Zanubrutinib N = 111**	**BR N = 227**	**Zanubrutinib N = 240**	**Zanubrutinib N = 111**
Total number of deaths n (%)	15 (6.6)	16 (6.7)	8 (7.2)	22 (9.7)	23 (9.6)	10 (9.0)
Patients experiencing a fatal TEAE n (%)	7 (3.1)	11 (4.6)	3 (2.7)	7 (3.1)	15 (6.3)	4 (3.6)

Source: Reviewer generated from ADSL and ADAE datasets submitted for study BGB-3111-304 on Dec 20, 2021 and updated datasets submitted on May 23, 2022.

Data:

Study BGB-3111-305:

A higher proportion of patients in the ibrutinib arm had at least 1 adverse event, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to dose modification, and treatment-related adverse events compared with patients in the zanubrutinib arm.

Table 46: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients with at Least One TEAE	291 (89.8)	309 (95.4)
Grade 3 or Higher	143 (44.1)	144 (44.4)
Serious	70 (21.6)	82 (25.3)
Leading to Death	13 (4.0)	15 (4.6)
Leading to Treatment Discontinuation	21 (6.5)	34 (10.5)
Leading to Dose Modification	103 (31.8)	122 (37.7)
Leading to Dose Interruption	98 (30.2)	114 (35.2)
Leading to Dose Reduction	24 (7.4)	31 (9.6)
Treatment-Related	216 (66.7)	243 (75.0)
Treatment-Related Grade 3 or Higher	82 (25.3)	89 (27.5)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Adverse event grades were evaluated based on NCI-CTCAE Version 4.03.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ae-sum-i.sas 09AUG2021 23:25
t-20-ae-sum-i.rtf

The FDA's Assessment:

Updated data was requested by the Agency reflecting approximately one year of additional safety data for study BGB-3111-305, corresponding with the timing of the final analysis for the primary endpoint of ORR. The updated summary of treatment-emergent AEs for study BGB-3111-305 is provided in the table below.

Table 47: Updated Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set), CCOD December 1, 2021

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients with ≥ 1 TEAE	315 (97.2)	320 (98.8)
Grade 3 or Higher	192 (59.3)	211 (65.1)
Serious	104 (32.1)	141 (43.5)
Leading to Death	24 (7.4)	29 (9.0)
Leading to Treatment Discontinuation	42 (13.0)	57 (17.6)
Leading to Dose Modification	143 (44.1)	181 (55.9)
Leading to Dose Interruption	137 (42.3)	175 (54.0)
Leading to Dose Reduction	34 (10.5)	49 (15.1)

Source: Reviewer generated from ADAE dataset submitted on April 19, 2022 and the updated CSR submitted on June 30, 2022.

The updated data reflecting approximately one additional year from the original submission was generally consistent with the original data. The overall increased incidence of all TEAEs is expected given the longer exposure. No new safety issues were identified.

Data:

All Zanubrutinib (N=1550) safety data:

In the All Zanubrutinib group, 1483 of the 1550 patients (95.7%) reported ≥ 1 adverse event of any grade; 1 or more ≥ Grade 3 adverse events were reported in 57.9% of patients. A total of 623 patients (40.2%) reported events that met the criteria for seriousness. Adverse events leading to death and treatment discontinuation were reported in 4.9% and 9.3% of patients, respectively. Adverse events leading to at least 1 dose reduction were reported in 116 patients (7.5%). A total of 649 (41.9%) patients required 1 or more treatment interruptions due to an adverse event. An overview of all adverse events reported by pooling patient group is presented in Table 48.

Table 48: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	371 (94.9)	291 (89.8)	492 (93.7)	885 (94.3)	1483 (95.7)
Grade 3 or Higher	202 (51.7)	143 (44.1)	300 (57.1)	516 (55.0)	897 (57.9)
Serious	145 (37.1)	70 (21.6)	185 (35.2)	341 (36.4)	623 (40.2)
Leading to Death	14 (3.6)	13 (4.0)	21 (4.0)	36 (3.8)	76 (4.9)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Leading to Treatment Discontinuation	27 (6.9)	21 (6.5)	46 (8.8)	75 (8.0)	144 (9.3)
Leading to Dose Reduction	25 (6.4)	24 (7.4)	45 (8.6)	70 (7.5)	116 (7.5)
Leading to Dose Interruption	175 (44.8)	98 (30.2)	199 (37.9)	388 (41.4)	649 (41.9)
Treatment-Related	282 (72.1)	216 (66.7)	399 (76.0)	701 (74.7)	1181 (76.2)
Treatment-Related Grade 3 or Higher	93 (23.8)	82 (25.3)	191 (36.4)	292 (31.1)	485 (31.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-i.sas 24AUG2021 01:21 t-8-teae-i.rtf

The FDA's Assessment:

Updated data were requested by the Agency and provided in the review reflecting approximately one year of additional safety data for study BGB-3111-305, corresponding with the timing of the final analysis for the primary endpoint of ORR. The updated summary of TEAEs for the ISS with additional follow-up for study BGB-3111-305 is detailed in the table below. No new safety signals were identified with additional follow-up.

Table 49: Overall Summary of Treatment-Emergent Adverse Events (ISS) with additional follow-up from study BGB-3111-305 (CCOD December 1, 2021)

	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	1507 (97.2)
Grade 3 or Higher	946 (61.0)
Serious	657 (42.4)
Leading to Death	87 (5.6)
Leading to Treatment Discontinuation	177 (11.4)
Leading to Dose Reduction	126 (8.1)
Leading to Dose Interruption	688 (44.4)

Source: Reviewer generated from ADAE dataset submitted on April 19, 2022 and the updated CSR submitted on June 30, 2022.

8.2.4.2 Adverse events related to COVID-19

Data:

Study BGB-3111-304:

Table 50: Summary of COVID-19 Impact on Cohort 1 and Cohort 2 (ITT Analysis Set)

	Cohort 1		Cohort 2
	Zanubrutinib (N = 241) n (%)	B+R (N = 238) n (%)	Zanubrutinib (N = 111) n (%)
Patients with Following COVID-19 Related Occurrences:			
Any COVID-19 Related AE	24 (10.0)	8 (3.5)	4 (3.6)
≥ Grade 3 COVID-19 Related AE	15 (6.3)	2 (0.9)	2 (1.8)
Serious COVID-19 Related AE	14 (5.8)	1 (0.4)	2 (1.8)
COVID-19 Related AE Leading to Dose Interruption	14 (5.8)	0 (0.0)	3 (2.7)
COVID-19 Related AE Leading to Treatment Discontinuation	5 (2.1)	0 (0.0)	0 (0.0)
COVID-19 Related AE Leading to Death	5 (2.1)	0 (0.0)	0 (0.0)
Any Important Protocol Deviation due to COVID-19	2 (0.8)	0 (0.0)	0 (0.0)
Any Visit Missed due to COVID-19	22 (9.1)	35 (14.7)	3 (2.7)
Any Disease Assessment Missed due to COVID-19	10 (4.1)	13 (5.5)	6 (5.4)
≥ 2 Missed Disease Assessments due to COVID-19	4 (1.7)	3 (1.3)	1 (0.9)
Any Safety/Lab Assessment Missed due to COVID-19	28 (11.6)	45 (18.9)	26 (23.4)

Study BGB-3111-305:

Table 51: Summary of COVID-19 Impact (ITT Analysis Set)

	Zanubrutinib (N = 327) n (%)	Ibrutinib (N = 325) n (%)
Patients with Following COVID-19 Related Occurrences:		
Any COVID-19 Related TEAE	18 (5.6)	17 (5.2)
≥ Grade 3 COVID-19 related TEAE	11 (3.4)	8 (2.5)
Serious COVID-19 related TEAE	9 (2.8)	8 (2.5)
COVID-19 Related TEAE Leading to Dose Interruption	11 (3.4)	6 (1.9)
COVID-19 Related TEAE Leading to Treatment Discontinuation	3 (0.9)	4 (1.2)
COVID-19 Related AE Leading to Death [a]	3 (0.9)	6 (1.9)
Any Important Protocol Deviation due to COVID-19	0 (0.0)	0 (0.0)
Any Visit Missed due to COVID-19	6 (1.8)	4 (1.2)
Any Disease Assessment Missed due to COVID-19	38 (11.6)	37 (11.4)
≥ 2 Missed Disease Assessments due to COVID-19	6 (1.8)	7 (2.2)
Any Safety/Lab Assessment Missed due to COVID-19 [b]	18 (5.5)	15 (4.6)

Source: ADSL, ADAE, ADDV, ADLB, VE, SUPPVE, XM, SUPPXM.. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: AE, Adverse Event.
Note: AE summaries are based on the Safety Analysis Set; all other summaries are based on the Intent-to-Treat Analysis Set. Percentages will be calculated based on a denominator corresponding to the analysis set used.
[a] includes AEs that are not treatment-emergent.
[b] Safety/lab assessments include hematology and chemistry lab parameters.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-covid-i.sas 09AUG2021 23:10 t-6-covid-i.rtf

All Zanubrutinib (N=1550) safety data:

Overall, across all groups, a small proportion of patients reported adverse events related to COVID-19. The incidence of COVID-related TEAEs leading to death was comparable among all 5 groups.

Of a total of 1550 patients treated with zanubrutinib, 56 patients (3.6%) reported COVID-19-related TEAEs. This included 35 patients (2.3%) who reported ≥ Grade 3 adverse events; 32 patients (2.1%) reported COVID-19 related adverse events that met the criteria for seriousness, COVID-19 related adverse events leading to death and treatment discontinuation were reported in 12 patients (0.8%) each (Table 52).

Table 52: Overall Summary of Treatment-Emergent Adverse Events Related to COVID-19 (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	27 (6.9)	18 (5.6)	20 (3.8)	47 (5.0)	56 (3.6)
Grade 3 or Higher	16 (4.1)	11 (3.4)	12 (2.3)	28 (3.0)	35 (2.3)
Serious	15 (3.8)	9 (2.8)	11 (2.1)	26 (2.8)	32 (2.1)
Leading to Death	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	12 (0.8)
Leading to Treatment Discontinuation	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	12 (0.8)
Leading to Dose Reduction	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Leading to Dose Interruption	17 (4.3)	11 (3.4)	13 (2.5)	30 (3.2)	35 (2.3)
Treatment-Related	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Treatment-Related Grade 3 or Higher	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.

Summarized for adverse events related to COVID-19.

Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.

Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-i.sas 24AUG2021 01:21 t-9-teae-covid-i.rtf

The Applicant's Position:

The COVID-19 pandemic had no appreciable effect on data integrity of the studies following implementation of mitigating measures. COVID-19 infections were reported in a small fraction of patients, especially in regions with high prevalence of COVID-19. In study 304, although more COVID-19 infections and deaths occurred in patients in the zanubrutinib arm, all patients receiving B+R completed treatment by December 2019, prior to the onset of the pandemic, and therefore may have avoided clinically significant COVID-19 infections after recovery from immunosuppression associated with chemoimmunotherapy. The study therefore cannot directly compare the rate and severity of COVID-19 infections in patients who received B+R during the COVID-19 pandemic.

The FDA Assessment:

The Agency agrees with the Applicant's presentation of the number and rates of AEs associated with COVID-19. In study BGB-3111-304, there were a higher number of AEs related to COVID-19 in the zanubrutinib arm compared to the BR arm, both at the time of primary analysis and with additional follow-up. The Agency does not agree with the Applicant's position that the increase in AEs related to COVID-19 in the zanubrutinib arm can be attributed simply to the timing of therapy in related to the COVID-19 pandemic. Infections are a known risk associated with zanubrutinib therapy. Continuous zanubrutinib therapy carries this risk of ongoing immunosuppression and may place patients at a higher risk of contracting and having an increased severity of communicable infections including COVID-19. This risk should be considered in the overall benefit-risk assessment of zanubrutinib therapy compared to an alternative fixed-duration regimen.

8.2.4.3 Deaths

Data:

Study BGB-3111-304:

In Cohort 1, adverse events leading to death were reported in 11 (4.6%) patients in the zanubrutinib arm and 7 (3.1%) patients in the B+R arm (Table 53). No patients in the B+R arm died due to COVID-19 or COVID-19 pneumonia during the adverse event reporting period; 1 patient died due to COVID-19 after the adverse event reporting period in the B+R arm. In the zanubrutinib arm, the most commonly reported adverse event leading to death was COVID-19 in 4 (1.7%) patients. Other adverse events leading to death in the zanubrutinib arm occurred in 1 patient each and included COVID 19 pneumonia, endocarditis, lung neoplasm malignant, lung squamous cell carcinoma recurrent, metastatic squamous cell carcinoma, acute myocardial infarction, hemorrhagic transformation stroke, cardiac arrest, and cardiogenic shock in 1 (0.4%) patient each. In Cohort 2, adverse events leading to death were reported in 3 (2.7%) zanubrutinib patients. No patients in this arm died due to COVID-19 or COVID-19 pneumonia. Adverse events leading to death included pulseless electrical activity due to aortic dissection in 1 patient, renal failure in the context of progression in 1 patient, and pneumonia in 1 patient.

Table 53: Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
System Organ Class Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Patients With at Least One AE Leading to Death	7 (3.1)	11 (4.6)	3 (2.7)
Infections and infestations	2 (0.9)	6 (2.5)	1 (0.9)
COVID-19	0 (0.0)	4 (1.7)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	1 (0.4)	0 (0.0)
Endocarditis	0 (0.0)	1 (0.4)	0 (0.0)
Pneumonia	1 (0.4)	0 (0.0)	1 (0.9)
Pseudomonal sepsis	1 (0.4)	0 (0.0)	0 (0.0)
Sepsis	1 (0.4)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	3 (1.3)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.4)	0 (0.0)
Lung squamous cell carcinoma recurrent	0 (0.0)	1 (0.4)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)
Cardiac disorders	1 (0.4)	2 (0.8)	1 (0.9)
Acute myocardial infarction	0 (0.0)	1 (0.4)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.4)	0 (0.0)
Cardiogenic shock	0 (0.0)	1 (0.4)	0 (0.0)
Cardiovascular insufficiency	1 (0.4)	0 (0.0)	0 (0.0)
Pulseless electrical activity	0 (0.0)	0 (0.0)	1 (0.9)
Nervous system disorders	0 (0.0)	1 (0.4)	0 (0.0)
Hemorrhagic transformation stroke	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal disorders	3 (1.3)	0 (0.0)	0 (0.0)
Diarrhea	2 (0.9)	0 (0.0)	0 (0.0)
Enterocolitis	1 (0.4)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.9)
Renal failure	0 (0.0)	0 (0.0)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	0 (0.0)	0 (0.0)
Pneumonitis	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory failure	1 (0.4)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.9)

	Cohort 1		Cohort 2
System Organ Class Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Aortic dissection	0 (0.0)	0 (0.0)	1 (0.9)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arm A and 90 days after the last dose of B or R (Arm B) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first.
Patients with multiple events for a given preferred term and system organ class were counted only once for each preferred term and system organ class, respectively. Events were sorted by descending order within system organ class, and by preferred term within system organ class in the Treatment-Emergent Total column.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_teae_postteae_ab.sas
Output: t-14-3-1-2-8-2-1-teae-socpt-death-c1-saf.rtf (Date Generated: 06SEP2021:05:36)

The FDA's Assessment:

The Agency agrees with the Applicant's description of fatal AEs in Cohort 1 and Cohort 2. The increased number of fatal AEs in the zanubrutinib arm compared to the BR arm of Cohort 1 and the resulting OS HR of 1.07 raised a concern for potential harm in the zanubrutinib arm in this TN population. There were a limited number of events at the time of primary analysis for PFS (CCOD May 7, 2021). Additional survival information with longer follow-up was requested to further assess the potential for harm with zanubrutinib. The Applicant provided updated overall survival data and details regarding deaths with a CCOD of 7 March 2022. The updated breakdown of TEAEs resulting in death for Cohort 1 and Cohort 2 is detailed in the tables below.

Table 54: Fatal Treatment-Emergent Adverse Events with Additional Follow-up (CCOD March 7, 2022)

	Treatment Emergent[a]		Outside TE Window[b]		All Timepoints	
Parameter	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**
Total Deaths	**7 (3.1)**	**13 (5.4)**	**15 (6.6)**	**10 (4.2)**	**22 (9.7)**	**23 (9.6)**
Fatal AE	**7 (3.1)**	**13 (5.4)**	**11 (4.8)**	**3 (1.3)**	**18 (7.9)**	**16 (6.7)**
Infections and infestations	**2 (0.9)**	**8 (2.5)**	**7 (3.1)**	**1 (0.4)**	**8 (3.5)**	**9 (3.8)**
COVID-19 (including COVID-19 pneumonia)	0	6 (2.5)	3 (1.3)*	0	3 (1.3)	6 (2.5)
Pneumonia (excluding COVID-19)	1 (0.4)	1 (0.4)	2 (0.9)	0	3 (1.3)	1 (0.4)
Endocarditis	0	1 (0.4)	0	0	0	1 (0.4)
Septic Shock	2 (0.9)	0	0	1 (0.4)	2 (0.9)	1 (0.4)
Secondary Primary Neoplasm	**0**	**4 (1.7)**	**2 (0.9)**	**0**	**2 (0.9)**	**4 (1.7)**
Cardiac disorders	**1 (0.4)**	**2 (0.8)**	**0**	**0**	**1**	**2 (0.8)**
Acute myocardial infarction	0	1 (0.4)	0	0	0	1 (0.4)
Congestive Heart Failure	0	1 (0.4)	0	0	0	1 (0.4)
Cardiovascular Insufficiency	1 (0.4)	0	0	0	1 (0.4)	
Nervous system disorders	**0 (0.0)**	**1 (0.4)**	**0**	**0**	**0**	**1 (0.4)**
Hemorrhagic stroke	0 (0.0)	1 (0.4)	0	0	0	1 (0.4)
Gastrointestinal disorders	**3 (1.3)**	**0**	**0**	**0**	**3 (1.3)**	**0**
Diarrhea	2 (0.9)	0	0	0	2 (0.9)	0
Enterocolitis	1 (0.4)	0	0	0	1 (0.4)	0
Renal and urinary disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Acute Kidney Injury	0	0	1 (0.4)	0	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0	1 (0.4)	0	2 (0.9)	0
Pneumonitis	1 (0.4)	0	0	0		0
Respiratory failure	0	0	1(0.4)	0		0

Source: FDA analysis generated from ADSL and ADAE updated datasets with a CCOD of 7 March 2022 submitted on May 23, 2022.

[a]Treatment emergent was considered ≤ 30 days of last zanubrutinib or ≤ 90 days from BR.

[b]Outside the treatment emergent window was considered ≥ 30 days of last zanubrutinib or ≥ 90 days from BR therapy.

*One patient randomized to the BR arm had a fatal AE of COVID-19 after crossover to the zanubrutinib arm.

Table 55: Fatal Treatment-Emergent Adverse Events in Cohort 2 (17p del CLL/SLL) with Additional Follow-up (CCOD March 7, 2022)

Parameter	Treatment Emergent	Outside of TE window	All
Fatal AE	**4 (3.5)**	**1 (0.9)**	**5 (4.5)**
Infections and infestations	**2 (1.8)**	**0**	**2 (1.8)**
COVID-19 (including COVID-19 pneumonia)	1 (0.9)	0	1 (0.9)
Pneumonia (excluding COVID-19)	1 (0.9)	0	1 (0.9)
Vascular Disorders	**1 (0.9)**	**0**	**1 (0.9)**
Aortic Dissection	1 (0.9)	0	1 (0.9)
Metabolism and nutrition disorders	**0**	**1 (0.9)**	**1 (0.9)**
Renal and urinary disorders	**1 (0.9)**	**0**	**1 (0.9)**
Renal Failure	1 (0.9)	1 (0.9)	1 (0.9

Source: FDA analysis generated from ADSL and ADAE updated datasets with a CCOD of 7 March 2022, submitted on May 23, 2022.

With additional follow-up, there were a similar number of fatal AE on the BR arm compared to the zanubrutinib arm. In the BR arm the additional events occurred outside of the treatment emergent window including one fatal event of COVID-19 that occurred after crossover to zanubrutinib therapy. In the BR arm, the most common cause of fatal AEs were infections, and gastrointestinal disorders. In the zanubrutinib arm, the most common cause of fatal AEs were infections and second primary malignancies. This information provides some reassurance regarding the overall benefit risk of zanubrutinib with extended therapy compared to a comparator arm. The rate of fatal AEs other than PD is slightly higher in the BR arm compared to the zanubrutinib arm with no clear signal of an increased risk of fatal AEs in the zanubrutinib arm compared to BR. Rates and types of fatal AEs occurring in Cohort 2 (patients with 17p del) were similar to that observed in the zanubrutinib arm of Cohort 1. There were no new safety signals for fatal AEs identified in the 17p del cohort.

Data:

Study BGB-3111-305:

Adverse events leading to death were reported in 13 (4.0%) patients in the zanubrutinib arm and 15 (4.6%) patients in the ibrutinib arm. COVID-19 and COVID-19 pneumonia were the most common adverse events leading to death in both arms, reported in 3 patients in the zanubrutinib arm (all reported COVID-19) and 5 patients in the ibrutinib arm (2 patients reported COVID-19; 3 patients reported COVID-19 pneumonia)

Table 56: Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE Leading to Death	13 (4.0)	15 (4.6)
Infections and infestations	11 (3.4)	9 (2.8)
COVID-19	3 (0.9)	2 (0.6)
Pneumonia	3 (0.9)	2 (0.6)
COVID-19 pneumonia	0 (0.0)	3 (0.9)
Infection	1 (0.3)	0 (0.0)
Influenza	0 (0.0)	1 (0.3)
Pneumonia cryptococcal	1 (0.3)	0 (0.0)
Pneumonia fungal	1 (0.3)	0 (0.0)
Respiratory tract infection	1 (0.3)	0 (0.0)
Sepsis	1 (0.3)	0 (0.0)
Septic shock	0 (0.0)	1 (0.3)
General disorders and administration site conditions	2 (0.6)	2 (0.6)
Malaise	2 (0.6)	0 (0.0)
Death	0 (0.0)	1 (0.3)
Multiple organ dysfunction syndrome	0 (0.0)	1 (0.3)
Cardiac disorders	0 (0.0)	3 (0.9)
Myocardial infarction	0 (0.0)	2 (0.6)
Cardiac arrest	0 (0.0)	1 (0.3)
Nervous system disorders	0 (0.0)	2 (0.6)
Central nervous system hemorrhage	0 (0.0)	1 (0.3)
Cerebral infarction	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)
Acute respiratory failure	1 (0.3)	0 (0.0)
Respiratory failure	0 (0.0)	1 (0.3)
Gastrointestinal disorders	1 (0.3)	0 (0.0)
Colitis	1 (0.3)	0 (0.0)
Hepatobiliary disorders	1 (0.3)	0 (0.0)
Jaundice	1 (0.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.3)	0 (0.0)
Mobility decreased	1 (0.3)	0 (0.0)

The FDA's Assessment:

At the Agency's request, the Applicant provided updated safety data with a CCOD of 1 Dec 2021 consistent with the date of the final ORR analysis. The updated safety data was consistent with the original safety data with regards to types of TEAEs in both arms. Causes of deaths were reviewed and adjudicated by FDA based on review of the ADAE dataset and death narratives. Unless otherwise indicated, when multiple grade 5 AEs were associated with the same patient , the AE considered to be the AE primary associated with the fatal outcome is listed. The most common cause of fatal AEs in both arms were infections. The breakdown of fatal AEs is displayed in the table below.

Table 57: Summary of Deaths and Fatal AEs in Study BGB-3111-305 (CCOD December 1, 2021)

System Organ Class Preferred Term*	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Total Number of Deaths	**33 (10.2)**	**40 (12.3)**
Deaths within 30 days of treatment discontinuation	15 (4.6)	18 (5.5)
Deaths due to PD	11 (3.4%)	16 (4.9%)
Indeterminate Cause of Death	3 (0.9%)	2 (0.6%)
Deaths due to AE	**19 (5.9)**	**22 (6.8)**
Infections and infestations	**13 (5.2)**	**16 (4.9)**
COVID-19 (including COVID-19 pneumonia)	8 (2.5)	11 (3.4)***
Pneumonia (excluding COVID-19 pneumonia)*	3 (0.9)	2 (0.6)
Sepsis*	2 (0.6)	2 (0.6)
Endocarditis	0 (0.0	1 (0.3)
General disorders and administration site conditions	**1(0.6)**	**0 (0.0)**
Malaise	1 (0.3)	0 (0.)
Cardiac disorders	**0 (0.0)**	**5 (1.5)**
Myocardial infarction*	0 (0.0)	2 (0.6)**
Ventricular Arrhythmia	0 (0.0)	1 (0.3)
Cardiac failure acute	0 (0.0)	1 (0.3)
Congestive cardiomyopathy	0 (0.0)	1 (0.3)
Nervous system disorders	**1 (0.3)**	**2 (0.9)**
Central nervous system hemorrhage	1 (0.3)**	1 (0.3)
Cerebral infarction	0 (0.0)	1 (0.3)
Neoplasms, benign, malignant and unspecified	**3 (0.9)**	**1 (0.3)**
Vascular disorders	**1 (0.3)**	**0 (0.0)**
Aortic aneurysm rupture	1 (0.3)	0 (0.0)

Source: Reviewer generated from ADAE and ADSL datasets submitted on September 20, 2022
* includes multiple preferred terms. Refer to section 17.6 for a detailed description of FDA grouping
** CNS hemorrhage occurred after fall associated with head trauma.
***One patient had fatal myocardial infarction in the setting of COVID-19.

Data:

All Zanubrutinib (N=1550) safety data:

Table 58: TEAE Leading to Death by System Organ Class and Preferred Term (≥ 3 patients in any group) (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Death	14 (3.6)	13 (4.0)	21 (4.0)	36 (3.8)	76 (4.9)
Infections and infestations	7 (1.8)	11 (3.4)	16 (3.0)	23 (2.5)	39 (2.5)
Pneumonia	1 (0.3)	3 (0.9)	6 (1.1)	7 (0.7)	11 (0.7)
COVID-19	4 (1.0)	3 (0.9)	4 (0.8)	8 (0.9)	9 (0.6)
COVID-19 pneumonia	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
General disorders and administration site conditions	0 (0.0)	2 (0.6)	4 (0.8)	4 (0.4)	11 (0.7)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	5 (0.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)

Data cut-off: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304); Data Source: ADSL, ADAE
Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.

Programmer: qiannan.tong, Location: /bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t_te

ae_soc_pt.sas Output: t-2-7-4-2-2-4-teae-soc-pt-dth.rtf (Date Generated: 23AUG2021:23:12)

The FDA's Assessment:

The updated summary of fatal TEAEs in the ISS pool, that includes the 1 Dec 2021 CCOD for study BGB-3111-305 is shown below. Overall with the exception of the increased number of overall deaths, the rates and types of AEs are similar to the original ISS analysis.

Table 59: TEAEs Leading to Death in ≥ 3 Patients in the ISS (Safety Analysis Set)

System Organ Class Preferred Term	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Death	91 (5.8)
Infections and infestations	45 (2.9)
Pneumonia	23 (1.5)
COVID-19 (including COVID-19 pneumonia)	17 (1.1)
General disorders and administration site conditions	13 (0.7)
Multiple organ dysfunction syndrome	6 (0.4)
Death	5 (0.3)
Neoplasms benign, malignant and unspecified	12 (0.8)
Cardiac disorders	10 (0.6)
Cardiac Failure	3 (0.2)
MI	3 (0.2)
Ventricular Arrhythmia	3 (0.2)
Nervous system disorders	5 (0.3)
CNS hemorrhage	4 (0.3)
Injury, poisoning and procedural complications	4 (0.3)
Respiratory thoracic and mediastinal disorders	4 (0.3)
Respiratory Failure	3 (0.2)

Source: FDA analysis

Data:

The following Grade 5 (fatal) TEAE were reported for each group:

In **Study BGB-3111-304 zanubrutinib population (N=391 including cohort 1 and 1a and cohort2)**, Grade 5 adverse events (by preferred terms) were reported for 14 patients (3.6%), with fatal adverse events resulting from infections and infestations (7 patients, 1.8%) or COVID-19 (4 patients, 1.0%) (Table 58).

In **Study BGB-3111-305,** In zanubrutinib arm, Grade 5 adverse events were reported for 13 patients (4.0%), with fatal adverse events resulting from infections and infestations (11 patients, 3.4%), pneumonia (3 patients, 0.9%), or COVID-19 (3 patients, 0.3%) (Table 58). In the ibrutinib arm, Grade 5 adverse events were reported for 15 patients (4.6%), with fatal adverse events resulting from infections and infestations (9 patients, 2.8%), pneumonia (2 patients, 0.6%), or COVID-19 (2 patients, 0.6%)

In the **All Zanubrutinib** group, Grade 5 adverse events (by preferred terms) were reported for 76 patients (4.9%), with fatal adverse events resulting from pneumonia (11 patients, 0.7%), COVID-19 (9 patients, 0.6%) or multiple organ dysfunction syndrome (5 patients, 0.3%). (Table 58).

In the **All R/R CLL/SLL** group, Grade 5 adverse events were reported for 21 patients (4.0%) (Table 58). No deaths for unknown reasons were reported while on treatment or within 30 days of the last dose of zanubrutinib.

In the **All CLL/SLL** group, Grade 5 adverse events were reported for 36 patients (3.8%). No deaths for unknown reasons were reported while on treatment or within 30 days of the last dose of zanubrutinib.

The Applicant's Position:

Given the co-morbidities and underlying malignancies in an elderly population, it is not unexpected for patients receiving immunosuppressive treatments to experience fatal AEs. In the CLL studies (304 and 305), the incidence rate of fatal AEs for zanubrutinib treatment was comparable to, or lower than, that for active comparators. Zanubrutinib was well tolerated and showed an acceptable safety profile that is consistent with what had been in the zanubrutinib clinical trials for the treatment of B-cell malignancies.

The FDA's Assessment:

The Agency disagrees with the Applicant's position regarding treatment-emergent AEs in the TN CLL/SLL population in study BGB-3111-304. At the time of the Cohort 1 primary (late interim) PFS analysis (CCOD 7 March 2021), there were increased deaths in the zanubrutinib arm (16; 6.6%) compared to the BR arm (14; 5.9%). The OS HR at the time of the primary PFS analysis was 1.07 (95% CI: 0.51, 2.22); raising a concern for the potential for harm in the zanubrutinib arm despite the observed advantage observed on PFS. Additional OS follow-up was requested by the Agency and provided by the Applicant with a CCOD of March 7, 2022. The additional follow-up, although still reflected limited OS events, was reassuring for a non-worsening trend in OS.

The safety profile of zanubrutinib in the ISS population (N = 1550) was consistent with the know safety profile for zanubrutinib and similar to that of the CLL/SLL population. Of note, a potential signal for ventricular arrhythmias was identified, with fatal events occurring in 2 (0.2%) of the ISS population. Refer to section 8.2.5.2 regarding cardiac arrhythmias and revised labeling to address this issue.

8.2.4.4 Serious Adverse Events

Data:

Study BGB-3111-304

The incidence of serious adverse events was generally comparable in the zanubrutinib arms in Cohort 1 and 2, and BR arm in Cohort 1.

In **Cohort 1**, serious adverse events were reported in 87 (36.3%) and 93 (41.0%) patients in the zanubrutinib (Arm A) and B+R (Arm B) arms, respectively. The most common serious adverse events were COVID-19 (8 [3.3%] patients) and COVID-19 pneumonia (7 [2.9%] patients) in the zanubrutinib arm (Arm A) and pyrexia (16 [7.0%] patients) and febrile neutropenia (11 [4.8%] patients) in the B+R arm (Arm B).

In **Cohort 2**, serious adverse events were reported in 45 (40.5%) patients (Table 60). The most common serious adverse events were pneumonia (6 [5.4%] patients), fall, and atrial fibrillation (each 3 [2.7%] patients).

Table 60: **Serious Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients in Any Arm by System Organ Class and Preferred Term in Cohort 1 and Cohort2 (Safety Analysis Set)**

	Cohort1		Cohort2
System Organ Class Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Patients With at Least One Serious AE	93 (41.0)	87 (36.3)	45 (40.5)
Infections and infestations	28 (12.3)	41 (17.1)	19 (17.1)
COVID-19	0 (0.0)	7 (2.9)	1 (0.9)
COVID-19 pneumonia	0 (0.0)	7 (2.9)	1 (0.9)
Pneumonia	6 (2.6)	4 (1.7)	6 (5.4)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Cardiac disorders	6 (2.6)	17 (7.1)	3 (2.7)
Atrial fibrillation	1 (0.4)	4 (1.7)	3 (2.7)
Injury, poisoning and procedural complications	10 (4.4)	9 (3.8)	7 (6.3)
Fall	0 (0.0)	0 (0.0)	3 (2.7)
Infusion related reaction	7 (3.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	18 (7.9)	7 (2.9)	2 (1.8)
Febrile neutropenia	11 (4.8)	1 (0.4)	1 (0.9)
Gastrointestinal disorders	11 (4.8)	5 (2.1)	3 (2.7)
Diarrhea	5 (2.2)	0 (0.0)	0 (0.0)

	Cohort1		Cohort2
System Organ Class Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
General disorders and administration site conditions	16 (7.0)	5 (2.1)	2 (1.8)
Pyrexia	16 (7.0)	2 (0.8)	2 (1.8)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arm A and 90 days after the last dose of B or R (Arm B) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first.
Post-Treatment AEs include AEs that had an onset date or was worsening in severity during the post-treatment follow-up phase, defined as from the day after the last dose (either zanubrutinib in Arm A, or B or R in Arm B) to the date of PD, except for the events after patients in Arm B crossover to zanubrutinib.
Patients with multiple events for a given preferred term and system organ class were counted only once for each preferred term and system organ class, respectively. Events were sorted by descending order within system organ class, and by preferred term within system organ class in the Treatment-Emergent and Post-treatment Cohort 1 Zanubrutinib column.
Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_teae_postteae_ab.sas
Output: t-14-3-1-2-3-2-1-teae-pt-ser-c1-saf.rtf (Date Generated: 06SEP2021:05:36)

FDA Assessment:

For increased sensitivity, the Agency conducted an additional analysis using revised grouping of some preferred terms. The Agency's revised grouping included COVID-19 and COVID-19 pneumonia in the group "COVID-19" which was the most common SAE in the zanubrutinib group (5.4%). Additional SAEs occurring in ≥ 2% of patients in the zanubrutinib arm and not included in the Applicant's table were myocardial infarction (2.9%), and SPM (2.9%). Refer to section 8.2.5 for further discussion of cardiac adverse events and second primary malignancies. SAEs using revised grouping is displayed in the table below. Refer to the Appendix (Table 124) for additional grouping descriptions.

Table 61: Serious Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients in Any Arm by System Organ Class and Preferred Term in Cohort 1 and Cohort 2 (Safety Analysis Set) – Revised FDA Grouping

	Cohort1		Cohort2
System Organ Class Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Patients With at Least One Serious AE	93 (41.0)	87 (36.3)	45 (40.5)
Infections and infestations	28 (12.3)	41 (17.1)	19 (17.1)
COVID-19 (including COVID-19 pneumonia)	0 (0.0)	13 (5.4)	2 (1.8)
Pneumonia (excluding COVID-19 pneumonia)	7 (3.0)	5 (2.1)	7 (6.3)
Sepsis	9 (4.0)	4 (1.7)	4 (3.6)
Cardiac disorders	6 (2.6)	17 (7.1)	3 (2.7)
Myocardial infarction	2 (0.9)	7 (2.9)	0 (0.0)
Atrial fibrillation	1 (0.4)	4 (1.7)	3 (2.7)
Injury, poisoning and procedural complications	10 (4.4)	9 (3.8)	7 (6.3)
Fall	0 (0.0)	0 (0.0)	3 (2.7)
Infusion related reaction	7 (3.1)	0 (0.0)	0 (0.0)
Neoplasms, benign, malignant and unspecified	2 (0.9)	14 (5.8)	11 (9.9)
Second Primary Neoplasm	1 (0.4)	7 (2.9)	5 (4.5)
Blood and lymphatic system disorders	18 (7.9)	7 (2.9)	2 (1.8)
Febrile Neutropenia	11 (4.8)	1 (0.4)	1 (0.9)
Gastrointestinal disorders	11 (4.8)	5 (2.1)	3 (2.7)
Diarrhea	5 (2.2)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	16 (7.0)	5 (2.1)	2 (1.8)
Pyrexia	16 (7.0)	2 (0.8)	2 (1.8)

Source: FDA analysis

Data:

Study BGB-3111-305

The incidence of serious adverse events was generally comparable between the zanubrutinib arm and ibrutinib arm. Serious adverse events reported in ≥ 2 patients in either arm in the Safety Analysis Set are presented in Table 62. Serious adverse events within the cardiac

disorders were reported in 14 (4.3%) patients in the ibrutinib arm, while only 2 patients (one with atrial flutter [(b) (6)] and the other with cardiac failure [(b) (6)] reported serious adverse events related to cardiac disorders in the zanubrutinib arm (Table 14.3.1.2.2.3 of BGB-3111-305 CSR Body). Patient (b) (6) had a medical history of atrial flutter, and Patient (b) (6) had a medical history of left ventricular dysfunction, pulmonary hypertension, ventricular hypokinesia, mitral valve incompetence, tricuspid valve incompetence and hypertension (Listing 16.2.7.2 and Listing 16.2.8.2 of BGB-3111-305 CSR Body).

Table 62: Serious Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2 Patients in Either Arm (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One Serious TEAE	70 (21.6)	82 (25.3)
Blood and lymphatic system disorders		
Anaemia	3 (0.9)	3 (0.9)
Hypoglobulinaemia	1 (0.3)	2 (0.6)
Haemolytic anaemia	0 (0.0)	2 (0.6)
Cardiac disorders		
Atrial fibrillation	0 (0.0)	4 (1.2)
Cardiac arrest	0 (0.0)	2 (0.6)
Myocardial infarction	0 (0.0)	2 (0.6)
Ventricular fibrillation	0 (0.0)	2 (0.6)
General disorders and administration site conditions		
Pyrexia	2 (0.6)	3 (0.9)
Malaise	2 (0.6)	0 (0.0)
Infections and infestations		
Pneumonia	10 (3.1)	15 (4.6)
COVID-19	7 (2.2)	3 (0.9)
Urinary tract infection	3 (0.9)	5 (1.5)
COVID-19 pneumonia	2 (0.6)	5 (1.5)
Sepsis	3 (0.9)	1 (0.3)
Upper respiratory tract infection	0 (0.0)	2 (0.6)
Investigations		
Platelet count decreased	2 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders		
Haemarthrosis	2 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder transitional cell carcinoma	2 (0.6)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident	3 (0.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	1 (0.3)	2 (0.6)
Respiratory failure	0 (0.0)	2 (0.6)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.

TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Patients with multiple events for a given preferred term and system organ class were counted only once for each preferred term and system organ class, respectively.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ae-socpt-cut-i.sas 09AUG2021 23:26 t-23-ae-socpt-ser-i.rtf

The FDA's Assessment:
The Applicant provided updated data with a CCOD of 1 Dec 2021 reflecting the primary analysis date for ORR. In addition, for increased sensitivity FDA analysis included revised grouping (refer to the Appendix). In general, the pattern of SAEs was similar at the interim and final ORR analysis timepoints, but with increased rates of SAEs with longer follow-up. SAEs are detailed in the table below.

Table 63: Serious Adverse Events Reported in ≥ 2 Patients in Either Arm of Study BGB-3111-305

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients with at least one serious TEAE	104 (32.1)	141 (43.5)
Infections and infestations		
COVID-19 (including COVID-19 pneumonia)	24 (7.4)	16 (4.9)
Pneumonia (excluding COVID-19 pneumonia)	17 (5.2)	26 (8.0)
Sepsis	6 (1.9)	3 (0.9)
Lower respiratory tract infection	5 (1.5)	1 (0.3)
Urinary Tract Infection	4 (1.2)	5 (1.5)
Urinary tract infection	3 (0.9)	5 (1.5)
Cellulitis	3 (0.9)	1 (0.3)
Herpesvirus infection	1 (0.4)	2 (0.6
Upper respiratory tract infection	1 (0.3)	2 (0.6)
Blood and lymphatic system disorders*		
Anemia	4 (1.2)	4 (1.2)
Thrombocytopenia	3 (0.9)	2 (0.6)
Neutropenia	2 (0.6)	2 (0.6)
Hypogammaglobulinemia	1 (0.3)	2 (0.6)
Lymphadenopathy	1 (0.3)	2 (0.6)
Hemolytic anemia	0 (0.0)	2 (0.6)
Cardiac disorders		
Atrial fibrillation or flutter	2 (0.6)	8 (2.5)
Myocardial infarction or ischemia	2 (0.6)	3 (0.9)
Ventricular arrhythmia	0 (0.0)	3 (0.9)
Cardiac failure	2 (0.6)	5 (1.4)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
General disorders and administration site conditions		
Pyrexia	2 (0.6)	5 (1.5)
Death, unspecified	1 (0.3)	2 (0.6)
Malaise	2 (0.6)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Hemarthrosis	2 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified		
Second primary neoplasm	18 (5.5)	14 (4.3)
Injury Poisoning and Procedural Complications		
Fall	2 (0.6)	2 (0.6)
Nervous system disorders		
Cerebrovascular accident	3 (0.9)	2 (0.6)
Transient ischemic attack	1 (0.3)	2 (0.6)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	2 (0.6)	2 (0.6)
Acute respiratory failure	1 (0.3)	4 (1.2)
Gastrointestinal disorders		
Colitis	2 (0.6)	1 (0.3)
Inguinal hernia	1 (0.3)	2 (0.6)
Constipation	0 (0.0)	2 (0.6)
Hepatobiliary disorders		
Hepatitis	0 (0.0)	2 (0.6)
Renal and Urinary Disorders		
Renal insufficiency	0 (0.0)	2 (0.6)
Multiple SOCs		
Hemorrhage	5 (1.5)	10 (3.1)
Investigations		
Hypoglobulinemia	1 (0.3)	2 (0.6)

Source: FDA analysis
*Includes laboratory investigations

Data:

All Zanubrutinib (N=1550) safety data:

The below table presents the serious treatment-emergent adverse events reported in the BGB-3111-304, BGB-3111-305, All R/R CLL/SLL, All CLL/SLL, and All Zanubrutinib groups. Pneumonia was the most common serious adverse event in every group (Table 64).

Table 64: Serious TEAE Reported in ≥ 1% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Serious TEAE	145 (37.1)	70 (21.6)	185 (35.2)	341 (36.4)	623 (40.2)
Infections and infestations	63 (16.1)	35 (10.8)	110 (21.0)	179 (19.1)	307 (19.8)
Pneumonia	12 (3.1)	10 (3.1)	44 (8.4)	57 (6.1)	106 (6.8)
Urinary tract infection	3 (0.8)	3 (0.9)	8 (1.5)	11 (1.2)	20 (1.3)
Cellulitis	3 (0.8)	1 (0.3)	5 (1.0)	8 (0.9)	19 (1.2)
COVID-19	8 (2.0)	7 (2.2)	9 (1.7)	17 (1.8)	18 (1.2)
COVID-19 pneumonia	8 (2.0)	2 (0.6)	2 (0.4)	10 (1.1)	14 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25 (6.4)	10 (3.1)	23 (4.4)	49 (5.2)	80 (5.2)
Lung adenocarcinoma	4 (1.0)	0 (0.0)	0 (0.0)	4 (0.4)	4 (0.3)
Blood and lymphatic system disorders	13 (3.3)	9 (2.8)	16 (3.0)	29 (3.1)	61 (3.9)
Anaemia	4 (1.0)	3 (0.9)	5 (1.0)	9 (1.0)	21 (1.4)
Cardiac disorders	20 (5.1)	2 (0.6)	13 (2.5)	33 (3.5)	60 (3.9)
Atrial fibrillation	7 (1.8)	0 (0.0)	2 (0.4)	9 (1.0)	15 (1.0)
Respiratory, thoracic and mediastinal disorders	8 (2.0)	5 (1.5)	12 (2.3)	20 (2.1)	54 (3.5)
Pleural effusion	4 (1.0)	1 (0.3)	2 (0.4)	6 (0.6)	17 (1.1)
General disorders and administration site conditions	8 (2.0)	5 (1.5)	8 (1.5)	18 (1.9)	52 (3.4)
Pyrexia	4 (1.0)	2 (0.6)	3 (0.6)	8 (0.9)	26 (1.7)
Reproductive system and breast disorders	5 (1.3)	0 (0.0)	1 (0.2)	6 (0.6)	9 (0.6)
Benign prostatic hyperplasia	4 (1.0)	0 (0.0)	1 (0.2)	5 (0.5)	5 (0.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg

QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-15-ser-teae-soc-pt-1-i.rtf

The FDA's Assessment:

FDA analysis of SAEs focused primarily on the two randomized studies in CLL/SLL and the ISS safety population comprised of 1550 patients with hematologic malignancies treated with the approved zanubrutinib dosage. The Applicant provided updated data reflecting a CCOD of 1 Dec 2021 for study BGB-3111-305. The revised summary of SAEs for the ISS population is displayed in the table below. The most common SAEs in the ISS safety pool were pneumonia (8.3%), second primary malignancies (5.0%), hemorrhage (3.2%), COVID-19 (3%) and sepsis (2.2%). Generally, rates and types of SAEs were similar in the ISS population compared to the CLL/SLL population in the two randomized studies.

Table 65: Serious TEAEs Reported in ≥ 1% of the ISS population (N = 1550)

System Organ Class Preferred Term	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Serious TEAE	623 (40.2)
Infections and infestations	
Pneumonia (excluding COVID-19_	128 (8.3)
COVID-19 (including COVID-19 pneumonia)	46 (3.0)
Sepsis	34 (2.2)
Lower respiratory tract infection	23 (1.5)
Urinary tract infection	21 (1.3)
Cellulitis	21 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Second Primary Malignancy	77 (5.0)
Blood and lymphatic system disorders*	61 (3.9)
Neutropenia	30 (1.9)
Anemia	22 (1.4)
Cardiac disorders	60 (3.9)
Atrial fibrillation	20 (1.3)
Multiple SOC	
Hemorrhage	49 (3.2)
General disorders and administration site conditions	
Pyrexia	26 (1.7)
Respiratory, thoracic and mediastinal disorders	
Pleural effusion	18 (1.2)

*includes laboratory abnormalities
Source: FDA analysis

The Applicant's Position:

As expected for patients with hematologic malignancies, infections were the most commonly reported serious events. The incidences of serious adverse events remained comparable among the different groups.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment. There was no notable difference in the rate or distribution of SAEs in the ISS population compared to the study BGB-3111-304 and study BGB-3111-305 populations.

8.2.4.5 Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Study BGB-3111-304:

In **Cohort 1**, the incidence of treatment-emergent adverse events leading to treatment discontinuation was numerically lower in the zanubrutinib arm (Arm A; 8.3%) than in the B+R arm (Arm B; 13.7%) in the Safety Analysis Set. COVID-19, occurring in 2.1% of patients, was the most common treatment-emergent adverse event leading to treatment discontinuation in the zanubrutinib arm (Arm A). Neutropenia, occurring in 1.8% of patients, was the most common treatment-emergent adverse event leading to treatment discontinuation in the B+R arm.

In **Cohort 2**, 6 (5.4%) patients experienced treatment-emergent adverse events leading to treatment discontinuation. The events that led to treatment discontinuation included pulseless electrical activity and aortic dissection in 1 patient and malignant melanoma, pneumonia, pseudomonal sepsis, renal failure, and arthralgia, each in 1 patient.

Table 66: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term in Cohort 1 and Cohort 2 (Safety Analysis Set)

System Organ Class Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One TEAE Leading to Treatment Discontinuation	31 (13.7)	20 (8.3)	6 (5.4)
Blood and lymphatic system disorders	10 (4.4)	0 (0.0)	0 (0.0)
Neutropenia	4 (1.8)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (1.3)	0 (0.0)	0 (0.0)
Anaemia	1 (0.4)	0 (0.0)	0 (0.0)
Febrile neutropenia	1 (0.4)	0 (0.0)	0 (0.0)
Immune thrombocytopenia	1 (0.4)	0 (0.0)	0 (0.0)
Lymphopenia	1 (0.4)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	8 (3.3)	1 (0.9)
Anal squamous cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)
Breast cancer	0 (0.0)	1 (0.4)	0 (0.0)
Chronic myeloid leukaemia	0 (0.0)	1 (0.4)	0 (0.0)
Fibroadenoma of breast	1 (0.4)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	1 (0.4)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.4)	0 (0.0)
Lung squamous cell carcinoma recurrent	0 (0.0)	1 (0.4)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	1 (0.9)
Metastatic squamous cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)
Ovarian cancer	0 (0.0)	1 (0.4)	0 (0.0)
Infections and infestations	4 (1.8)	6 (2.5)	2 (1.8)
COVID-19	0 (0.0)	5 (2.1)	0 (0.0)
Clostridium difficile colitis	1 (0.4)	0 (0.0)	0 (0.0)
Endocarditis	0 (0.0)	1 (0.4)	0 (0.0)

System Organ Class Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Pneumonia	1 (0.4)	0 (0.0)	1 (0.9)
Pneumonia chlamydial	1 (0.4)	0 (0.0)	0 (0.0)
Pseudomonal sepsis	1 (0.4)	0 (0.0)	1 (0.9)
Urinary tract infection	1 (0.4)	0 (0.0)	0 (0.0)
Wound infection	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (0.9)	1 (0.4)	1 (0.9)
Angina unstable	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)	0 (0.0)
Pulseless electrical activity	0 (0.0)	0 (0.0)	1 (0.9)
Renal and urinary disorders	0 (0.0)	1 (0.4)	1 (0.9)
Hydronephrosis	0 (0.0)	1 (0.4)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	2 (0.8)	0 (0.0)
Pneumonitis	1 (0.4)	1 (0.4)	0 (0.0)
Pulmonary fibrosis	0 (0.0)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.4)	0 (0.0)
Hyponatraemia	0 (0.0)	1 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.9)
Arthralgia	0 (0.0)	0 (0.0)	1 (0.9)
Nervous system disorders	0 (0.0)	1 (0.4)	0 (0.0)
Haemorrhagic transformation stroke	0 (0.0)	1 (0.4)	0 (0.0)
Skin and subcutaneous tissue disorders	3 (1.3)	1 (0.4)	0 (0.0)
Ischaemic skin ulcer	0 (0.0)	1 (0.4)	0 (0.0)
Rash	3 (1.3)	0 (0.0)	0 (0.0)
Vascular disorders	1 (0.4)	0 (0.0)	1 (0.9)
Aortic dissection	0 (0.0)	0 (0.0)	1 (0.9)
Hypotension	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders	4 (1.8)	0 (0.0)	0 (0.0)
Drug hypersensitivity	2 (0.9)	0 (0.0)	0 (0.0)
Cytokine release syndrome	1 (0.4)	0 (0.0)	0 (0.0)
Infusion related hypersensitivity reaction	1 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	3 (1.3)	0 (0.0)	0 (0.0)
Enterocolitis	1 (0.4)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.4)	0 (0.0)	0 (0.0)
Nausea	1 (0.4)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	3 (1.3)	0 (0.0)	0 (0.0)
Infusion related reaction	3 (1.3)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
General disorders and administration site conditions	2 (0.9)	0 (0.0)	0 (0.0)
Asthenia	1 (0.4)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.4)	0 (0.0)	0 (0.0)
Investigations	1 (0.4)	0 (0.0)	0 (0.0)
Transaminases increased	1 (0.4)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.4)	0 (0.0)	0 (0.0)
Insomnia	1 (0.4)	0 (0.0)	0 (0.0)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0. Adverse event grades are evaluated based on NCI-CTCAE (version 4.03)
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arm A and 90 days after the last dose of B or R (Arm B) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first. Patients with multiple events for a given preferred term and system organ class were counted only once at the worst severity for the preferred term and system organ class, respectively. Events were sorted by descending order within system organ class, and by preferred term within system organ class in the Treatment-Emergent Total column.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_teae_postteae_ab.sas
Output: t-14-3-1-2-5-2-1-teae-socpt-disc-mgrd-c1-saf.rtf (Date Generated: 06SEP2021:05:36)

The FDA's Assessment:

The Agency agrees with the Applicant's description of AEs resulting in discontinuation in Cohort 1 of study BGB-3111-304. A simplified, revised table using FDA grouping is displayed in the table below. In Cohort 1, AEs led to permanent discontinuation of zanubrutinib in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 67: Adverse Events Leading to Treatment Discontinuation in > 1 Patient in Either Arm (Study BGB-3111-304 Cohort 1)

System Organ Class Preferred Term	Cohort 1	
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)
Patients With at Least One TEAE Leading to Treatment Discontinuation	31 (13.7)	20 (8.3)
Blood and lymphatic system disorders		
Neutropenia (including febrile neutropenia)	5 (2.2)	0 (0.0)
Thrombocytopenia	3 (1.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Second Primary Malignancy	0 (0.0)	8 (3.3)
Infections and infestations		
COVID-19 (including COVID-19 pneumonia)	0 (0.0)	5 (2.1)
Pneumonia (excluding COVID-19)	2 (0.9)	0 (0.0)
Cardiac disorders		
Myocardial infarction	2 (0.8)	0 (0.0)
Aortic dissection	0 (0.)	0 (0.0)
Gastrointestinal disorders		
Colitis	2 (0.9)	0 (0.0)
Skin and subcutaneous tissue disorders		
Rash	3 (1.3)	0 (0.0)
Immune system disorders		
Drug hypersensitivity	2 (0.9)	0 (0.0)
Injury, poisoning and procedural complications		
Infusion related reaction	4 (1.7)	0 (0.0)

Source: FDA analysis

In Cohort 2, AEs led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51% by FDA analysis. AEs resulting in treatment discontinuation included aortic dissection, sepsis, pneumonia, renal failure, SPM, and arthralgia (1 each). The leading causes of dose modification (≥5% of all patients) were pneumonia, neutropenia, SPM, and diarrhea.

Data:

Study BGB-3111-305:

The incidence of adverse events leading to treatment discontinuation was lower in the zanubrutinib arm (6.5%) than in the ibrutinib arm (10.5%) in the Safety Analysis Set (Table 68). The most common TEAEs leading to treatment discontinuation were COVID-19 (0.9%) and pneumonia (0.6%) for zanubrutinib; and pneumonia and atrial fibrillation (0.9% each) for ibrutinib.

Table 68: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE Leading to Treatment Discontinuation	21 (6.5)	34 (10.5)
Infections and infestations	10 (3.1)	9 (2.8)
COVID-19	3 (0.9)	2 (0.6)
Pneumonia	2 (0.6)	3 (0.9)
COVID-19 pneumonia	0 (0.0)	2 (0.6)
Bronchitis	0 (0.0)	1 (0.3)
Infection	1 (0.3)	0 (0.0)
Pneumonia cryptococcal	1 (0.3)	0 (0.0)
Pneumonia fungal	1 (0.3)	0 (0.0)
Respiratory tract infection	1 (0.3)	0 (0.0)
Septic shock	0 (0.0)	1 (0.3)
Sinusitis	1 (0.3)	0 (0.0)
Cardiac disorders	0 (0.0)	8 (2.5)
Atrial fibrillation	0 (0.0)	3 (0.9)
Cardiac arrest	0 (0.0)	1 (0.3)
Cardiac failure	0 (0.0)	1 (0.3)
Myocardial infarction	0 (0.0)	1 (0.3)
Palpitations	0 (0.0)	1 (0.3)
Ventricular fibrillation	0 (0.0)	1 (0.3)
Blood and lymphatic system disorders	1 (0.3)	3 (0.9)
Haemolytic anaemia	0 (0.0)	2 (0.6)
Anaemia	0 (0.0)	1 (0.3)
Neutropenia	1 (0.3)	0 (0.0)
Thrombocytopenia	0 (0.0)	1 (0.3)
Gastrointestinal disorders	3 (0.9)	1 (0.3)
Diarrhoea	1 (0.3)	1 (0.3)
Haemorrhoids	1 (0.3)	0 (0.0)
Oral mucosal blistering	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	2 (0.6)
Anal squamous cell carcinoma	0 (0.0)	1 (0.3)
Laryngeal cancer	1 (0.3)	0 (0.0)
Small cell lung cancer metastatic	1 (0.3)	0 (0.0)
Thymoma malignant	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	3 (0.9)
Acute respiratory failure	1 (0.3)	1 (0.3)
Dyspnoea	0 (0.0)	1 (0.3)
Epistaxis	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	3 (0.9)	1 (0.3)
Pruritus	1 (0.3)	0 (0.0)
Rash	1 (0.3)	0 (0.0)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Rash maculo-papular	0 (0.0)	1 (0.3)
Skin haemorrhage	1 (0.3)	0 (0.0)
General disorders and administration site conditions	1 (0.3)	2 (0.6)
Malaise	1 (0.3)	0 (0.0)
Oedema peripheral	0 (0.0)	1 (0.3)
Swelling face	0 (0.0)	1 (0.3)
Nervous system disorders	0 (0.0)	2 (0.6)
Central nervous system haemorrhage	0 (0.0)	1 (0.3)
Cerebral infarction	0 (0.0)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	0 (0.0)
Cholecystitis	1 (0.3)	0 (0.0)
Investigations	0 (0.0)	1 (0.3)
Blood bilirubin increased	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.3)
Pain in extremity	0 (0.0)	1 (0.3)
Renal and urinary disorders	0 (0.0)	1 (0.3)
Haematuria	0 (0.0)	1 (0.3)
Vascular disorders	0 (0.0)	1 (0.3)
Hypertension	0 (0.0)	1 (0.3)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Adverse event grades were evaluated based on NCI-CTCAE Version 4.03.
Patients with multiple events for a given preferred term were counted only once for each preferred term.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ae-socpt-i.sas 09AUG2021 23:29 t-25-ae-socpt-dis-i.rtf

The FDA's Assessment:

The Applicant provide updated data reflecting a CCOD of 1 Dec 2021 used for the primary efficacy analysis. Compared to the original CCOD of 30 Dec 2020, there were more patients who discontinued therapy due to AEs. Similar to the original analysis, there was a numerically higher number of patients who discontinued therapy due to an AE in the ibrutinib arm (17.6%) compared to the zanubrutinib arm (13.0%). The most common reason for discontinuation in both arms was pneumonia. A summary of discontinuations due to AEs is displayed in the table below.

Table 69: Summary of Treatment Discontinuations Due to AEs in Study BGB-3111-305 (CCOD December 1, 2021)

System Organ Class Preferred Term	Zanubrutinib N = 324	Ibrutinib N = 324
Patients With at Least One TEAE Leading to Treatment Discontinuation, n (%)	42 (13)	57 (18)
Infections and infestations		
COVID-19 (including COVID-19 pneumonia)	8 (2.5)	11 (3.4)
Pneumonia (excluding COVID-19)*	8 (2.5)	5 (1.5)
Respiratory tract Infection	1 (0.3)	1 (0.3)
Upper Respiratory Tract Infection*	1 (0.3)	0 (0.0)
Infection	1 (0.3)	0 (0.0)
Lower Respiratory Tract Infection*	0 (0.0)	1 (0.3)
Pulmonary Tuberculosis	0 (0.0)	1 (0.3)
Sepsis*	0 (0.0)	1 (0.0)
Neoplasms		
Second Primary Malignancy	8 (2.5)	5 (1.5)
Blood and lymphatic system disorders**		
Neutropenia (including febrile neutropenia)	2 (0.6)	1 (0.3)
Anemia	1 (0.3)	1 (0.3)
Thrombocytopenia	0 (0.0)	3 (0.9)
Hemolytic anemia	0 (0.0)	2 (0.6)
Cardiac disorders		
Ventricular arrhythmia	1 (0.3)	2 (0.6)
Atrial fibrillation and flutter	0 (0)	5 (1.5)
Cardiac failure*	0 (0.0)	4 (1.2)
Myocardial infarction or ischemia	0 (0.0)	1 (0.3)
Palpitations	0 (0.0)	1 (0.3)
Gastrointestinal disorders		
Diarrhea*	1 (0.3)	2 (0.6)
Hemorrhoids	1 (0.3)	0 (0.0)
Mucositis*	1 (0.3)	0 (0.0)
Vomiting	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders		
Rash	1 (0.3)	3 (0.9)
Pruritis	1 (0.3)	0 (0.0)
Purpura	1 (0.3)	0 (0.0)
Vascular disorders		
Hemorrhage*	2 (0.6)	5 (1.5)
Aortic aneurysm rupture	1 (0.3)	0 (0.0)
Hypertension	0 (0.0)	1 (0.3)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	3 (0.9)
Respiratory failure	2 (0.6)	1 (0.3)

System Organ Class Preferred Term	Zanubrutinib N = 324	Ibrutinib N = 324
Dyspnea	0 (0.0)	1 (0.3)
Nervous system disorders		
Cerebral infarction	0 (0.0)	1 (0.3)
Hepatobiliary disorders**		
Cholecystitis	1 (0.3)	0 (0.0)
Hypercalcemia	0 (0.0)	1 (0.3)
ALT increased	1 (0.3)	1 (0.3)
AST increased	1 (0.3)	0 (0.0)
Bilirubin increased	1 (0.3)	1 (0.3)
Gamma-glutamyl transferase increased		
Psychiatric disorders		
Agitation	0 (0.0))	1 (0.3)
Disorientation	0 (0.0)	1 (0.3)
General disorders		
Death NOS	1 (0.3)	1 (0.3)
Malaise	1 (0.3)	0 (0.0)
Edema	0 (0.0)	2 (0.6)
Swelling Face	0 (0.0)	1 (0.3)
Pyrexia	0 (0.0))	1 (0.3)
Metabolism and nutrition disorders		
Hypoalbuminemia	1 (0.3)	0 (0.0)
Cachexia	1 (0.0)	1 (0.0)
Hypercalcemia	0 (0.0)	1 (0.3)
Musculoskeletal and Connective System Disorders		
Pain in extremity	0 (0.0	1 (0.3)

Source: Reviewer generated from Applicant CSR with CCOD December 1, 2021, verified with ADSL and ADAE datasets submitted on September 20, 2022
*includes multiple FDA grouped terms, refer to section 17.5.1 for grouping
**includes laboratory investigations reported as adverse events

The Applicant's Description:
Data:

All Zanubrutinib (N=1550) safety data:

Adverse events leading to treatment discontinuation reported in ≥ 2 patients in any patient group are presented in Table 70 by system organ class and preferred term

Table 70: TEAEs Leading to Treatment Discontinuation Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Treatment Discontinuation	27 (6.9)	21 (6.5)	46 (8.8)	75 (8.0)	144 (9.3)
Infections and infestations	8 (2.0)	10 (3.1)	20 (3.8)	28 (3.0)	47 (3.0)
Pneumonia	1 (0.3)	2 (0.6)	6 (1.1)	7 (0.7)	14 (0.9)
COVID-19	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	10 (0.6)
Hepatitis B	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	3 (0.2)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Infection	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Pneumonia cryptococcal	0 (0.0)	1 (0.3)	2 (0.4)	2 (0.2)	2 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.3)	2 (0.6)	7 (1.3)	17 (1.8)	32 (2.1)
Breast cancer	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	4 (0.3)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Chronic myeloid leukaemia	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Laryngeal cancer	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Myelodysplastic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cardiac disorders	2 (0.5)	0 (0.0)	3 (0.6)	5 (0.5)	11 (0.7)
Cardiac arrest	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	1 (0.3)	4 (0.8)	6 (0.6)	10 (0.6)
Pleural effusion	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Nervous system disorders	2 (0.5)	0 (0.0)	3 (0.6)	5 (0.5)	9 (0.6)
Cerebral haemorrhage	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Haemorrhage intracranial	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Gastrointestinal disorders	0 (0.0)	3 (0.9)	5 (1.0)	5 (0.5)	8 (0.5)
Diarrhoea	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	3 (0.2)
General disorders and administration site conditions	0 (0.0)	1 (0.3)	2 (0.4)	2 (0.2)	8 (0.5)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Renal and urinary disorders	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)	7 (0.5)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Haematuria	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	3 (0.9)	3 (0.6)	4 (0.4)	7 (0.5)
Pruritus	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)	3 (0.6)	3 (0.3)	5 (0.3)
Anaemia	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	2 (0.1)
Neutropenia	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
Subdural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.

Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and

then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-16-teae-soc-pt-dsc-2p-i.rtf

The Applicant's Position:

The incidence of adverse events leading to treatment discontinuation was similar among all groups, with pneumonia and COVID-19 consistently being the most common adverse events leading to treatment discontinuation reported in all 5 groups.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment.

8.2.4.6 Dose Reduction Due to Adverse Effects

Data:

Study BGB-3111-304:

A numerically lower number of patients with dose reductions was observed in the zanubrutinib arm (18 [7.5%]) compared with the B+R arm (84 [37.0%]). Adverse events were the primary reason for dose reduction in both arms. Infusion interruptions occurred in 67 [29.5%] patients during rituximab treatment and 8 (3.5%) patients during bendamustine treatment.

Table 71: TEAEs Leading to Dose Reduction Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term in Cohort 1 (Safety Analysis Set)

System Organ Class Preferred Term	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)
Patients With at Least One TEAE Leading to Dose Reduction	84 (37.0)	18 (7.5)
Blood and lymphatic system disorders	62 (27.3)	1 (0.4)
Neutropenia	50 (22.0)	1 (0.4)
Thrombocytopenia	8 (3.5)	0 (0.0)
Febrile neutropenia	4 (1.8)	0 (0.0)
Anaemia	3 (1.3)	0 (0.0)
Leukopenia	2 (0.9)	0 (0.0)
Investigations	12 (5.3)	1 (0.4)
Neutrophil count decreased	9 (4.0)	1 (0.4)
Infections and infestations	6 (2.6)	1 (0.4)
Pneumonia	3 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (2.6)	1 (0.4)

System Organ Class Preferred Term	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)
Rash	3 (1.3)	0 (0.0)
Cardiac disorders	0 (0.0)	4 (1.7)
Atrial fibrillation	0 (0.0)	4 (1.7)
Gastrointestinal disorders	3 (1.3)	1 (0.4)
Nausea	2 (0.9)	0 (0.0)
General disorders and administration site conditions	3 (1.3)	1 (0.4)
Pyrexia	2 (0.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	4 (1.7)
Arthralgia	0 (0.0)	2 (0.8)
Injury, poisoning and procedural complications	0 (0.0)	3 (1.3)
Contusion	0 (0.0)	2 (0.8)
Nervous system disorders	1 (0.4)	2 (0.8)
Dizziness	0 (0.0)	2 (0.8)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0. Adverse event grades are evaluated based on NCI-CTCAE (version 4.03)
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arm A and 90 days after the last dose of B or R (Arm B) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first.
Post-Treatment AEs include AEs that had an onset date or was worsening in severity during the post-treatment follow-up phase, defined as from the day after the last dose (either zanubrutinib in Arm A, or B or R in Arm B) to the date of PD, except for the events after patients in Arm B crossover to zanubrutinib.
Patients with multiple events for a given preferred term and system organ class were counted only once at the worst severity for the preferred term and system organ class, respectively.
Events were sorted by descending order within system organ class, and by preferred term within system organ class in the Treatment-Emergent Total column.
Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_teae_postteae_ab.sas
Output: t-14-3-1-2-5-1-1-teae-socpt-dmod-mgrd-c1-saf.rtf (Date Generated: 06SEP2021:05:36)

Table 72: TEAEs Leading to Dose modification Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term in Cohort 2 (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 111) n (%)
Patients With at Least One TEAE Leading to Dose Modification	57 (51.4)
Infections and infestations	17 (15.3)
COVID-19	2 (1.8)
Pneumonia	5 (4.5)
COVID-19 pneumonia	2 (1.8)
Lower respiratory tract infection	2 (1.8)
Upper respiratory tract infection	2 (1.8)
Appendicitis	2 (1.8)
Gastrointestinal disorders	15 (13.5)
Diarrhoea	7 (6.3)
Vomiting	3 (2.7)
Nausea	4 (3.6)
Dental caries	2 (1.8)
Blood and lymphatic system disorders	10 (9.0)
Neutropenia	7 (6.3)
Cardiac disorders	4 (3.6)
Atrial fibrillation	4 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (7.2)
Basal cell carcinoma	3 (2.7)
Injury, poisoning and procedural complications	5 (4.5)
Fall	2 (1.8)
Nervous system disorders	4 (3.6)
Headache	2 (1.8)
Musculoskeletal and connective tissue disorders	2 (1.8)
Myalgia	2 (1.8)
Eye disorders	3 (2.7)
Vitreous detachment	2 (1.8)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0. Adverse event grades are evaluated based on NCI-CTCAE (version 4.03)
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after the last dose of zanubrutinib for zanubrutinib arms (A and C) following study drug discontinuation or the start of new anticancer therapy (including the zanubrutinib for Arm B patients crossed over), whichever comes first.
Patients with multiple events for a given preferred term and system organ class were counted only once at the worst severity for the preferred term and system organ class, respectively.
Events were sorted by descending order within system organ class, and by preferred term within system organ class in the Total column.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_teae_c.sas
Output: t-14-3-1-2-5-1-3-teae-socpt-mod-mgr-asaf-csaf.rtf (Date Generated: 06SEP2021:06:05)

Study BGB-3111-305:

A lower number of patients with dose reduction or dose interruption was observed in the zanubrutinib arm than in the ibrutinib arm.

Table 73: TEAEs Leading to Dose Reduction Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE Leading to Dose Reduction	24 (7.4)	31 (9.6)
Blood and lymphatic system disorders	3 (0.9)	7 (2.2)
Neutropenia	2 (0.6)	6 (1.9)
Infections and infestations	3 (0.9)	7 (2.2)
Pneumonia	2 (0.6)	3 (0.9)
Urinary tract infection	0 (0.0)	2 (0.6)
Musculoskeletal and connective tissue disorders	3 (0.9)	3 (0.9)
Muscle spasms	2 (0.6)	0 (0.0)
Pain in extremity	0 (0.0)	2 (0.6)
Vascular disorders	6 (1.9)	0 (0.0)
Hypertension	4 (1.2)	0 (0.0)
Haematoma	2 (0.6)	0 (0.0)
Cardiac disorders	2 (0.6)	2 (0.6)
Atrial fibrillation	2 (0.6)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	1 (0.3)
Epistaxis	2 (0.6)	1 (0.3)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Adverse event grades were evaluated based on NCI-CTCAE Version 4.03.
Patients with multiple events for a given preferred term and system organ class were counted only once at the worst severity for the preferred term and system organ class, respectively.

Events were sorted by decreasing frequency of system organ class and preferred term in the Total group.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ae-socptsev.sas 10AUG2021 01:47 t-14-3-1-2-4-5-ae-socptsev-dosered.rtf

All Zanubrutinib (N=1550) safety data:

Adverse events leading to dose reduction reported in ≥ 2 patients in any patient group are presented in Table 74 by system organ class and preferred term.

Table 74: TEAEs Leading to Dose Reduction Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Dose Reduction	25 (6.4)	24 (7.4)	45 (8.6)	70 (7.5)	116 (7.5)
Infections and infestations	2 (0.5)	3 (0.9)	11 (2.1)	13 (1.4)	21 (1.4)
Pneumonia	0 (0.0)	2 (0.6)	6 (1.1)	6 (0.6)	9 (0.6)
Hepatitis B reactivation	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.3)	3 (0.2)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	2 (0.1)
Gastrointestinal disorders	2 (0.5)	1 (0.3)	6 (1.1)	8 (0.9)	16 (1.0)
Diarrhoea	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	10 (0.6)
Vomiting	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	3 (0.2)
Nausea	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Blood and lymphatic system disorders	2 (0.5)	3 (0.9)	5 (1.0)	7 (0.7)	14 (0.9)
Neutropenia	1 (0.3)	2 (0.6)	4 (0.8)	5 (0.5)	9 (0.6)
Thrombocytopenia	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	3 (0.2)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Febrile neutropenia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	4 (1.2)	5 (1.0)	6 (0.6)	12 (0.8)
Purpura	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Petechiae	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Cardiac disorders	5 (1.3)	2 (0.6)	3 (0.6)	8 (0.9)	11 (0.7)
Atrial fibrillation	5 (1.3)	2 (0.6)	3 (0.6)	8 (0.9)	9 (0.6)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Musculoskeletal and connective tissue disorders	5 (1.3)	3 (0.9)	3 (0.6)	8 (0.9)	10 (0.6)
Arthralgia	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.3)	5 (0.3)
Muscle spasms	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Myalgia	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Injury, poisoning and procedural complications	3 (0.8)	1 (0.3)	2 (0.4)	5 (0.5)	9 (0.6)
Contusion	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	7 (0.5)
Investigations	2 (0.5)	1 (0.3)	3 (0.6)	5 (0.5)	9 (0.6)
Neutrophil count decreased	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	5 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.6)	3 (0.6)	4 (0.4)	8 (0.5)
Fatigue	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	3 (0.2)
Pain	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Vascular disorders	0 (0.0)	6 (1.9)	6 (1.1)	6 (0.6)	7 (0.5)
Hypertension	0 (0.0)	4 (1.2)	4 (0.8)	4 (0.4)	4 (0.3)
Haematoma	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Nervous system disorders	3 (0.8)	2 (0.6)	2 (0.4)	5 (0.5)	6 (0.4)
Dizziness	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Headache	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	6 (0.4)
Epistaxis	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	4 (0.3)
Tumour lysis syndrome	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg

QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-17-teae-soc-pt-redc-2p-i.rtf

Adverse Events Leading to Dose Interruption

Adverse events leading to dose interruption reported in ≥ 1% of patients in any patient group are presented in Table 75 by system organ class and preferred term.

Table 75: TEAEs Leading to Dose Interruption Reported in ≥ 1% Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Dose Interruption	175 (44.8)	98 (30.2)	199 (37.9)	388 (41.4)	649 (41.9)
Infections and infestations	57 (14.6)	39 (12.0)	85 (16.2)	148 (15.8)	258 (16.6)
Pneumonia	10 (2.6)	8 (2.5)	30 (5.7)	40 (4.3)	69 (4.5)
COVID-19	11 (2.8)	8 (2.5)	10 (1.9)	21 (2.2)	23 (1.5)
Cellulitis	3 (0.8)	0 (0.0)	1 (0.2)	4 (0.4)	16 (1.0)
Urinary tract infection	3 (0.8)	3 (0.9)	5 (1.0)	8 (0.9)	16 (1.0)
Upper respiratory tract infection	4 (1.0)	2 (0.6)	4 (0.8)	10 (1.1)	15 (1.0)
COVID-19 pneumonia	8 (2.0)	2 (0.6)	2 (0.4)	10 (1.1)	14 (0.9)
Lower respiratory tract infection	4 (1.0)	1 (0.3)	1 (0.2)	5 (0.5)	10 (0.6)
Hepatitis B reactivation	1 (0.3)	2 (0.6)	5 (1.0)	6 (0.6)	9 (0.6)
Gastrointestinal disorders	40 (10.2)	6 (1.9)	26 (5.0)	66 (7.0)	121 (7.8)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Diarrhoea	16 (4.1)	3 (0.9)	8 (1.5)	24 (2.6)	35 (2.3)
Vomiting	12 (3.1)	0 (0.0)	2 (0.4)	14 (1.5)	27 (1.7)
Nausea	8 (2.0)	1 (0.3)	2 (0.4)	10 (1.1)	19 (1.2)
Abdominal pain	5 (1.3)	1 (0.3)	1 (0.2)	6 (0.6)	6 (0.4)
Blood and lymphatic system disorders	22 (5.6)	18 (5.6)	32 (6.1)	55 (5.9)	107 (6.9)
Neutropenia	13 (3.3)	14 (4.3)	26 (5.0)	40 (4.3)	74 (4.8)
Thrombocytopenia	4 (1.0)	2 (0.6)	3 (0.6)	7 (0.7)	16 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (4.1)	11 (3.4)	26 (5.0)	45 (4.8)	76 (4.9)
Basal cell carcinoma	4 (1.0)	1 (0.3)	3 (0.6)	7 (0.7)	16 (1.0)
Investigations	12 (3.1)	5 (1.5)	17 (3.2)	31 (3.3)	55 (3.5)
Neutrophil count decreased	4 (1.0)	2 (0.6)	9 (1.7)	13 (1.4)	24 (1.5)
Cardiac disorders	17 (4.3)	1 (0.3)	10 (1.9)	27 (2.9)	48 (3.1)
Atrial fibrillation	8 (2.0)	1 (0.3)	4 (0.8)	12 (1.3)	16 (1.0)
General disorders and administration site conditions	7 (1.8)	6 (1.9)	8 (1.5)	15 (1.6)	44 (2.8)
Pyrexia	2 (0.5)	3 (0.9)	3 (0.6)	5 (0.5)	20 (1.3)
Nervous system disorders	11 (2.8)	5 (1.5)	9 (1.7)	21 (2.2)	34 (2.2)
Headache	4 (1.0)	0 (0.0)	1 (0.2)	5 (0.5)	7 (0.5)
Dizziness	4 (1.0)	0 (0.0)	0 (0.0)	4 (0.4)	6 (0.4)
Renal and urinary disorders	13 (3.3)	3 (0.9)	6 (1.1)	20 (2.1)	32 (2.1)
Haematuria	5 (1.3)	0 (0.0)	1 (0.2)	7 (0.7)	13 (0.8)
Vascular disorders	7 (1.8)	9 (2.8)	10 (1.9)	17 (1.8)	29 (1.9)
Hypertension	0 (0.0)	6 (1.9)	6 (1.1)	6 (0.6)	10 (0.6)
Musculoskeletal and connective tissue disorders	8 (2.0)	3 (0.9)	6 (1.1)	15 (1.6)	27 (1.7)
Arthralgia	4 (1.0)	0 (0.0)	2 (0.4)	6 (0.6)	9 (0.6)
Ear and labyrinth disorders	6 (1.5)	0 (0.0)	1 (0.2)	7 (0.7)	10 (0.6)
Vertigo	5 (1.3)	0 (0.0)	0 (0.0)	5 (0.5)	6 (0.4)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-18-teae-soc-pt-int-1-i.rtf

The Applicant's Position:
The incidence of adverse events leading to dose reduction was infrequent and similar between all groups.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment of AEs leading to dose modifications. In study BGB-311-304 Cohort 1, the most common reasons for dose modifications in ≥ 5% of all patients receiving zanubrutinib were respiratory infections (COVID-19, pneumonia) and hemorrhage. In Cohort 2 the most common reason for dose modifications in ≥ 5% of patients were pneumonia, neutropenia, SPM and diarrhea. In study BGB-3111-305, the most common reason for dose modifications in ≥ 5% of patients were respiratory infections (COVID-19, pneumonia) and neutropenia.

The Agency agrees that the rates and types of AEs resulting in dose reduction and dose interruption are similar between the ISS safety population and the CLL/SLL studies (BGB-3111-304 and BGB-3111-305) supporting the CLL/SLL indication. Compared to the known safety profile of zanubrutinib, there were no new safety issues identified based on dose modifications.

Significant Adverse Events
Data:

Adverse events that are known to be associated with the class of BTK inhibitors are analyzed throughout zanubrutinib clinical development as Adverse Events of Special Interest (AESI). Definitions of AESIs are described below:

Table 76: Adverse Events of Special Interest

Adverse Event of Special Interest Category	Search Criteria
Hemorrhage (including minor bleeding such as contusion and petechiae)	Haemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage - Defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade	Major haemorrhage: • Subdural haematoma PT, Subdural haemorrhage PT • All haemorrhage PTs if adverse event SOC is "Nervous system disorders" or • Serious or ≥ Grade 3 haemorrhage PT if adverse event SOC is not "Nervous system disorders"
Atrial fibrillation and flutter	Atrial fibrillation PT, atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant tumours (SMQ) Narrow Subcategory - Skin malignant tumours (SMQ) narrow
Tumor lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
Infections Opportunistic infections	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (SMQ) Narrow
Cytopenia	
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anaemia PT, Haemoglobin decreased PT

Data:

Study BGB-3111-304

In **Cohort 1**, the incidence of adverse events of special interest overall was comparable between the zanubrutinib arm (Arm A) and B+R arm (Arm B). However, for individual categories, the incidence was higher in the B+R arm compared with the zanubrutinib arm for

the categories of anemia, neutropenia, and thrombocytopenia and higher in the zanubrutinib arm compared with the B+R arm for the category of hemorrhage.

Table 77: Overview of Treatment-Emergent Adverse Events of Special Interest by Category in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One TEAE of Special Interest	187 (82.4)	199 (82.9)	101 (91.0)
Grade 3 or Higher	143 (63.0)	92 (38.3)	43 (38.7)
Serious	46 (20.3)	63 (26.3)	27 (24.3)
Leading to Treatment Discontinuation	12 (5.3)	15 (6.3)	3 (2.7)
Leading to Dose Reduction	73 (32.2)	13 (5.4)	3 (2.7)
Leading to Dose Interruption	NA	65 (27.1)	40 (36.0)
Patients With at Least One TEAE Leading to Dose Delay/Held	104 (45.8)	NA	NA

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE Abbreviation: TEAE, treatment-emergent adverse event. Notes: Adverse events were classified based on MedDRA Version 24.0Patients with multiple events for a given preferred term were counted only once for each preferred term.Events were sorted by descending order within Category, and by preferred term within Category in the Total column.Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_aesi_c.sasOutput: t-14-3-1-2-10-5-3-teae-aesi-disc-asaf-csaf.rtf (Date Generated: 06SEP2021:06:08)

Table 78: Treatment-Emergent Adverse Events of Special Interest by Category

	Cohort1		Cohort2
Category	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Patients With at Least One AE of Special Interest	187 (82.4)	199 (82.9)	101 (91.0)
Anemia	41 (18.1)	11 (4.6)	6 (5.4)
Atrial fibrillation and flutter	5 (2.2)	8 (3.3)	5 (4.5)
Hemorrhage	16 (7.0)	108 (45.0)	57 (51.4)
Major hemorrhage	2 (0.9)	12 (5.0)	8 (7.2)
Hypertension	12 (5.3)	34 (14.2)	12 (10.8)
Infections	97 (42.7)	148 (61.7)	79 (71.2)
Opportunistic infections	2 (0.9)	2 (0.8)	0 (0.0)
Neutropenia	127 (55.9)	38 (15.8)	21 (18.9)

	Cohort1		Cohort2
Category	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Second primary malignancies	3 (1.3)	31 (12.9)	24 (21.6)
Skin cancers	3 (1.3)	16 (6.7)	17 (15.3)
Thrombocytopenia	38 (16.7)	11 (4.6)	8 (7.2)
Tumor lysis syndrome	3 (1.3)	0 (0.0)	0 (0.0)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0
Patients with multiple events for a given preferred term were counted only once for each preferred term.
Events were sorted by descending order within category, and by preferred term within category in the Treatment-Emergent and Post-treatment Cohort 1 Zanubrutinib column.
Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_aesi_postteae_ab.sas
Output: t-14-3-1-2-10-1-1-teae-aesi-c1-saf.rtf (Date Generated: 06SEP2021:05:40)

The FDA Assessment:

The Agency agrees with the Applicant's overall position regarding AEs of clinical interest in Cohorts 1 and 2 of study BGB-3111304. The Agency analysis of adverse events of special interest differed from the Applicant's analysis regarding the rates of hemorrhage and cytopenias. For the FDA analysis hemorrhage did not include contusion and petechiae; therefore the rate of hemorrhage was 27% (all grades) and 4% (≥ grade 3) in the zanubrutinib arm of Cohort 1 and 28% (all grades) and 4.5% (≥ grade 3) in Cohort 2. Cytopenias were analyzed including laboratory analysis which resulting generally in higher rates of cytopenias as displayed in the table below. The rates of grade 3 or 4 cytopenias, which are considered clinically meaningful, are displayed separately.

Table 79: Treatment-Emergent Cytopenias Using Laboratory Analysis in Cohort 1 of Study BGB-3111-304

Laboratory Abnormality by CTCAE grading	Cohort 1				Cohort 2	
	BR N = 227		Zanubrutinib N = 240		Zanubrutinib N = 110 to 111	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	80	53	37	15	42	19
Hemoglobin decreased	66	8	29	2.5	26	3.6
Platelets decreased	61	11	27	1.7	23	3.6

Source: FDA analysis of revised ADLB datasets submitted January 5, 2023

Data:

Study BGB-3111-305

The incidence of adverse events of special interest by category was generally comparable between the zanubrutinib arm and ibrutinib arm, except for atrial fibrillation and flutter (zanubrutinib: 1.9% versus ibrutinib: 8.0%), major hemorrhage (zanubrutinib: 1.9% versus ibrutinib: 3.1%), neutropenia (zanubrutinib: 21.3% versus ibrutinib: 17.3%), and infections ≥ Grade 3 (zanubrutinib: 11.4% versus ibrutinib: 13.9%)

Table 80: Treatment-Emergent Adverse Events of Special Interest by Category (Safety Analysis Set)

	BGB-3111-305	
	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE of Special Interest	240 (74.1)	245 (75.6)
Grade 3 or Higher	117 (36.1)	109 (33.6)
Serious	56 (17.3)	57 (17.6)
Leading to Treatment Discontinuation	14 (4.3)	18 (5.6)
Leading to Dose Reduction	18 (5.6)	19 (5.9)
Leading to Dose Interruption	75 (23.1)	85 (26.2)
Patients With at Least One TEAE of Special Interest Leading to Dose Modification	79 (24.4)	91 (28.1)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.Abbreviation: TEAE, treatment-emergent adverse event. TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose ofstudy drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the

grade 5 AE will be treatment-emergent.Notes: Adverse events were classified based on MedDRA Version 23.0.Patients with multiple events for a given preferred term and special interest category were counted only once for each preferred term and category, respectively.Events are first sorted by category alphabetically, then by decreasing frequency of preferred term in the Total column./bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-aesi-pt.sas 09AUG2021 21:57 t-14-3-1-2-5-1-1-aesi-pt-fst.rtf

Table 81: Treatment-Emergent Adverse Events of Special Interest by Category (Safety Analysis Set)

	Zanubrutinib (N = 324) n (%)		Ibrutinib (N = 324) n (%)	
Category	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Patients With ≥ 1 AESI	240 (74.1)	117 (36.1)	245 (75.6)	109 (33.6)
Anemia	39 (12.0)	7 (2.2)	47 (14.5)	8 (2.5)
Atrial fibrillation and flutter	6 (1.9)	3 (0.9)	26 (8.0)	5 (1.5)
Hemorrhage	108 (33.3)	6 (1.9)	104 (32.1)	7 (2.2)
Major hemorrhage	6 (1.9)	6 (1.9)	10 (3.1)	7 (2.2)
Hypertension	42 (13.0)	27 (8.3)	40 (12.3)	24 (7.4)
Infections	152 (46.9)	37 (11.4)	166 (51.2)	45 (13.9)
Opportunistic infections	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.6)
Neutropenia	69 (21.3)	45 (13.9)	56 (17.3)	41 (12.7)
Second primary malignancies	19 (5.9)	10 (3.1)	16 (4.9)	5 (1.5)
Skin cancers	8 (2.5)	3 (0.9)	12 (3.7)	2 (0.6)
Thrombocytopenia	30 (9.3)	9 (2.8)	35 (10.8)	9 (2.8)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Patients with multiple events for a special interest category were counted only once for each category, respectively.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-aesi-pt-i.sas 09AUG2021 23:31 t-26-aesi-pt-i.rtf

The FDA's Assessment:

The Agency agrees with the Applicant's summary of AESIs for study BGB-3111-305 from the original CCOD of December 30, 2020. The Applicant submitted additional safety data with a

CCOD of December 1, 2021. Adverse events of special interest reflecting additional follow-up with a CCOD of December 1, 2021 are summarized in the table below. The leading AEs of special interest (all grades) were infections (60%), hemorrhage (40%) and neutropenia 43%. The leading AEs of greater than grade 3 AESIs were infections (19%), neutropenia (19%), and hypertension (13%). In general, the rates of AESIs were similar between the zanubrutinib and ibrutinib arms. AESIs (all grades) that were at least 2% lower in the zanubrutinib arm compared to the ibrutinib arm were atrial fibrillation or flutter (4.6% vs 12%), infections 61% vs. 64%, and thrombocytopenia 29% vs 37% . The one AESI that was higher in the zanubrutinib arm compared to the ibrutinib arm by at least 2% was all-grade neutropenia (43% vs 32%), although rates of grade 3 or 4 neutropenia were similar.

Table 82: Summary of Adverse Events of Special Interest in Study BGB-3111-305 Based on CCOD of December 1, 2021

	Zanubrutinib (N = 324) n (%)		Ibrutinib (N = 324) n (%)	
Category	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Patients With ≥ 1 AESI	281 (86.7)	160 (49.4)	289 (89.2)	167 (51.5)
Anemia*	91 (28.0)	13 (4.0)	102 (32)	12 (3.7)
Atrial fibrillation and flutter	15 (4.6)	8 (2.5)	29 (12.0)	12 (3.7)
Hemorrhage	129 (39.8)	10 (3.1)	130 (40.1)	12 (3.7)
Major hemorrhage	10 (3.1)	10 (3.1)	14 (4.3)	12 (3.7)
Hypertension	63 (19.4)	42 (13.0)	66 (20.4)	41 (12.7)
Infections	196 (60.5)	60 (18.5)	207 (63.9)	73 (22.5)
Opportunistic infections	6 (1.9)	4 (1.2)	9 (2.8)	5 (1.5)
Neutropenia*	138 (43)	47 (15)	107 (33)	52 (16)
Second primary malignancies	33 (10.2)	18 (5.6)	32 (9.9)	10 (3.1)
Skin cancers	17 (5.2)	5 (1.5)	22 (6.8)	3 (0.9)
Thrombocytopenia*	321 (71)	13 (4.0)	77 (24)	11 (3.4)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)

Source: FDA analysis. Lab analysis based on revised ADLB dataset submitted 1/5/2023.
*By CTCAE grading and laboratory-shift analysis; the denominator is 322 for zanubrutinib) and ranged from 320 to 321 for ibrutinib based on the number of patients with both pre- and post- treatment values.

All Zanubrutinib (N=1550) safety data:

Data:

Adverse events of special interest are those that are known to be associated with the class of BTK inhibitors. In the All Zanubrutinib group, 1333 (86.0%) patients reported at least 1 adverse event of special interest. Events that met the criteria for seriousness and/or were ≥ Grade 3 were reported in 440 (28.4%) and 718 (46.3%) patients, respectively. Events within the categories of infections (65.7%), hemorrhage (48.1%), and neutropenia (27.5%) were reported the most frequently. Adverse events of special interest are presented in Table 83.

Table 83: Overall Summary of TEAE of Special Interest (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE of Special Interest	332 (84.9)	240 (74.1)	438 (83.4)	792 (84.4)	1333 (86.0)
Grade 3 or Higher	147 (37.6)	117 (36.1)	256 (48.8)	415 (44.2)	718 (46.3)
Serious	99 (25.3)	56 (17.3)	145 (27.6)	250 (26.7)	440 (28.4)
Leading to Death	11 (2.8)	11 (3.4)	16 (3.0)	28 (3.0)	51 (3.3)
Leading to Treatment Discontinuation	19 (4.9)	14 (4.3)	31 (5.9)	51 (5.4)	91 (5.9)
Leading to Dose Reduction	17 (4.3)	18 (5.6)	32 (6.1)	49 (5.2)	78 (5.0)
Leading to Dose Interruption	112 (28.6)	75 (23.1)	152 (29.0)	272 (29.0)	469 (30.3)
Treatment-Related of Special Interest	219 (56.0)	164 (50.6)	337 (64.2)	575 (61.3)	965 (62.3)
Treatment-Related Grade 3 or Higher	77 (19.7)	69 (21.3)	169 (32.2)	254 (27.1)	419 (27.0)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-aesi-i.sas 24AUG2021 02:31 t-19-aesi-i.rtf

Table 84: TEAE of Special Interest by Category (Safety Analysis Set)

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE of Special Interest	332 (84.9)	240 (74.1)	438 (83.4)	792 (84.4)	1333 (86.0)
Anemia	25 (6.4)	39 (12.0)	92 (17.5)	117 (12.5)	218 (14.1)
Atrial fibrillation and flutter	13 (3.3)	6 (1.9)	13 (2.5)	26 (2.8)	49 (3.2)
Hemorrhage	179 (45.8)	108 (33.3)	253 (48.2)	447 (47.7)	746 (48.1)
Major hemorrhage	22 (5.6)	6 (1.9)	12 (2.3)	34 (3.6)	70 (4.5)
Hypertension	50 (12.8)	42 (13.0)	74 (14.1)	128 (13.6)	201 (13.0)
Infections	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Opportunistic infections	2 (0.5)	2 (0.6)	11 (2.1)	15 (1.6)	31 (2.0)
Neutropenia	67 (17.1)	69 (21.3)	172 (32.8)	241 (25.7)	427 (27.5)
Second primary malignancies	55 (14.1)	19 (5.9)	47 (9.0)	109 (11.6)	192 (12.4)
Skin cancers	33 (8.4)	8 (2.5)	23 (4.4)	62 (6.6)	115 (7.4)
Thrombocytopenia	29 (7.4)	30 (9.3)	92 (17.5)	122 (13.0)	247 (15.9)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	5 (0.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-aesi-cate-i.sas 24AUG2021 02:08 t-20-aesi-cate-i.rtf

The Applicant's Position:

Significant improvement of safety for zanubrutinib vs other BTK inhibitors is demonstrated in statistically significant reduction of atrial fibrillation as compared to ibrutinib as a pre-defined endpoint in Study 305. The proportion of patients that had adverse events of neutropenia was higher in the zanubrutinib arm (69 [21.3%] patients) than in the ibrutinib arm (56 [17.3%] patients) in study 305. However, the proportion of patients that had infection adverse events

was lower in the zanubrutinib arm (152 [46.9%] patients) than that in the ibrutinib arm (166 [51.2%] patients) in Study 305. Additionally, numerical reduction in discontinuation was observed in patients who received zanubrutinib (6.5%) vs ibrutinib (10.5%). Overall AESI of zanubrutinib in this pooled dataset is consistent with the overall zanubrutinib safety profile.

The FDA's Assessment:

The Agency disagrees with the Applicant's position regarding the favorable safety profile of zanubrutinib compared to ibrutinib, as the study was not blinded or adequately powered to compare safety findings. There appears to be a trend towards decreased rates of some AEs with zanubrutinib compared to ibrutinib, however whether the difference in the rates of some AEs represent a clinically meaningful difference has not been established (b) (4) (b) (4). The Agency agrees that the AESIs observed in the pooled dataset are generally similar to the known safety profile of zanubrutinib.

Treatment Emergent Adverse Events and Adverse Reactions

Study BGB-3111-304:

Data:

Adverse events including grouped terms reported by the investigator in ≥ 10% of patients are presented in Table 85 for Study BGB-3111-304 cohort 1 and Table 86 for cohort 2, by system organ class and preferred term.

Table 85: All Grade and Grade 3 or 4 Treatment-Emergent Adverse Events (≥ 10% of Patients in the Zanubrutinib Group) by System Organ Class and Preferred Term (Including Grouped Terms): Study 304 Cohort 1 (Safety Analysis Set)

	BGB-3111-304			
	Zanubrutinib (N = 240)		B + R (N = 227)	
System Organ Class Preferred Term	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Blood and lymphatic system disorders				
Neutropenia [a, b]	37 (15.4)	27 (11.3)	128 (56.4)	113 (49.8)
Gastrointestinal disorders				
Diarrhea	33 (13.8)	2 (0.8)	26 (11.5)	2 (0.9)
Constipation	24 (10.0)	1 (0.4)	40 (17.6)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
General disorders and administration site conditions				
Fatigue [a, c]	34 (14.2)	3 (1.3)	47 (20.7)	4 (1.8)

	BGB-3111-304			
	Zanubrutinib (N = 240)		B + R (N = 227)	
System Organ Class Preferred Term	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Infections and infestations				
Upper respiratory tract infection [a, d]	67 (27.9)	3 (1.3)	33 (14.5)	2 (0.9)
Respiratory tract infection [a, e†]	34 (14.2)	7 (2.9)	13 (5.7)	4 (1.8)
Pneumonia [a,f,† #]	30 (12.5)	12 (5.0)	18 (7.9)	9 (4.0)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [a, g]	79 (32.9)	4 (1.7)	39 (17.2)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Second primary malignancy [a, h , †]	31 (12.9)	15 (6.3)	3 (1.3)	1 (0.4)
Nervous system disorders				
Headache [a, i]	28 (11.7)	0 (0.0)	17 (7.5)	0 (0.0)
Dizziness [a, j]	26 (10.8)	2 (0.8)	11 (4.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Cough [a, k]	37 (15.4)	0 (0.0)	23 (10.1)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash [a, l]	57 (23.8)	3 (1.3)	68 (30.0)	11 (4.8)
Bruising [a, m]	57 (23.8)	0 (0.0)	6 (2.6)	0 (0.0)
Vascular disorders				
Hemorrhage [a, n†]	63 (26.3)	8 (3.3)	9 (4.0)	1 (0.4)
Hypertension [a, o]	32 (13.3)	16 (6.7)	12 (5.3)	6 (2.6)

Data Source: Table 1 in Module 2.7.4 Appendix (ADR Analysis); Data cut-off: 07MAY2021
Abbreviations: B + R, bendamustine plus rituximab; BID, twice daily; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse

Events; PT, preferred term; QD, once daily; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an adverse event that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib (or 90 days after the last dose of bendamustine or rituximab) or initiation of a new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of zanubrutinib (or 90 days after last dose of bendamustine or rituximab) and prior to initiation of a new anticancer therapy is also considered a treatment-emergent adverse event.
Patients with multiple events for a given Preferred Term and with multiple Preferred Terms within a System Organ Class are counted only once at the Preferred Term and System Organ Class levels, respectively. Events were sorted by alphabetical order of System Organ Class and decreasing frequency of Preferred Term in the 'Zanubrutinib/All Grades' column, and then by decreasing frequency in the 'Zanubrutinib/Grade 3 or 4' column and alphabetical order (for events of equal frequency). Adverse events were graded by NCI-CTCAE v4.03, except for hematologic toxicities where IWCLL 2008 Grading Scale was used. MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t_teae_soc_grppt_grd345grp.sasOutput: t-2-7-4-2-20-8-2-1-teae-soc-grppt-grd34grp-304c1.rtf (Date Generated: 12OCT2021:00:44)
[a] Include multiple preferred terms. Detailed preferred terms are described in Table 2.7.4.2.16.2.1.
[b] Neutropenia: neutropenia, neutrophil count decreased and granulocytopenia*
[c] Fatigue: fatigue, asthenia and lethargy
[d] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, chronic sinusitis, human rhinovirus test positive, acute sinusitis, pharyngitis, upper respiratory tract congestion, laryngitis*, tonsillitis* and upper respiratory tract inflammation*
[e] Respiratory tract infection: COVID-19, respiratory tract infection, influenza, influenza like illness, respiratory tract infection viral, tracheitis, haemophilus infection* and respiratory syncytial virus infection*
[f] Pneumonia: pneumonia, lower respiratory tract infection, COVID-19 pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, pneumonia viral, lung consolidation*, lung infiltration* and pneumonia chlamydial*
[g] Musculoskeletal pain: arthralgia, back pain, pain in extremity, myalgia, musculoskeletal chest pain, neck pain, spinal pain, musculoskeletal discomfort, bone pain and musculoskeletal pain*
[h]Second primary malignancy: basal cell carcinoma, squamous cell carcinoma of skin, lung adenocarcinoma, rectal adenocarcinoma, renal cancer, anal squamous cell carcinoma, bladder cancer, Bowen's disease, breast cancer, chronic myeloid leukaemia, external ear neoplasm malignant, keratoacanthoma, lung cancer metastatic, lung neoplasm malignant, lung squamous cell carcinoma recurrent, metastatic squamous cell carcinoma, ovarian cancer, prostate cancer, skin cancer, squamous cell carcinoma of lung and skin squamous cell carcinoma metastatic*
[i] Headache: headache, sinus headache, migraine and tension headache*

[j] Dizziness: dizziness and vertigo
[k] Cough: cough, productive cough and upper-airway cough syndrome
[l] Rash: Rash, rash maculo-papular, erythema, dermatitis acneiform, urticaria, dermatitis, dermatitis allergic, drug eruption, hand dermatitis, rash erythematous, skin disorder, stasis dermatitis, macule, palmar erythema, photosensitivity reaction, rash macular, rash papular, skin exfoliation, vulvovaginal rash, dermatitis bullous*, hyperkeratosis*, injection site rash*, photodermatosis*, rash pruritic*, solar dermatitis* and toxic skin eruption*.
[m] Bruising: contusion, ecchymosis, increased tendency to bruise, vessel puncture site bruise, bone contusion, eye contusion, injection site bruising and post procedural contusion
[n] Hemorrhage: Haematoma, haematuria, epistaxis, mouth haemorrhage, rectal haemorrhage, subcutaneous haematoma, post procedural haemorrhage, haemorrhoidal haemorrhage, heavy menstrual bleeding, post procedural haematoma, skin haemorrhage, aortic intramural haematoma, breast haematoma, conjunctival haemorrhage, eye haemorrhage, gastric ulcer haemorrhage, gastritis haemorrhagic, haemoptysis, haemorrhagic transformation stroke, pelvic haematoma, periorbital haemorrhage, red blood cells urine positive, retinal haemorrhage, retroperitoneal haematoma, scrotal haematoma, scrotal haemorrhage, spermatic cord haemorrhage, traumatic haematoma, umbilical haematoma, upper gastrointestinal haemorrhage, and gastrointestinal haemorrhage*
[o] Hypertension: hypertension, blood pressure increased and essential hypertension
* Terms reported only in the B + R Arm
†Includes events with fatal outcome in BRUKINSA arm.
Includes event with fatal outcome in BR arm.

Table 86: Treatment-Emergent Adverse Events Occurring in ≥ 10% Patients with del(17p) mutation Who Received BRUKINSA: Study 304 Cohort 2 (Safety Analysis Set)

	BRUKINSA (N = 111)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3 or 4 n (%)**
Blood and lymphatic system disorders		
Neutropenia [a,b]	20 (18.0)	17 (15.3)
Cardiac disorders		
Cardiac arrhythmias [a,c]	12 (10.8)	4 (3.6)
Gastrointestinal disorders		
Diarrhea	20 (18.0)	1 (0.9)
Nausea	18 (16.2)	0 (0.0)
Constipation	17 (15.3)	0 (0.0)
Abdominal pain [a,d]	13 (11.7)	2 (1.8)
General disorders and administration site conditions		
Fatigue [a,e]	15 (13.5)	1 (0.9)
Infections and infestations		
Upper respiratory tract infection [a,f]	42 (37.8)	0 (0.0)
Pneumonia [a,g,†]	22 (19.8)	9 (8.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [a,h]	42 (37.8)	3 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Second primary malignancy [a,i]	24 (21.6)	7 (6.3)
Nervous system disorders		
Headache	12 (10.8)	2 (1.8)
Respiratory, thoracic and mediastinal disorders		
Cough [a,j]	20 (18.0)	0 (0.0)
Dyspnea [a,k]	14 (12.6)	0 (0.0)
Skin and subcutaneous tissue disorders		
Rash [a,l]	31 (27.9)	0 (0.0)
Bruising [a,m]	29 (26.1)	1 (0.9)
Vascular disorders		
Hemorrhage [a,n]	31 (27.9)	5 (4.5)

[a] Grouped preferred terms.

[b] Neutropenia: neutropenia and neutrophil count decreased

[c] Cardiac arrhythmias: atrial fibrillation, bradycardia, sinus bradycardia, tachycardia, atrioventricular block and pulseless electrical activity
[d] Abdominal pain: Abdominal pain, abdominal pain upper, abdominal pain lower and abdominal discomfort.
[e] Fatigue: fatigue, asthenia and lethargy
[f] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, chronic sinusitis, pharyngitis, upper respiratory tract congestion, laryngitis viral, upper respiratory tract inflammation and viral upper respiratory tract infection
[g] Pneumonia: pneumonia, lower respiratory tract infection, COVID-19 pneumonia, atypical pneumonia and pneumonia pneumococcal
[h] Musculoskeletal pain: arthralgia, back pain, pain in extremity, myalgia, musculoskeletal chest pain, neck pain, bone pain and musculoskeletal pain
[i] Second primary malignancy: basal cell carcinoma, squamous cell carcinoma of skin, bladder cancer, breast cancer, prostate cancer, skin cancer, bladder transitional cell carcinoma, clear cell renal cell carcinoma, malignant melanoma, malignant melanoma in situ, non-small cell lung cancer and transitional cell cancer of the renal pelvis and ureter
[j] Cough: cough, productive cough and upper-airway cough syndrome
[k] Dyspnea: dyspnoea and dyspnoea exertiona
[l] Rash: Rash, rash maculo-papular, erythema, urticaria, dermatitis, dermatitis allergic, rash macular, rash papular, livedo reticularis, neutrophilic dermatosis, rash pruritic and toxic skin eruption
[m] Bruising: contusion, ecchymosis, increased tendency to bruise, bone contusion and post procedural contusion.
[n] Hemorrhage: Haematoma, haematuria, epistaxis, mouth haemorrhage, subcutaneous haematoma, post procedural haemorrhage, skin haemorrhage, conjunctival haemorrhage, haemoptysis, haemorrhage, haemorrhagic diathesis, injection site haematoma, intra-abdominal haematoma, large intestinal haemorrhage, melaena, mucocutaneous haemorrhage, procedural haemorrhage and subdural haematoma.
[†:] includes one event with a fatal outcome

The Applicant's Position:

Zanubrutinib is tolerable and safe in the treatment of patients with untreated CLL/SLL. The safety profile of zanubrutinib is consistent with previous published studies. Of particular benefit, the rates of atrial fibrillation or flutter for zanubrutinib were similar to the B+R comparator arm, reports of ventricular arrhythmias arrhythmia were rare, and no sudden deaths were reported in either study arm. The safety profile of the B+R arm also in this study is similar to previous reports of B+R in this patient population, including the ALLIANCE A041202 study (Woyach et al 2018).Woyach et al 2018). In the Cohort 1 Safety Analysis Set, the overall median treatment durations were 5.52 months, 5.59 months, and 26.07 months among patients treated with bendamustine, rituximab, and zanubrutinib, respectively. The median relative dose intensities were 96.46%, 98.74%, and 98.00% for bendamustine, rituximab, and zanubrutinib respectively. The incidence of adverse events leading to treatment discontinuation was numerically lower in the zanubrutinib arm (8.3%) than in the B+R arm (13.7%).

The safety profile of zanubrutinib in patients in Cohort 2 overall appeared similar to patients treated with zanubrutinib in Cohort 1.

The FDA's Assessment:

BGB-3111-304 Cohort 1

The FDA's analysis of common TEAS in patients in Cohort 1 of study BGB-3111-304 varied slightly from the Applicant's based on revised grouping for increased sensitivity. See the Appendix for definitions of the FDA's grouped terms. The revised table using FDA grouping is provided below.

Table 87: TEAEs Occurring in ≥ 10% of Patients in the Zanubrutinib Group of Cohort 1

	BR (N=227)						Zanubrutinib (N=240)					
System Organ Class Preferred Term	**All Grades**		**Grade 3 or 4**		**Grade 5**		**All Grades**		**Grade 3 or 4**		**Grade 5**	
	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Musculoskeletal and connective tissue disorders												
Musculoskeletal Pain	39	(17.1)	1	(0.4)	0	(0.0)	79	(33)	4	(1.7)	0	(0.0)
Infections and Infestations												
URI	34	(14.9)	3	(1.3)	0	(0.0)	67	(28)	3	(1.3)	0	(0.0)
Pneumonia	18	(8)	7	(3.1)	2	(0.9)	31	(13)	12	(5)	3	(1.2)
Vascular disorders												
Hemorrhage	9	(3.9)	1	(0.4)	0	(0.0)	64	(27)	8	(3.3)	1	(0.4)
Hypertension	12	(5)	6	(2.6)	0	(0.0)	33	(14)	16	(7)	0	(0.0)
Edema	21	(9)	0	(0.0)	0	(0.0)	27	(11)	0	(0.0)	0	(0.0)
Skin and subcutaneous disorders												
Rash	68	(30)	11	(5)	0	(0.0)	51	(21)	3	(1.3)	0	(0.0)
Bruising	6	(2.6)	0	(0.0)	0	(0.0)	56	(23)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders												
Cough	21	(9)	0	(0.0)	0	(0.0)	27	(11)	0	(0.0)	0	(0.0)
Neutropenia	128	(56)	113	(50)	0	(0.0)	38	(16)	28	(12)	0	(0.0)
Gastrointestinal disorders												
Diarrhea	26	(11)	2	(0.9)	2	(0.9)	33	(14)	2	(0.9)	0	(0.0)
Constipation	40	(18)	0	(0.0)	0	(0.0)	24	(10)	1	(0.4)	0	(0.0)
Nausea	74	(33)	3	(1.3)	0	(0.0)	24	(10)	0	(0.0)	0	(0.0)
General disorders												
Fatigue	47	(21)	4	(1.8)	0	(0.0)	33	(14)	3	(1.3)	0	(0.0)
Neoplasms												
Second Primary Neoplasm	3	(1.3)	1	(0.4)	0	(0.0)	31	(13)	14	(3)	3	(1.3)
Nervous system disorders												
Headache	17	(8)	0	(0.0)	0	(0.0)	28	(12)	0	(0.0)	0	(0.0)
Dizziness	11	(4.9)	0	(0.0)	0	(0.0)	26	(11)	2	(0.8)	0	(0.0)

Source: FDA analysis

BGB-3111-Cohort 2:
The FDA's analysis of common TEAS occurring in patients in Cohort 2 of study 304 varied slightly

Table 88: TEAEs Occurring in ≥ 10% of Patients in Cohort 2

	Zanubrutinib Cohort 2 (N=111)					
System Organ Class Preferred term	All Grades n (%)		>= Grade 3 n (%)		Grade 5 n (%)	
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain	42	(38)	3	(2.7)	0	(0.0)
Infections and infestations						
Upper respiratory tract infection	42	(38)	0	(0.0)	0	(0.0)
Pneumonia	17	(20)	9	(8.1)	1	(0.9)
Skin and Subcutaneous disorders						
Rash	30	(28)	0	(0.0)	0	(0.0)
Bruising	27	(24)	0	(0.0)	0	(0.0)
Vascular disorders						
Hemorrhage	33	(29)	5	(4.5)	0	(0.0)
Hypertension	12	(11)	6	(5.4)	0	(0.0)
Neoplasms						
SPM	24	(22)	7	(6.3)	0	(0.0)
Gastrointestinal disorders						
Diarrhea	20	(18)	1	(0.9)	0	(0.0)
Nausea	18	(16)	0	(0.0)	0	(0.0)
Constipation	17	(15)	0	(0.0)	0	(0.0)
Abdominal Pain	13	(12)	2	(1.8)	0	(0.0)
Blood and lymphatic system disorders						
Neutropenia	21	(19)	18	(16.2)	0	(0.0)

	Zanubrutinib Cohort 2 (N=111)					
System Organ Class Preferred term	All Grades n (%)		>= Grade 3 n (%)		Grade 5 n (%)	
Respiratory, thoracic and mediastinal disorders						
Cough	14	(13)	0	(0.0)	0	(0.0)
Dyspnea	14	(13)	0	(0.0)	0	(0.0)
General disorders and administration site conditions						
Fatigue	14	(14)	1	(0.9)	0	(0.0)
Nervous system disorders						
Headache	12	(11)	2	(1.8)	0	(0.0)

Source: FDA analysis of ADAEG dataset submitted on September 20, 2022

Study BGB-3111-305:

Data:
Adverse events including grouped terms reported by the investigator in ≥ 10% of patients are presented in Table 89 for Study BGB-3111-305.

Table 89: All Grade and Grade 3 or 4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Including Grouped Terms): Study 305 (Safety Analysis Set)

	BGB-3111-305			
	Zanubrutinib (N = 324)		Ibrutinib (N = 324)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3 or 4 n (%)**	**All Grades n (%)**	**Grade 3 or 4 n (%)**
Blood and lymphatic system disorders				
Neutropenia [a, b]	70 (21.6)	45 (13.9)	56 (17.3)	41 (12.7)
Anemia [a, c]	39 (12.0)	7 (2.2)	45 (13.9)	8 (2.5)
Gastrointestinal disorders				
Diarrhea	38 (11.7)	4 (1.2)	61 (18.8)	1 (0.3)
General disorders and administration site conditions				
Fatigue [a, d]	36 (11.1)	1 (0.3)	35 (10.8)	1 (0.3)
Infections and infestations				
Upper respiratory tract infection [a, e]	71 (21.9)	2 (0.6)	62 (19.1)	4 (1.2)
Pneumonia [a, f† #]	36 (11.1)	15 (4.6)	41 (12.7)	22 (6.8)

	BGB-3111-305			
	Zanubrutinib (N = 324)		Ibrutinib (N = 324)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3 or 4 n (%)**	**All Grades n (%)**	**Grade 3 or 4 n (%)**
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [a, g]	52 (16.0)	0 (0.0)	73 (22.5)	2 (0.6)
Skin and subcutaneous tissue disorders				
Rash [a, h]	48 (14.8)	3 (0.9)	52 (16.0)	2 (0.6)
Bruising [a, i]	45 (13.9)	0 (0.0)	31 (9.6)	0 (0.0)
Vascular disorders				
Hemorrhage [a, j]	62 (19.1)	6 (1.9)	65 (20.1)	7 (2.2)
Hypertension [a, k]	42 (13.0)	27 (8.3)	40 (12.3)	24 (7.4)

Data Source: Table 5 in Module 2.7.4 Appendix (ADR Assessment); Data cut-off: 31DEC2020
Abbreviations: BID, twice daily; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; QD, once daily; SMQ, standardised MedDRA query; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an adverse event that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after the last dose of study drug and prior to initiation of a new anticancer therapy is also considered a treatment-emergent adverse event.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events were sorted by alphabetical order of system organ class and decreasing frequency of preferred term in the 'Zanubrutinib/All Grades' column, and then by decreasing frequency in the 'Zanubrutinib/Grade 3 or 4' column and alphabetical order (for events of equal frequency). Adverse events were graded by NCI-CTCAE v4.03, except for hematologic toxicities where IWCLL 2008 Grading Scale was used. MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t_teae_soc_grppt_grd345grp.sas
Output: t-2-7-4-2-22-8-2-teae-soc-grppt-grd34grp-305.rtf (Date Generated: 17SEP2021:07:57)
[a] Include multiple preferred terms. Detailed preferred terms are described in Table 2.7.4.2.16.3.
[b] Neutropenia: Neutrophil count decreased, Granulocytopenia, Agranulocytosis
[c] Anemia: Anemia, Iron deficiency anaemia*, Microcytic anaemia*, Blood loss anaemia**
[d] Fatigue: Asthenia, Fatigue, Lethargy

[e] Upper respiratory tract infection: Upper respiratory tract infection, Sinusitis, Pharyngitis, Rhinitis, Nasopharyngitis, Laryngitis, Tonsillitis, Upper respiratory tract congestion*, Upper respiratory tract inflammation**, Viral upper respiratory tract infection**
[f] Pneumonia: Pneumonia, Lower respiratory tract infection, COVID-19 pneumonia, Atypical pneumonia*, Lower respiratory tract infection bacterial*, Lung infiltration*, Pneumonia cryptococcal*, Pneumonia fungal*, Pneumonia respiratory syncytial viral*, Bronchopulmonary aspergillosis**, Idiopathic interstitial pneumonia**, Pneumocystis jirovecii pneumonia**, Pneumonia haemophilus**, Pneumonia legionella**, Pneumonia pneumococcal**
[g] Musculoskeletal pain: Arthralgia, Back pain, Pain in extremity, Myalgia, Neck pain, Musculoskeletal chest pain*, Musculoskeletal pain, Spinal pain, Bone pain**, Musculoskeletal discomfort**
[h] Rash: Rash, Rash maculo-papular, Erythema, Rash erythematous, Dermatitis, Dermatitis allergic, Rash pustular, Urticaria, Dermatitis acneiform, Dermatitis contact, Impetigo*, Rash macular, Rash pruritic*, Skin disorder, Skin exfoliation*, Application site rash**, Erythema multiforme**, Nodular rash**, Palmar-plantar erythrodysaesthesia syndrome**, Photosensitivity reaction**, Rash popular**[i] Bruising: Contusion, Increased tendency to bruise, Ecchymosis, Eye contusion*, Post procedural contusion**
[j] Hemorrhage: Epistaxis, Haematoma, Haematuria, Skin haemorrhage, Conjunctiva l haemorrhage, Haemarthrosis, Mouth haemorrhage, Rectal haemorrhage, Subcutaneous haematoma, Breast haematoma*, Ear haemorrhage*, Graft haemorrhage*, Haematoma muscle*, Haemorrhage subcutaneous, Haemorrhagic diathesis, Haemorrhoidal haemorrhage, Penile haematoma*, Periorbital haemorrhage*, Pharyngeal haemorrhage, Retinal haemorrhage*, Splenic haematoma*, Tongue haemorrhage, Traumatic haematoma*, Vaginal haemorrhage*, Blood urine present**, Breast haemorrhage**, Catheter site haematoma**, Central nervous system haemorrhage**, Eye haemorrhage**, Gastrointestinal haemorrhage**, Haemothorax**, Injection site haematoma**, Injection site haemorrhage**, Intra-abdominal haematoma**, Occult blood positive**, Post procedural haemorrhage**, Splenic haemorrhage**, Vitreous haemorrhage**
[k] Hypertension: Hypertension, Blood pressure increased
* Terms reported only in the Zanubrutinib Arm
** Terms reported only in the Ibrutinib Arm
† includes events with fatal outcome in BRUKINSA arm.
#: includes events with fatal outcome in ibrutinib arm.

The FDA Assessment:

The FDA's analysis of common TEAS occurring in patients in study BGB-3111-305 varied slightly from the Applicant's based on revised grouping for increased sensitivity. See the Appendix for details on FDA grouping. The revised table using FDA grouping is displayed below. The TEAEs in patients in study BGB-3111-305 were generally consistent with the known safety profile of zanubrutinib.

Table 90: TEAEs Occurring in > 10% of Patients in Either Arm of Study BGB-3111-305

	Zanubrutinib (N=324)			Ibrutinib (N=324)		
System Organ Class Preferred Term	All Grades n (%)	≥ Grade 3 n (%)	Grade 5 n (%)	All Grades n (%)	≥ Grade 3 n (%)	Grade 5 n (%)
Infections and Infestations						
URI	87 (27)	4 (1.2)	0 (0.0)	71 (22)	4 (1.2)	0 (0.0)
Pneumonia	64 (20)	35 (11)	9 (2.8)	74 (23)	40 (12)	10 (3.1)
Covid-19	46 (14)	25 (8)	8 (2.5)	31 (10)	16 (5)	9 (2.8)
Blood and lymphatic system disorders						
Neutropenia	88 (27)	60 (19)	0 (0.0)	78 (24)	60 (19)	0 (0.0)
Anemia	45 (14)	8 (2.5)	0 (0.0)	52 (16)	8 (2.5)	0 (0.0)
Thrombocytopenia	36 (11)	11 (3.4)	0 (0.0)	49 (15)	14 (4.3)	0 (0.0)
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain	83 (26)	2 (0.6)	0 (0.0)	91 (28)	2 (0.6)	0 (0.0)
Muscle spasms	9 (2.8)	2 (0.6)	0 0	40 (13)	0 (0.0)	0 (0.0
Vascular Disorders						
Hemorrhage	78 (24)	8 (2.5)	1 (0.3)	83 (26)	12 (3.7)	2 (0.6)
Hypertension	62 (19)	42 (13)	0 (0.0)	66 (20)	41 (13)	0 (0.0)
Edema	25 (8)	1 (0.3)	0 (0.0)	44 (14)	2 (0.6	0 (0.0)
Skin and Subcutaneous disorders						
Rash	61 (19)	4 (1.2)	0 (0.0)	66 (20)	2 (0.6)	0 (0.0)
Bruising	52 (16)	0 (0.0)	0 (0.0)	42 (13)	0 (0.0)	0 (0.0)
Gastrointestinal disorders						
Diarrhea	45 (14)	5 (1.5)	0 (0.0)	71 (22)	3 (0.9)	0 (0.0)
General disorders						
Fatigue	41 (13)	3 (0.9)	0 (0.0)	43 (13)	3 (0.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders						
Cough	36 (11)	1 (0.3)	0 (0.0)	32 (10)	0 (0.0)	0 (0.0)
Nervous System disorders						
Dizziness	33 (10)	0 (0.0)	0 (0.0)	24 (7)	0 (0.0)	0 (0.0)
Cardiac disorders						
Atrial fibrillation	15 (4.6)	8 (2.5)	0 (0.0)	39 (12)	12 (3.7)	0 (0.0)

Source: Reviewer table from ADAEG dataset submitted September 20, 2022

The Applicant's Position:

Zanubrutinib is tolerable and safe in the treatment of patients with R/R CLL/SLL. A favorable safety profile was demonstrated, in particular regarding the cardiac toxicity of zanubrutinib compared to ibrutinib. The median treatment duration was approximately 14 months for patients who received zanubrutinib. The median relative dose intensity was 99.7% in the

zanubrutinib arm. Patients in the zanubrutinib arm had a lower incidence of occurring at least 1 adverse event, serious adverse events, adverse events leading to dose modification and a lower incidence of adverse events leading to treatment discontinuation compared with patients in the ibrutinib arm.

Zanubrutinib is tolerable and safe in the treatment of patients with R/R CLL/SLL. A favorable safety profile was demonstrated, in particular regarding the cardiac toxicity of zanubrutinib compared to ibrutinib in study 305. Similarly, study 304 demonstrated that Zanubrutinib is tolerable and safe in the treatment of patients with untreated CLL/SLL.

The FDA's Assessment:

The Agency disagrees with the Applicant's position regarding (b) (4) (b) (4). While there is a tendency toward decreased rate of TEAEs for some AEs, the clinical meaningfulness of the differences has not been established and the study was not powered to evaluate safety findings. Refer to section 8.2.5.2 for further discussion regarding cardiac arrhythmias.

The terms "safe" and "tolerable" are generalizations; however the safety data support that zanubrutinib has an acceptable safety profile, with generally manageable toxicities, in the intended populations of patients with CLL/SLL.

All Zanubrutinib (N=1550) safety data:

Data:

Similar proportions of patients experienced ≥ 1 treatment emergent adverse event among those patients received zanubrutinib in the BGB-3111-304, BGB-3111-305, All R/R CLL/SLL, All CLL/SLL, and All Zanubrutinib groups.

Adverse events at all grades reported across different pooling groups by the investigator in ≥ 10% of patients are presented in Table 91, by system organ class and preferred term.

Table 91: TEAE Reported in ≥ 10% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	371 (94.9)	291 (89.8)	492 (93.7)	885 (94.3)	1483 (95.7)
Infections and infestations	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Upper respiratory tract infection	73 (18.7)	48 (14.8)	152 (29.0)	236 (25.2)	432 (27.9)
Pneumonia	28 (7.2)	20 (6.2)	80 (15.2)	110 (11.7)	184 (11.9)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Urinary tract infection	28 (7.2)	24 (7.4)	63 (12.0)	97 (10.3)	179 (11.5)
Gastrointestinal disorders	194 (49.6)	116 (35.8)	256 (48.8)	464 (49.5)	809 (52.2)
Diarrhoea	55 (14.1)	38 (11.7)	98 (18.7)	158 (16.8)	292 (18.8)
Constipation	43 (11.0)	14 (4.3)	50 (9.5)	98 (10.4)	191 (12.3)
Nausea	43 (11.0)	24 (7.4)	49 (9.3)	96 (10.2)	164 (10.6)
Skin and subcutaneous tissue disorders	178 (45.5)	105 (32.4)	223 (42.5)	416 (44.3)	730 (47.1)
Rash	46 (11.8)	22 (6.8)	62 (11.8)	112 (11.9)	233 (15.0)
Respiratory, thoracic and mediastinal disorders	136 (34.8)	77 (23.8)	196 (37.3)	343 (36.6)	599 (38.6)
Cough	43 (11.0)	28 (8.6)	94 (17.9)	144 (15.4)	251 (16.2)
Musculoskeletal and connective tissue disorders	160 (40.9)	70 (21.6)	143 (27.2)	318 (33.9)	565 (36.5)
Arthralgia	56 (14.3)	28 (8.6)	55 (10.5)	115 (12.3)	199 (12.8)
General disorders and administration site conditions	122 (31.2)	74 (22.8)	158 (30.1)	292 (31.1)	557 (35.9)
Fatigue	38 (9.7)	20 (6.2)	46 (8.8)	90 (9.6)	185 (11.9)
Investigations	73 (18.7)	64 (19.8)	186 (35.4)	269 (28.7)	518 (33.4)
Neutrophil count decreased	19 (4.9)	21 (6.5)	103 (19.6)	123 (13.1)	235 (15.2)
Platelet count decreased	13 (3.3)	10 (3.1)	54 (10.3)	68 (7.2)	144 (9.3)
Injury, poisoning and procedural complications	134 (34.3)	64 (19.8)	145 (27.6)	296 (31.6)	503 (32.5)
Contusion	68 (17.4)	36 (11.1)	87 (16.6)	168 (17.9)	281 (18.1)
Blood and lymphatic system disorders	94 (24.0)	103 (31.8)	178 (33.9)	275 (29.3)	497 (32.1)
Anaemia	25 (6.4)	38 (11.7)	86 (16.4)	111 (11.8)	211 (13.6)
Neutropenia	46 (11.8)	48 (14.8)	75 (14.3)	122 (13.0)	206 (13.3)
Nervous system disorders	102 (26.1)	68 (21.0)	146 (27.8)	258 (27.5)	454 (29.3)
Headache	40 (10.2)	17 (5.2)	51 (9.7)	96 (10.2)	161 (10.4)
Vascular disorders	92 (23.5)	55 (17.0)	95 (18.1)	194 (20.7)	325 (21.0)
Hypertension	43 (11.0)	40 (12.3)	70 (13.3)	117 (12.5)	187 (12.1)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Renal and urinary disorders	59 (15.1)	22 (6.8)	101 (19.2)	169 (18.0)	287 (18.5)
Haematuria	24 (6.1)	7 (2.2)	63 (12.0)	95 (10.1)	148 (9.5)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-10-teae-soc-pt-10-i.rtf

The Applicant's Position:

Events of special interest for BTK inhibitors occurred with zanubrutinib but at generally lower rates than with ibrutinib in Study BGB-3111-305. These lower rates are perhaps most notable because the events can be treatment-limiting with ibrutinib. Zanubrutinib also demonstrated improved safety in terms of key adverse event analyses relative to B+R, the comparator in Study BGB-3111-304.

The spectrum of commonly reported TEAEs among patients treated with zanubrutinib is consistent with the expected safety profile of zanubrutinib, and commonly reported TEAEs in the CLL/SLL group is consistent with TEAEs reported in the All Zanubrutinib group.

The FDA's Assessment:
In general, the Agency agrees with the Applicant's position regarding the rates and types of TEAEs in study BGB-3111-304, study BGB-3111-305, and the zanubrutinib ISS population. Refer to section 8.2.5.2 for further discussion regarding cardiac arrhythmias.

The FDA conducted additional analysis of the ISS population using FDA grouping and including the study BGB-3111-305 data with a CCOD of December 1, 2021. The results were similar to the analysis conducted by the Applicant with no new safety signals identified. The most common TEAEs (≥ 20%) occurring in the ISS population were upper respiratory tract infection (39%), hemorrhage 931%), bruising (22%), musculoskeletal pain (30%), neutropenia (30%), rash (27%), and diarrhea (20%).

Table 92: Treatment-Emergent Adverse Events Occurring in ≥10% of Patients Receiving Zanubrutinib in the ISS Population (N = 1550)

System Organ Class Preferred Term	All Grades n (%)		≥ Grade 3 n (%)		Grade 5 n (%)	
Infections and infestations						
Upper respiratory tract infection	609	(39)	38	(2.5)	0	(0.0)
Urinary Tract Infection	210	(14)	33	(2.1)	0	(0.0)
Pneumonia	256	(17)	162	(10.5)	24	(1.5)
Vascular disorders						
Hemorrhage	479	(31)	59	(3.8)	4	0.3)
Bruising	341	(22)	1	(0.1)	0	(0.0)
Hypertension	223	(14)	116	(7.5)	0	(0.0)
Musculoskeletal and connective tissue disorders						
Musculoskeletal Pain	469	(30)	33	(2.1)	0	(0.0)
Blood and lymphatic system disorders						
Neutropenia*	458	(30)	315	(20.3)	0	(0.0)
Thrombocytopenia*	264	(17)	99	(6.4)	0	(0.0)
Anemia*	244	(16)	93	(6.0)	0	(0.0)
Skin and connective tissue disorders						
Rash	416	(27)	14	(0.9)	1	(0.1)
Gastrointestinal disorders						
Diarrhea	304	(20)	26	(1.7)	0	(0.0)
Constipation	204	(13)	4	(0.3)	0	(0.0)
Abdominal Pain	156	(10)	10	(0.6)	0	(0.0)
Nausea	169	(11)	4	(0.3)	0	(0.0)
Respiratory, thoracic and mediastinal disorders						
Cough	301	(19)	2	(0.1)	0	(0.0)
Neoplasms						
SPM	210	(14)	95	(6.1)	11	(0.7)

System Organ Class Preferred Term	All Grades n (%)	≥ Grade 3 n (%)	Grade 5 n (%)
General disorders			
Fatigue	252 (16)	19 (1.2)	0 (0.0)
Pyrexia	171 (11)	16 (1.0)	0 (0.0)
Edema	180 (12)	9 (0.6)	0 (0.0)
Nervous system disorders			
Headache	179 (12)	7 (0.5)	0 (0.0)
Dizziness	170 (11)	5 (0.3)	0 (0.0)

Source: Reviewer-generated table using FDA grouping (Appendix section 17.5) of the ISS ADAEG dataset submitted by the Applicant on 9-20-2022
*includes investigations: neutrophils decreased, hemoglobin decreased and platelets decreased

Data

Grade 3 or Higher Adverse Events reported across different pooling groups:

With the exception of the BGB-3111-305 group, at least 50% of patients in all groups reported at least one Grade 3 or higher adverse event. Across all groups, neutropenia and hypertension were the most commonly (> 5% of patients) reported ≥ Grade 3 adverse events. Patients in the BGB-3111-304 and BGB-3111-305 groups reported lower frequencies of pneumonia and neutrophil count decreased when compared with the **All R/R CLL/SLL**, **All CLL/SLL**, and **All Zanubrutinib groups** (Table 93).

Table 93: Grade 3 or Higher TEAE Reported in ≥ 3% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Grade 3 or Higher TEAE	202 (51.7)	143 (44.1)	300 (57.1)	516 (55.0)	897 (57.9)
Infections and infestations	64 (16.4)	37 (11.4)	119 (22.7)	190 (20.3)	338 (21.8)
Pneumonia	13 (3.3)	11 (3.4)	45 (8.6)	59 (6.3)	109 (7.0)
Blood and lymphatic system disorders	46 (11.8)	44 (13.6)	85 (16.2)	132 (14.1)	258 (16.6)
Neutropenia	34 (8.7)	33 (10.2)	54 (10.3)	89 (9.5)	151 (9.7)
Anaemia	1 (0.3)	7 (2.2)	24 (4.6)	25 (2.7)	80 (5.2)
Thrombocytopenia	7 (1.8)	7 (2.2)	17 (3.2)	24 (2.6)	47 (3.0)
Investigations	23 (5.9)	18 (5.6)	75 (14.3)	102 (10.9)	188 (12.1)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Neutrophil count decreased	12 (3.1)	12 (3.7)	65 (12.4)	78 (8.3)	135 (8.7)
Vascular disorders	30 (7.7)	28 (8.6)	41 (7.8)	75 (8.0)	122 (7.9)
Hypertension	21 (5.4)	26 (8.0)	36 (6.9)	60 (6.4)	97 (6.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'All Zanubrutinib' column.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-12-teae-soc-pt-grd3-3-i.rtf

The FDA's Assessment:

The Agency agrees with the Applicant's position regarding the reported rates of TEAEs observed with zanubrutinib versus the comparator arms in studies BGB-3111-304 and BGB-3111-305. The (b) (4) The Agency notes that for some common TEAEs, rates of grade 3 or higher TEAEs were higher in the zanubrutinib arm. These included COVID-19 in study BGB-3111-305 (7% zanubrutinib vs. 4.6% ibrutinib) and in study BGB-3111-304, musculoskeletal pain (1.7% zanubrutinib vs. 0.4% BR), upper respiratory tract infection (1.3% zanubrutinib vs. 0.9% BR), pneumonia (5% zanubrutinib

vs. 4% BR), hypertension (7% zanubrutinib vs. 2.6% BR), and second primary malignancy (6% zanubrutinib vs. 0.4% BR). In the case of the BGB-5111-304 study, the longer patient exposure with zanubrutinib compared to BR may be a contributing factor. However these findings warrant consideration particularly in a TN population (see PMR section 12 regarding characterization of second primary malignancies).

The Agency agrees that the incidence and severity of the common TEAEs associated with zanubrutinib in the CLL/SLL population are similar to those observed in the ISS safety population overall.

Laboratory Findings

Data:

Missed Laboratory Assessments Due to COVID-19

Study BGB-3111-304

The number of patients in each arm with missed laboratory assessments due to COVID 19 were low, with 11.6% of patients in the zanubrutinib arm and 18.9% of patients in the B+R arm.

Study BGB-3111-305

The number of patients in each arm with missed laboratory assessments due to COVID-19 were low, with 5.5% of patients in the zanubrutinib arm and 4.6% of patients in the ibrutinib arm.

All Zanubrutinib (N=1550) safety data:

A total of 146 (9.4%) patients missed hematology or chemistry assessments because of the COVID-19 pandemic and most of these missed 1 visit (96 patients [6.2%]) or 2 visits (33 [2.1%] patients).

Incidence of Abnormal Laboratory Values

Hematology:

Study BGB-3111-304

In Cohort 1, decreased neutrophils were the most common hematology parameter abnormality with shifts of ≥ 2 toxicity grades from baseline in both treatment arms. The proportions of patients with decreased neutrophils were higher in B+R arm (72.7%) compared with the zanubrutinib arm (21.7%). Decreased lymphocytes and decreased leukocytes were more commonly observed in B+R arm compared with the zanubrutinib arm; however, increased leukocytes were more commonly observed in the zanubrutinib arm compared with the B+R arm. The proportion of patients who had hematology laboratory changes to Grade 3 or 4 was higher in the B+R arm (90.3%) compared with the zanubrutinib arm (35.8%) (Table 94). Decreased leukocytes and decreased lymphocytes were the most common Grade 3 or 4 hematology parameter abnormalities observed in the B+R arm (75.8% and 82.8%, respectively); increased leukocytes were the most common Grade 3 or 4 hematology parameters observed in the zanubrutinib arm (20.4%), which were treatment related and expected.

In Cohort 2, decreased neutrophils (30.6%) and increased leukocytes (15.3%) were the most common hematology parameter abnormality with shifts of ≥ 2 toxicity grades from baseline (Table 94). The proportion of patients who had hematology laboratory changes to Grade 3 or 4 was 35.1%.

Table 94: Worsening Shifts of ≥ 2 CTCAE Toxicity Grades Compared with Baseline: Hematology Parameters in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Absolute Lymphocytes Count(10^9/L) (Low)	188 (82.8)	2 (0.8)	4 (3.6)
Absolute Lymphocytes Count(10^9/L) (High)	0 (0.0)	11 (4.6) [a]	3 (2.7) [a]
Absolute Lymphocytes Count-Selected(10^9/L) (Low) [b]	210 (92.5)	8 (3.3)	5 (4.5)
Absolute Lymphocytes Count-Selected(10^9/L) (High) [b]	0 (0.0)	11 (4.6) [a]	4 (3.6) [a]
Absolute Neutrophil Count-Selected(10^9/L) (Low) [b]	165 (72.7)	52 (21.7)	34 (30.6)
Hemoglobin(g/L) (Low)	22 (9.7)	6 (2.5)	4 (3.6)
Hemoglobin(g/L) (High)	0 (0.0)	1 (0.4)	---
Leukocytes(10^9/L) (Low)	172 (75.8)	5 (2.1)	4 (3.6)
Leukocytes(10^9/L) (High)	1 (0.4)	49 (20.4) [a]	17 (15.3) [a]
Platelets(10^9/L) (Low)	36 (15.9)	4 (1.7)	3 (2.7)
Prothrombin Intl. Normalized Ratio(RATIO) (High)	0 (0.0)	1 (0.4)	---

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADLB
Abbreviation: BR, Bendamustine and Rituximab; NCI-CTCAE, national cancer institute-common terminology criteria for adverse event
Notes: Only patients with at least one assessment (either baseline or postbaseline) were included in the table. The percentages were based on the number of patients with at least one assessment (either baseline or postbaseline).
Laboratory results were graded using NCI-CTCAE Version 4.03
Patients from BR arm only include their assessments before crossing over to the Zanubrutinib arm.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_lb_shift_c1_i.sas
Output: t-14-3-5-86-lb-shift2-hema-c1-saf-i.rtf (Date Generated: 06SEP2021:06:20)
[a] Increase in lymphocytes, absolute lymphocyte count-selected, and leukocytes in patients treated with zanubrutinib is a known temporary treatment-related phenomenon (Cheson et al 2012).
[b] Source laboratory was used for independent central review.
Source: Table 14.3.5.1.4.1

Study BGB-3111-305

Decreased neutrophils and increased leukocytes were the most common hematology parameter abnormalities with shifts of ≥ 2 toxicity grades from baseline in both treatment arms. The proportion of patients with decreased neutrophils was higher in the zanubrutinib arm compared with the ibrutinib arm. The proportions of patients with increased lymphocyte, however, was lower in the zanubrutinib arm compared with the ibrutinib arm (Table 95). The proportion of patients who had hematology laboratory changes to Grade 3 or 4 was comparable between the zanubrutinib arm and the ibrutinib arm. Increased leukocytes and increased lymphocytes were the most common Grade 3 or 4 hematology parameter abnormalities.

Table 95: Worsening Shifts of ≥ 2 CTCAE Toxicity Grades Compared with Baseline: Hematology Parameters (Safety Analysis Set)

Parameter (Directional Change)	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Absolute Lymphocytes Count (Derived) (Low)	5 (1.5)	13 (4.0)
Absolute Lymphocytes Count (Derived) (High)	22 (6.8)	29 (9.0)
Absolute Neutrophils Count (Derived) (Low)	10 (3.1)	11 (3.4)
Hemoglobin (Low)	6 (1.9)	10 (3.1)
Lymphocytes (Low)	5 (1.5)	13 (4.0)
Lymphocytes (High)	20 (6.2)	29 (9.0)
Neutrophils (Low)	68 (21.0)	51 (15.7)
Platelets (Low)	3 (0.9)	6 (1.9)
Leukocytes (Low)	15 (4.6)	9 (2.8)
Leukocytes (High)	68 (21.0)	68 (21.0)

Source: ADSL, ADLB. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: NCI-CTCAE, national cancer institute-common terminology criteria for adverse event
Laboratory results were graded using NCI-CTCAE Version 4.03.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-lab-hem-shift-i.sas 09AUG2021 23:33 t-28-lab-hem-shift1-i.rtf

All Zanubrutinib (N=1550) safety data:

Data

Decreased neutrophil counts of any grade were common in treated patients, occurring in nearly half of the patients in each group. Any-grade decreases in platelets and hemoglobin were less common across all groups.

No clinically relevant differences between groups were observed for other hematology parameters of interest (decreased hemoglobin concentration, increased hemoglobin concentration, decreased platelet count, decreased lymphocyte count, increased lymphocyte count) for postbaseline shifts of ≥ 2 toxicity grades.

Table 96: Shifts of ≥ 2 Toxicity Grades From Baseline to the Worst Postbaseline Grade for Selected Hematology Parameters (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Hemoglobin (g/L)					
n	391	324	525	938	1550
Low directionality	11 (2.8)	6 (1.9)	19 (3.6)	30 (3.2)	67 (4.3)
High directionality	1 (0.3)	0 (0.0)	3 (0.6)	4 (0.4)	6 (0.4)
Platelets (10^9/L)					
n	391	324	525	938	1550
Low directionality	10 (2.6)	3 (0.9)	13 (2.5)	23 (2.5)	91 (5.9)
Neutrophils (10^9/L)					
n	391	324	525	938	1550
Low directionality	90 (23.0)	10 (3.1)	107 (20.4)	207 (22.1)	391 (25.2)
Lymphocytes (10^9/L)					
n	391	324	525	938	1550
Low directionality	14 (3.6)	5 (1.5)	43 (8.2)	61 (6.5)	166 (10.7)
High directionality	18 (4.6)	22 (6.8)	46 (8.8)	65 (6.9)	175 (11.3)

Source: ADSL, ADLB. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on n, the number of patients with at least one assessment at

baseline or any time postbaseline, respectively.
Postbaseline laboratory results were summarized up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first.
Laboratory results are graded using CTCAE v4.03.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-hem-abn-shift2-i.sas 24AUG2021 01:23 t-36-hem-abn-shift2-i.rtf

Chemistry:

Data:

Study BGB-3111-304

In Cohort 1, decreased phosphate and increased glucose were the most common serum chemistry parameters with shifts of ≥ 2 toxicity grades from baseline in both treatment arms. The proportions of patients with decreased phosphate and increased glucose were higher in the B+R arm (25.1% and 13.2%, respectively) compared with the zanubrutinib arm (17.9% and 6.7%, respectively) (Table 97). The proportion of patients who had serum chemistry laboratory changes to Grade 3 or 4 was higher in the B+R arm (15.9%) compared with the zanubrutinib arm (10.8%). Increased glucose, increased ALT, and decreased phosphate were the most common Grade 3 or 4 serum chemistry parameter abnormalities observed in the B+R arm (4.4%, 3.1%, and 3.1%, respectively); decreased sodium and increased glucose were the most common Grade 3 or 4 serum chemistry parameters observed in the zanubrutinib arm (3.8% and 3.3%, respectively).

In Cohort 2, decreased phosphate (18.0%) and increased glucose (9.9%) were the most common serum chemistry parameter abnormalities with shifts of ≥ 2 toxicity grades from baseline (Table 97). The proportion of patients who had serum chemistry laboratory changes to Grade 3 or 4 was 10.8%.

Table 97: Worsening Shifts of ≥ 2 CTCAE Toxicity Grades Compared with Baseline: Serum Chemistry Parameters in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Alanine Aminotransferase(U/L) (High)	10 (4.4)	6 (2.5)	3 (2.7)
Albumin(g/L) (Low)	10 (4.4)	4 (1.7)	4 (3.6)
Alkaline Phosphatase(U/L) (High)	0 (0.0)	2 (0.8)	2 (1.8)

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N = 111) n (%)**
Aspartate Aminotransferase(U/L) (High)	9 (4.0)	6 (2.5)	1 (0.9)
Bilirubin(umol/L) (High)	6 (2.6)	1 (0.4)	5 (4.5)
Calcium(mmol/L) (Low)	21 (9.3)	4 (1.7)	3 (2.7)
Calcium(mmol/L) (High)	0 (0.0)	3 (1.3)	--
Corrected Calcium (mmol/L) (Low)	7 (3.1)	2 (0.8)	--
Corrected Calcium (mmol/L) (High)	0 (0.0)	3 (1.3)	--
Creatinine(umol/L) (High)	9 (4.0)	5 (2.1)	3 (2.7)
Glucose(mmol/L) (Low)	5 (2.2)	0 (0.0)	2 (1.8)
Glucose(mmol/L) (High)	31 (13.7)	16 (6.7)	11 (9.9)
Magnesium(mmol/L) (Low)	3 (1.3)	2 (0.8)	--
Magnesium(mmol/L) (High)	2 (0.9)	0 (0.0)	--
Phosphate(mmol/L) (Low)	58 (25.6)	43 (17.9)	20 (18.0)
Potassium(mmol/L) (Low)	4 (1.8)	0 (0.0)	--
Potassium(mmol/L) (High)	11 (4.8)	11 (4.6)	2 (1.8)
Sodium(mmol/L) (Low)	5 (2.2)	9 (3.8)	1 (0.9)
Sodium(mmol/L) (High)	0 (0.0)	1 (0.4)	1 (0.9)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADLB
Abbreviation: BR, Bendamustine and Rituximab.m NCI-CTCAE, national cancer institute-common terminology criteria for adverse event
Notes: Only patients with at least one assessment (either baseline or postbaseline) were included in the table. The percentages were based on the number of patients with at least one assessment (either baseline or postbaseline).
Laboratory results were graded using NCI-CTCAE Version 4.03
Patients from BR arm only include their assessments before crossing over to the Zanubrutinib arm.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_lb_shift_c1_i.sas
Output: t-14-3-5-89-lb-shift2-chem-c1-saf-i.rtf (Date Generated: 06SEP2021:06:20)
Source: Table 14.3.5.1.6.1 and Source: Table 14.3.5.1.6.3

Study BGB-3111-305

The proportion of patients with worsening shifts of 2 or more toxicity grades from baseline was generally comparable between the zanubrutinib and ibrutinib arms for each of the serum chemistry analytes evaluated except for decreased potassium (higher proportion in the zanubrutinib arm) and increased bilirubin (higher proportion in the ibrutinib arm) (Table 98) The proportion of patients with Grade 3 or 4 serum chemistry laboratory changes was slightly higher in the zanubrutinib arm (34 [10.5%] patients) compared with the ibrutinib arm (20 [6.2%] patients).

Table 98: Worsening Shifts of ≥ 2 CTCAE Toxicity Grades Compared with Baseline: Chemistry Parameters (Safety Analysis Set)

Parameter (Directional Change)	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Albumin (Low)	2 (0.6)	2 (0.6)
Alkaline Phosphatase (High)	1 (0.3)	3 (0.9)
Alanine Aminotransferase (High)	3 (0.9)	5 (1.5)
Aspartate Aminotransferase (High)	0 (0.0)	2 (0.6)
Bilirubin (High)	1 (0.3)	10 (3.1)
Calcium (Low)	2 (0.6)	4 (1.2)
Calcium (High)	2 (0.6)	0 (0.0)
Creatinine (High)	3 (0.9)	2 (0.6)
Glucose (Low)	0 (0.0)	1 (0.3)
Glucose (High)	13 (4.0)	12 (3.7)
Potassium (Low)	4 (1.2)	0 (0.0)
Potassium (High)	4 (1.2)	2 (0.6)
Magnesium (Low)	2 (0.6)	0 (0.0)
Magnesium (High)	1 (0.3)	0 (0.0)
Phosphate (Low)	41 (12.7)	29 (9.0)
Sodium (Low)	5 (1.5)	1 (0.3)

Source: ADSL, ADLB. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.
Laboratory results were graded using NCI-CTCAE Version 4.03.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-lab-chem-shift-i.sas
09AUG2021 23:36 t-30-lab-chem-shift1-i.rtf

All Zanubrutinib (N=1550) safety data:

In **Study BGB-3111-304**, there were 4 (1.0%) increases to Grade 3 and 3 (0.8%) increases to Grade 4 in ALT levels; for AST, there were 7 (1.8%) increases to Grade 3 reported, and none to Grade 4. In **Study BGB-3111-305**, there were no reported postbaseline increases to Grade 3 or 4 in ALT or AST.

No clinically relevant differences between groups were observed for serum chemistry analytes of interest for postbaseline shifts of ≥ 2 toxicity grades (Table 99). Increases in ALT or AST were reported in less than 3% of patients in every group, with a particularly low incidence in Study BGB-3111-305.

Table 99: Shifts in ≥ 2 Toxicity Grades From Baseline to the Worst Postbaseline Grade for Selected Chemistry Parameters (Safety Analysis Set)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Alanine Aminotransferase (U/L)					
n	391	324	525	938	1550
High directionality	10 (2.6)	3 (0.9)	13 (2.5)	24 (2.6)	41 (2.6)
Aspartate Aminotransferase (U/L)					
n	391	324	525	938	1550
High directionality	8 (2.0)	0 (0.0)	4 (0.8)	13 (1.4)	25 (1.6)

Source: ADSL, ADLB. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on n, number of patients with at least one assessment at baseline or any time postbaseline.
Postbaseline laboratory results were summarized up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first.
Laboratory results are graded using CTCAE v4.03.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-chem-abn-shift2-i.sas 24AUG2021 01:23 t-37-chem-abn-shift2-i.rtf

The Applicant's Position:
In Study BGB-3111-304 and Study BGB-3111-305, no clinically relevant changes were observed in parameters of either hematologic or serum chemistry in either treatment arm, except for absolute lymphocyte count, which showed changes consistent with the known treatment effect of study drugs against malignant CLL cells. Serum chemistry findings in Study BGB-3111-304 and Study BGB-3111-305 are consistent with Zanubrutinib's overall safety profile.

The FDA's Assessment:
Although laboratory data included in this submission were consistent with the known safety

profile of zanubrutinib, the Agency disagrees with the Applicant's position that, apart from absolute lymphocyte count, there were no clinically relevant changes in any laboratory data in either randomized study.

The Applicant's tables of laboratory data do not provide sufficient detail on the grades of treatment-emergent laboratory abnormalities. Additionally, there were errors predominantly in the hematology labs in the proposed labeling, primarily due to the interchanging of iwCLL and CTCAE grading criteria. For both randomized studies, the Agency conducted lab-shift analysis for chemistries and hematologic abnormalities using CTCAE criteria. Laboratory analyses are presented by study, followed by comments regarding the pooled ISS population.

Study BGB-3111-304 laboratory data:
In Study BGB-3111-304, the rates of treatment-emergent cytopenias, including grade 3 and 4 cytopenias were higher in the BR arm compared to the zanubrutinib arm. Laboratory abnormalities in Cohort 2 were similar to those observed in the zanubrutinib arm of Cohort 1 and are summarized in the table below.

Table 100: Treatment-Emergent Laboratory Abnormalities in ≥ 10% of Zanubrutinib Recipients in Study BGB-3111-304 (Cohorts 1 and 2) by Maximum CTCAE Grade

	Cohort 1: CLL without 17p del						Cohort 2: CLL with 17p del		
	Zanubrutinib, %			BR, %			Zanubrutinib, %		
Parameter [a]	All grades	Grade 3 or 4	Grade 4	All grades	Grade 3 or 4	Grade 4	All grades	Grade 3 or 4	Grade 4
Hematology									
Neutrophil decrease	37	15	8.4	80	53	27	42	19	9
Hemoglobin decrease	29	2.5	0	66	8	0	26	3.6	0
Platelet decrease	27	1.7	0.4	61	11	3.1	23	0.9	0
Leukocytes increase	21	21	0	0.4	0.4	0	15	15	0
Lymphocytes increase	15	11	0	0	0	0	14	10	0
Leukocyte decrease	13	2.1	0.4	88	44	8	14	0.9	0
Lymphocyte decrease	9	0.8	0.4	92	81	26	13	0.9	0
Chemistry									
In ≥ 20% of zanubrutinib recipients									
Glucose increase	55	7	0.4	67	10	1.3	52	6	0
Creatinine increase	22	0.8	0.8	18	0.4	0	27	0.9	0
Magnesium increase	22	0	0	14	0.4	0	31	0	0
ALT increase	21	2.1	0.4	23	2.2	0.4	19	0.9	0.9
Other chemistries									
Phosphate decrease	19	2.1	0	22	3.1	0	19	0.9	0
Sodium increase	15	0	0	15	0	0	11	0	0
Potassium increase	14	0	0.4	7	0	0.4	10	0.9	0

Parameter [a]	Cohort 1: CLL without 17p del						Cohort 2: CLL with 17p del		
	Zanubrutinib, %			BR, %			Zanubrutinib, %		
	All grades	Grade 3 or 4	Grade 4	All grades	Grade 3 or 4	Grade 4	All grades	Grade 3 or 4	Grade 4
AST increase	12	2.1	0	28	1.3	0.4	9	0.9	0
Sodium decrease	10	3.8	0.4	11	2.2	0.4	11	0.9	0
Alkaline phos increase	10	0	0	15	0.4	0	16	0.9	0
Bilirubin increase	10	0	0	15	0.9	0	13	0.9	0
Potassium decrease	9	0	0	17	0.9	0.4	5	0	0
Glucose decrease	7	0	0	8	0	0	14	0	0
Albumin decrease	5	0	0	14	0	0	13	0	0

Source: FDA CDTL analysis of ADLB dataset submitted 1/5/2023

[a] Denominator was based on the number of patients with a baseline grade and at least one post-treatment grade: 239 in zanubrutinib cohort 1, 227 in BR arm, and 110 to 111 in zanubrutinib cohort 2.

Study BGB-3111-305 laboratory data

In Study BGB-3111-305, the rates of grade 3 and 4 cytopenias and chemistries were similar in the zanubrutinib and ibrutinib arm as shown in the table below.

Table 101: Treatment-Emergent Laboratory Abnormalities in ≥ 10% of Zanubrutinib Recipients in Study BGB-3111-305 by Maximum CTCAE Grade

Parameter	Zanubrutinib, %			Ibrutinib, %		
	All grades	Grade 3 or 4	Grade 4	All grades	Grade 3 or 4	Grade 4
Hematology						
Neutrophils decrease	43	15	6	33	16	7
Hemoglobin decrease	28	4.0	0	32	3.7	0
Lymphocytes increase	24	19	0	26	19	0
Platelets decrease	22	4.0	1.2	24	3.4	0.9
Leukocytes increase	21	21	0	21	21	0
Leukocytes decrease	16	2.2	0.3	15	0.9	0.3
Lymphocytes decrease	10	0.9	0.3	12	1.9	0
Chemistry						
Glucose increase[b]	52	5.0	0	29	2.8	0.3
Creatinine increase	26	0.0	0	23	0.0	0
Phosphate decrease	21	2.5	0	13	2.2	0
Calcium decrease	21	0.6	0.6	29	0.0	0
ALT increase	17	0.0	0	14	1.6	0.3
Alk phos increase	14	0.3	0	13	0.0	0
Glucose decrease	13	0.0	0	28	0.3	0
AST increase	10	0.0	0	12	0.6	0
Sodium decrease	10	1.9	0	9	0.6	0

Source: FDA analysis of revised study-specific ADLB dataset submitted 1/5/2023
[a] Denominator was based on the number of patients with a baseline grade and at least one post-treatment grade: 321 in zanubrutinib arm, and 320 to 321 in ibrutinib arm.
[b] Not necessarily fasting

All-zanubrutinib ISS population (N= 1550):
In the zanubrutinib ISS population, laboratory abnormalities in >25% were glucose increased, neutrophils decreased, hemoglobin decreased, platelets decreased and leukocytes decreased. The most common grade 3 or 4 laboratory abnormalities were cytopenias. Grade 3 or higher neutropenia occurred in 20% of patients with grade 4 occurring in 10%. Grade 3 or higher thrombocytopenia occurred 7% of patients with grade 4 occuring in 2.3%. Details of laboratory abnormalities are provided in the Appendix, section 17.5.2.

Hy's law screen: Per the Applicant's summary of clinical safety (SCS) and data tables in the individual CSRs, there were no patients in studies BGB-3111-304, BGB-3111-305, BGB-3111-205, BGB-3111-1002, or BGB-3111-AU-003 who met criteria for Hy's law, defined as AST or ALT > 3 X ULN and totol bilirubin > 2 X ULN and with ALP < 2 X ULN. Two patients in the ISS met laboratory criteria for Hy's law, however alternative etiologies for hepatic injury were reported. One additional case of drug-induced liver injury was reported that did not meet laboratory criteria for Hy's law.

These cases are briefly summarized below.

- In study BGB-3111-214 one patient met laboratory criteria for Hy's law study on day 4. This was a 73 female who also recently initiated prophylactic acyclovir and sulfamethoxazole/trimethoprim. Zanubrutinib was interrupted and sulfamethoxazole/trimethoprim was discontinued. The laboratory findings resolved and did not recur with resumption of zanubrutinib. The laboratory abnormalities were assessed to be related to sulfamethoxazole/trimethoprim.

- In study BGB-3111-210, one patient met laboratory criteria for Hy's law, however this was in the context of acute hepatitis B and therefore was not considered to meet all criteria for Hy's law given the alternative etiology.

In study BGB-3111-302, one patient developed grade 4 DILI on study day 832, the patient had marked (50 X ULN) elevations of ALT, AST, and total bilirubin without elevations in alkaline phosphatase. Liver biopsy results were consistent with drug induced hepatitis. The patient had received phenoxymethylpenicillin 5 days prior to the event. Both phenoxymethylpenicillin and zanubrutinib were discontinued. The adverse event resolved. This event was considered likely related to phenoxymethylpenicillin. In summary there were no reported cases of patients meeting Hy's law laboratory criteria without an alternative potential etiology for the laboratory findings.

Vital Signs

Data:

Study BGB-3111-304:

In Cohort 1, no clinically meaningful changes from baseline in vital signs were observed in either treatment arm, except for weight. The median weight of patients in the B+R arm decreased from baseline during the first 6 cycles, especially before Cycle 3, and gradually increased after Cycle 6. In the zanubrutinib arm, the median weight was gradually increased after Cycle 2 and stayed relatively stable after Cycle 10.

Study BGB-3111-305

No clinically meaningful changes from baseline in vital signs were observed in either treatment arm.

All Zanubrutinib (N=1550) safety data:
No noteworthy changes from baseline were observed in median values for systolic or diastolic blood pressures, pulse rate, respiratory rate, temperature, or weight.

The proportion of patients with worsening shifts of 2 or more toxicity grades from baseline in systolic and diastolic blood pressures was generally comparable between all groups.

The Applicant's Position:
Laboratory findings in this pooled dataset is consistent with known safety profile of zanubrutinib.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment. There were no new safety signals identified based on vital sign analysis from this submission.

Electrocardiograms (ECGs)
Data:

Study BGB-3111-304

For Cohort 1 and Cohort 2, no patients in either treatment arm had a postbaseline QTcF interval measurement of > 500 msec. In Cohort 1, 2 (16.7%) of 12 evaluable patients in the B+R arm had a maximum increase from baseline in QTcF of > 60 msec. No patients in Cohort 2 had a maximum increase from baseline in QTcF of > 60 msec. Summaries of QTcF interval prolongation are provided in Table 102.

Table 102: QTcF Observed and Change from Baseline in Cohort 1

	Cohort 1		Cohort 2
	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
QTcF (msec)			
Patients with at least one postbaseline measure [a]	13	15	6
> 450 msec	0 (0.0)	0 (0.0)	0 (0.0)
> 480 msec	0 (0.0)	0 (0.0)	0 (0.0)
> 500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Patients with baseline and at least one postbaseline measure [b]	12	15	6
≤ 30 msec maximum increase from baseline	3 (25.0)	3 (20.0)	1 (16.7)
> 30 msec and ≤ 60 msec maximum increase from baseline	1 (8.3)	3 (20.0)	1 (16.7)
> 60 msec maximum increase from baseline	2 (16.7)	0 (0.0)	0 (0.0)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADEG
Abbreviation: BR, Bendamustine and Rituximab; QTcF, QT corrected with Fridericia's formula
[a] The denominator is the number of patients with at least one postbaseline measure
[b] The denominator is the number of patients with both baseline and at least one postbaseline measures.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_eg_i.sas
Output: t-14-3-5-3-2-1-98-eg-prolong-c1-saf-i.rtf (Date Generated: 06SEP2021:06:23)
Source: Table 14.3.5.3.2.1 (cohort 1) and Table 14.3.5.3.2.3 (cohort 2)

Study BGB-3111-305

Two of the 323 evaluable patients (0.6%) patients in the zanubrutinib arm and 1 of the 317 evaluable patients (0.3%) in the ibrutinib arm had at least 1 postbaseline QTcF interval measurement of > 500 msec. Six of the 323 evaluable patients (1.9%) patients in the zanubrutinib arm and 5 of the 317 evaluable patient (1.6%) in the ibrutinib arm had a maximum increase from baseline in QTcF of > 60 msec. Of these patients with QTcF > 500 msec, none experienced an adverse event of ECG QT prolonged, ventricular arrhythmia, torsades de pointes, or sudden death. Summaries of electrocardiograms are provided in Table 103.

Table 103: QTcF Observed and Change from Baseline (Safety Analysis Set)

	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
QTcF (msec)		
Patients with at least one postbaseline measure [a]	323	317
QTcF > 450 msec	57 (17.6)	25 (7.9)
QTcF > 480 msec	13 (4.0)	1 (0.3)
QTcF > 500 msec	2 (0.6)	1 (0.3)
Patients with baseline and at least one postbaseline measure [b]	323	317
≤ 30 msec maximum increase from baseline	221 (68.4)	135 (42.6)
> 30 msec and ≤ 60 msec maximum increase from baseline	45 (13.9)	17 (5.4)
> 60 msec maximum increase from baseline	6 (1.9)	5 (1.6)

Source: ADSL, ADEG. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: QTcF, QT corrected with Fridericia's formula
[a]The denominator is the number of patients with at least one postbaseline measure.
[b]The denominator is the number of patients with both baseline and at least one postbaseline measures.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eg-chg-category-i.sas 09AUG2021 23:38 t-32-eg-chg-category-i.rtf

All Zanubrutinib (N=1550) safety data:

Post-baseline electrocardiographic changes (in terms of either prolonged QT corrected with Fridericia's formula [QTcF] measurements or increases in QTcF from baseline) were infrequent across groups.

In the **BGB-3111-304** group, no patient had a postbaseline QTcF interval > 450 msec, and no patient had a maximal increase from baseline in QTcF of > 60 msec.

In the **BGB-3111-305** group 13 patients (4.0%) had a postbaseline interval measurement of > 480 msec and 2 patients (0.6%) had a postbaseline measurement of > 500 msec; 6 patients (1.9%) had a maximal increase from baseline in QTcF of > 60 msec.

In the **All Zanubrutinib** group, 13 patients (1.2%) had at least 1 postbaseline QTcF interval measurement of > 500 msec, and 42 patients (3.8%) had a maximal increase from baseline of > 60 msec.

In the **All R/R CLL/SLL** group, 6 patients (1.1%) had at least 1 postbaseline QTcF interval measurement of > 500 msec and 16 patients (3.1%) had a maximal increase from baseline of > 60 msec.

In the **All CLL/SLL** group, 6 patients (1.1%) had at least 1 postbaseline QTcF interval measurement of > 500 msec and 17 patients (3.0%) had a maximal increase from baseline of > 60 msec.

The Applicant's Position:

ECG findings in this pooled dataset is consistent with known safety profile of zanubrutinib.

The FDA's Assessment:
The Agency agrees with the Applicant's position regarding ECG findings. There are no new safety signals identified based on ECG analysis.

Immunogenicity
Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable.

8.2.5 Analysis of Submission-Specific Safety Issues

Study BGB-3111-304

In **Cohort 1,** the incidence of adverse events of special interest overall was comparable between the zanubrutinib arm (Arm A) and B+R arm (Arm B) in the Safety Analysis Set. However, for individual categories, the incidence was higher in the B+R arm compared with the zanubrutinib arm for the categories of anemia, neutropenia, and thrombocytopenia and higher in the zanubrutinib arm compared with the B+R arm for the category of hemorrhage.

The majority of patients in **Cohort 2** (101 [91.0%] patients) reported at least 1 adverse event of special interest. The most commonly reported categories of adverse events of special interest were infections (79 [71.2%]), hemorrhage (57 [51.4%]), and second primary malignancies (24 [21.6%]).

Table 104: Treatment-Emergent Adverse Events of Special Interest Reported in >= 2% of Patients by Category and Preferred Term in study 304 Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
Category Preferred Term	**BR (N = 227) n (%)**	**Zanubrutinib (N = 240) n (%)**	**Zanubrutinib (N =111) n (%)**
Patients With at Least One AE of Special Interest	187 (82.4)	199 (82.9)	101 (91.0)
Anemia	41 (18.1)	11 (4.6)	6 (5.4)

Category Preferred Term	Cohort 1 BR (N = 227) n (%)	Cohort 1 Zanubrutinib (N = 240) n (%)	Cohort 2 Zanubrutinib (N =111) n (%)
Anaemia	40 (17.6)	11 (4.6)	6 (5.4)
Atrial fibrillation and flutter	5 (2.2)	8 (3.3)	5 (4.5)
Atrial fibrillation	5 (2.2)	8 (3.3)	5 (4.5)
Hemorrhage	16 (7.0)	108 (45.0)	57 (51.4)
Contusion	5 (2.2)	46 (19.2)	22 (19.8)
Petechiae	0 (0.0)	18 (7.5)	5 (4.5)
Haematoma	1 (0.4)	13 (5.4)	6 (5.4)
Haematuria	2 (0.9)	13 (5.4)	10 (9.0)
Epistaxis	1 (0.4)	12 (5.0)	8 (7.2)
Ecchymosis	1 (0.4)	7 (2.9)	6 (5.4)
Purpura	0 (0.0)	5 (2.1)	4 (3.6)
Major hemorrhage	2 (0.9)	12 (5.0)	8 (7.2)
Haematuria	0 (0.0)	4 (1.7)	3 (2.7)
Hypertension	12 (5.3)	34 (14.2)	12 (10.8)
Hypertension	9 (4.0)	29 (12.1)	10 (9.0)
Infections	97 (42.7)	148 (61.7)	79 (71.2)
Upper respiratory tract infection	17 (7.5)	40 (16.7)	23 (20.7)
COVID-19	0 (0.0)	20 (8.3)	3 (2.7)
Urinary tract infection	14 (6.2)	17 (7.1)	9 (8.1)
Nasopharyngitis	10 (4.4)	16 (6.7)	10 (9.0)
Cellulitis	0 (0.0)	12 (5.0)	2 (1.8)
Sinusitis	4 (1.8)	12 (5.0)	6 (5.4)
Pneumonia	13 (5.7)	11 (4.6)	13 (11.7)
Lower respiratory tract infection	2 (0.9)	9 (3.8)	6 (5.4)
COVID-19 pneumonia	0 (0.0)	8 (3.3)	2 (1.8)
Bronchitis	10 (4.4)	7 (2.9)	3 (2.7)
Respiratory tract infection	7 (3.1)	7 (2.9)	5 (4.5)
Skin infection	1 (0.4)	6 (2.5)	2 (1.8)
Herpes zoster	2 (0.9)	5 (2.1)	1 (0.9)
Conjunctivitis	4 (1.8)	4 (1.7)	4 (3.6)
Oral herpes	6 (2.6)	3 (1.3)	2 (1.8)

Category Preferred Term	Cohort 1 BR (N = 227) n (%)	Cohort 1 Zanubrutinib (N = 240) n (%)	Cohort 2 Zanubrutinib (N =111) n (%)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Infection	5 (2.2)	1 (0.4)	2 (1.8)
Pharyngitis	0 (0.0)	1 (0.4)	4 (3.6)
Ear infection	0 (0.0)	0 (0.0)	3 (2.7)
Neutropenia	127 (55.9)	38 (15.8)	21 (18.9)
Neutropenia	102 (44.9)	31 (12.9)	13 (11.7)
Neutrophil count decreased	28 (12.3)	6 (2.5)	7 (6.3)
Febrile neutropenia	17 (7.5)	2 (0.8)	1 (0.9)
Second primary malignancies	3 (1.3)	31 (12.9)	24 (21.6)
Basal cell carcinoma	0 (0.0)	11 (4.6)	12 (10.8)
Squamous cell carcinoma of skin	0 (0.0)	5 (2.1)	4 (3.6)
Skin cancers	3 (1.3)	16 (6.7)	17 (15.3)
Basal cell carcinoma	0 (0.0)	11 (4.6)	12 (10.8)
Squamous cell carcinoma of skin	0 (0.0)	5 (2.1)	4 (3.6)
Thrombocytopenia	38 (16.7)	11 (4.6)	8 (7.2)
Thrombocytopenia	29 (12.8)	9 (3.8)	4 (3.6)
Platelet count decreased	11 (4.8)	2 (0.8)	4 (3.6)

Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event; MedDRA, medical dictionary for regulatory activities
Notes: Adverse events were classified based on MedDRA Version 24.0
Patients with multiple events for a given preferred term were counted only once for each preferred term.
Events were sorted by descending order within category, and by preferred term within category in the Treatment-Emergent and Post-treatment Cohort 1 Zanubrutinib column.

Programmer: jinling.li, Location:
/bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_aesi_postteae_ab.sas
Output: t-14-3-1-2-10-1-1-teae-aesi-c1-saf.rtf (Date Generated: 06SEP2021:05:40)

Study BGB-3111-305

The incidence of adverse events of special interests by category was generally comparable between the zanubrutinib arm and ibrutinib arm in the Safety Analysis Set, except for atrial

fibrillation and flutter (zanubrutinib: 1.9% versus ibrutinib: 8.0%), major hemorrhage (zanubrutinib: 1.9% versus ibrutinib: 3.1%), neutropenia (zanubrutinib: 21.3% versus ibrutinib: 17.3%).

Table 105: Treatment-Emergent Adverse Events of Special Interest Reported in > 2% of Patients by Category and Preferred Term: Study 305 (Safety Analysis Set)

Category Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One TEAE of Special Interest	240 (74.1)	245 (75.6)
Anemia	39 (12.0)	47 (14.5)
Anaemia	38 (11.7)	45 (13.9)
Atrial fibrillation and flutter	6 (1.9)	26 (8.0)
Atrial fibrillation	5 (1.5)	24 (7.4)
Hemorrhage	108 (33.3)	104 (32.1)
Contusion	36 (11.1)	25 (7.7)
Epistaxis	22 (6.8)	16 (4.9)
Petechiae	26 (8.0)	12 (3.7)
Haematoma	11 (3.4)	12 (3.7)
Haematuria	7 (2.2)	7 (2.2)
Skin haemorrhage	7 (2.2)	7 (2.2)
Increased tendency to bruise	7 (2.2)	3 (0.9)
Major hemorrhage	6 (1.9)	10 (3.1)
Hypertension	42 (13.0)	40 (12.3)
Hypertension	40 (12.3)	31 (9.6)
Blood pressure increased	3 (0.9)	12 (3.7)
Infections	152 (46.9)	166 (51.2)
Upper respiratory tract infection	48 (14.8)	34 (10.5)
Pneumonia	20 (6.2)	26 (8.0)
Urinary tract infection	24 (7.4)	20 (6.2)
COVID-19	14 (4.3)	12 (3.7)
Bronchitis	7 (2.2)	13 (4.0)
Sinusitis	9 (2.8)	10 (3.1)
Cellulitis	7 (2.2)	9 (2.8)
Lower respiratory tract infection	8 (2.5)	6 (1.9)
Pharyngitis	6 (1.9)	8 (2.5)
Oral herpes	4 (1.2)	9 (2.8)
Rhinitis	6 (1.9)	7 (2.2)
Paronychia	3 (0.9)	7 (2.2)
Neutropenia	69 (21.3)	56 (17.3)
Neutropenia	48 (14.8)	38 (11.7)
Neutrophil count decreased	21 (6.5)	17 (5.2)
Second primary malignancies	19 (5.9)	16 (4.9)
Squamous cell carcinoma of skin	5 (1.5)	7 (2.2)
Skin cancers	8 (2.5)	12 (3.7)
Squamous cell carcinoma of skin	5 (1.5)	7 (2.2)
Thrombocytopenia	30 (9.3)	35 (10.8)
Thrombocytopenia	20 (6.2)	21 (6.5)
Platelet count decreased	10 (3.1)	15 (4.6)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.

Category Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)

Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Patients with multiple events for a given preferred term and special interest category were counted only once for each preferred term and category, respectively.
Events are first sorted by category alphabetically, then by decreasing frequency of preferred term in the Total column.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-aesi-pt.sas 09AUG2021 21:57
t-14-3-1-2-5-1-aesi-pt.rtf

All Zanubrutinib (N=1550) Safety Data:

Adverse events of special interest for zanubrutinib were those that are known to be associated with the class of BTK inhibitors. The overall rates of each of the adverse events of special interest integrated Safety Analysis Set groups is presented in Table 106. Each category is briefly described in the subsequent sections.

Table 106: Treatment-Emergent Adverse Events of Special Interest by Category (Safety Analysis Set)

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE of Special Interest	332 (84.9)	240 (74.1)	438 (83.4)	792 (84.4)	1333 (86.0)
Anemia	25 (6.4)	39 (12.0)	92 (17.5)	117 (12.5)	218 (14.1)
Atrial fibrillation and flutter	13 (3.3)	6 (1.9)	13 (2.5)	26 (2.8)	49 (3.2)
Hemorrhage	179 (45.8)	108 (33.3)	253 (48.2)	447 (47.7)	746 (48.1)
Major hemorrhage	22 (5.6)	6 (1.9)	12 (2.3)	34 (3.6)	70 (4.5)
Hypertension	50 (12.8)	42 (13.0)	74 (14.1)	128 (13.6)	201 (13.0)
Infections	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Opportunistic infections	2 (0.5)	2 (0.6)	11 (2.1)	15 (1.6)	31 (2.0)
Neutropenia	67 (17.1)	69 (21.3)	172 (32.8)	241 (25.7)	427 (27.5)
Second primary malignancies	55 (14.1)	19 (5.9)	47 (9.0)	109 (11.6)	192 (12.4)
Skin cancers	33 (8.4)	8 (2.5)	23 (4.4)	62 (6.6)	115 (7.4)
Thrombocytopenia	29 (7.4)	30 (9.3)	92 (17.5)	122 (13.0)	247 (15.9)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	5 (0.3)

Source: Table 21 in Module 2.7.4
Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; R/R,

Relapsed/Refractory; TEAE, treatment-emergent adverse event; AESI, TEAE of special interest.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-aesi-cate-i.sas 24AUG2021 02:08 t-20-aesi-cate-i.rtf

8.2.5.1 Hemorrhage/Major Hemorrhage

Bleeding is a relatively frequent complication in patients treated with BTK inhibitors in real world situations and appears to be mediated by platelet dysfunction induced, at least in part, by BTK inhibition (Boriani e tal 2018).Boriani e tal 2018). Hemorrhage is listed in the Warnings and Precautions section of the prescribing information for zanubrutinib and other BTK inhibitors.

Hemorrhage of any severity grade was reported more commonly among patients in the **All Zanubrutinib**, **All R/R CLL/SLL**, and **All CLL/SLL** groups, respectively. Rates were also comparable when assessed by exposure-adjusted rates (EAIRs: 3.85. 4.98, and 4.04 persons/100 person-months, respectively). Sites of bleeding were consistent across the 3 integrated data pools. Consistent with prior experience, most bleeding adverse events were Grade 1 or 2 in severity, with most originating in skin or mucous membrane sites (eg, preferred terms including contusion, purpura, petechiae, epistaxis, hematuria). Hemorrhage events were more common among patients with thrombocytopenia prior to its onset (hazard ratio 1.44 (95% CI: 1.17, 1.77) in the **All Zanubrutinib** group). Similarly, antithrombotic use within 2 weeks was associated with a higher hazard ratio (1.34 [95% CI: 1.14, 1.58]) for hemorrhage. Hemorrhage events leading to death were reported in 3 patients (cerebral hemorrhage, hemorrhagic transformation stroke, subdural hematoma).

Major hemorrhages were uncommon in all 3 groups (4.5%, 2.3% and 3.6% crude incidence; 0.19, 0.11 and 0.16 persons/100 person-months in the **All Zanubrutinib**, **All R/R CLL/SLL**, and **All CLL/SLL** groups, respectively). Among patients in the **All Zanubrutinib** group, the prevalence of a first hemorrhage of any grade was highest in first 3 months of zanubrutinib exposure and decreased substantially in successive 6- to12-month intervals of exposure through Month 24 and beyond.

8.2.5.2 Atrial Fibrillation/Flutter

Atrial fibrillation is a major cause of morbidity and mortality worldwide and should be considered an important and clinically relevant adverse event that differentiates zanubrutinib from the first generation BTK inhibitor ibrutinib. It has been hypothesized that ibrutinib-induced atrial fibrillation may be due to on-target inhibition of BTK and off-target inhibition of related kinases such as TEC, HER2, or Csk, which hitherto were known to have functions in the

human heart (Xiao 2020). Under conditions of atrial fibrillation, expression of both BTK and TEC transcripts were found to be higher than when under sinus rhythm suggesting that BTK and TEC may have functional roles in the heart under conditions of cardiac stress (McMullen et al 2014).

In study 305, the superiority of zanubrutinib to ibrutinib in the key secondary endpoint of atrial fibrillation/flutter was tested. The interim analysis was performed in the Safety Analysis Set restricted to the first 415 randomized patients. Atrial fibrillation/flutter reported in the first 415 randomized patients in the zanubrutinib arm (5 [2.5%] patients) had a significantly lower frequency of atrial fibrillation/flutter compared with patients in the ibrutinib arm (21 [10.1%] patients). The rate difference between the 2 arms was -7.7% (95% CI: -12.3, -3.1), p = 0.0014.

Atrial fibrillation or flutter was uncommon across all other integrated groups, including patients the in the **All Zanubrutinib** group (crude incidence and EAIRs, 3.3% and 0.14 persons/100 person-months, respectively). Most patients with atrial fibrillation/flutter had known risk factors including a history of including hypertension (55.1%) and a prior history of atrial fibrillation (24.5%). No events led to treatment discontinuation or death in any of the groups. The frequency of atrial fibrillation/flutter varied little over successive 6- to 12-month periods of zanubrutinib exposure through Month 24 and beyond.

The crude and EAIRs of atrial fibrillation/flutter among patients in the **All R/R CLL/SLL** group (2.5%, 0.12 persons/100 person-months) was comparable to that noted for the **All Zanubrutinib** group. The crude and EAIRs of atrial fibrillation/flutter among patients in the **All CLL/SLL** group (2.8% and 0.12 persons/100 person-months) also were comparable. Serious adverse events and ≥ Grade 3 events of atrial fibrillation/flutter, each occurring in approximately 1% in the **All Zanubrutinib**, **All R/R CLL/SLL**, and **All CLL/SLL** data groups. These results were consistent with Study BGB-3111-305, in which the EAIR for atrial fibrillation and flutter was higher with ibrutinib treatment than with zanubrutinib (zanubrutinib: 0.16 persons per 100 person-months versus ibrutinib: 0.79 persons per 100 person-months). In Study BGB-3111-304 (cohort 1), the EAIR for atrial fibrillation/flutter was 0.13 and 0.31 persons per 100 person-months for zanubrutinib and B+R respectively.

The FDA's Assessment:

The Agency acknowledges the Applicant's testing of the rates of atrial fibrillation in patients receiving zanubrutinib compared to ibrutinib in study BGB-3111-305, however the Agency does not agree (b) (4) (b) (4) Study BGB-3111-305 was not sufficiently powered to demonstrate a clinically meaningful difference in the rates of atrial fibrillation or flutter between study arms. In addition the analysis conducted by the Applicant did not include the 305 ITT population and reflects decreased exposure compared to the ITT population. It is also noted that the rates of atrial fibrillation and flutter in the Applicant's analysis of the first 415 patients is less than that of the ITT population and the ISS population (2.5% vs 5% vs 3.7%) which may indicate increased risk with longer exposure. The Agency also notes that although the rate of all grades of atrial fibrillation and/or flutter was higher in the zanubrutinib arm of study BGB-3111-305, the rates of grade 3 or higher atrial fibrillation and/or flutter were similar, as displayed in the table below.

Table 107: Summary of Cardiac TEAEs in Study BGB-3111-305

	Zanubrutinib N = 324 n (%)			Ibrutinib N = 324 n (%)		
	All Grades	≥ Grade 3	Grade 5	All Grades	≥ Grade 3	Grade 5
Cardiac disorders SOC	63 (19)	17 (5)	0 (0)	89 (28)	28 (9)	5 (2)
Cardiac arrhythmias (HLGT)	44 (14)	9 (3)	0 (0)	63 (19)	17 (5)	1 (0.3)
Atrial fibrillation/Flutter	16 (5)	9 (3)	0 (0)	39 (12)	12 (4)	0 (0)
Ventricular arrhythmia and cardiac arrest (HLT - including PVCs)	5 (1.5)	0 (0)	0 (0)	5 (1.5)	3 (0.9)	1 (0.3)
Ventricular arrhythmia and cardiac arrest (HLT excluding PVCs)	2 (0.6)	0 (0)	0 (0)	4 (1.2)	3 (0.9)	1 (0.3)

PVCs = premature ventricular contraction, ventricular extrasystoles

Table 108: Summary of Treatment-Emergent Cardiac Arrhythmias in Study BGB-311-304

HLGT Preferred Term	BR N = 227 n (%)			Zanu Cohort 1 N = 240 n (%)			Zanu Cohort 2 N = 111 n (%)		
	All Gr	≥ Gr 3	Gr 5	All Gr	≥ Gr 3	Gr 5	All Gr	≥ Gr 3	Gr 5
HLGT Cardiac Arrhythmia	7 (3.1)	3 (1.3)	(0)	12 (5)	4 (1.7)	1 (0.4)	12 (11)	4 (3.6)	1 (0.9)
Atrial Fibrillation or Flutter	5 (2.2)	2 (0.9)	(0)	8 (3.3)	1 (0.4)	(0)	5 (5)	4 (3.6)	(0)
Bradycardia	(0)	(0)	(0)	1 (0.4)	1 (0.4)	(0)	3 (2.7)	(0)	(0)
Tachycardia	1 (0.4)	(0)	(0)	1 (0.4)	(0)	(0)	3 (2.7)	(0)	(0)
Ventricular arrhythmia*	(0)	(0)	(0)	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.9)	1 (0.9)	1 (0.9)
Sinus bradycardia	1 (0.4)	1 (0.4)	(0)	1 (0.4)	(0)	(0)	1 (0.9)	(0)	(0)
Atrioventricular block	(0)	(0)	(0)	(0)	(0)	(0)	1 (0.9)	(0)	(0)
Bundle branch block left	(0)	(0)	(0)	1 (0.4)	(0)	(0)	(0)	(0)	(0)

*includes ventricular tachycardia, cardiac arrest and pulseless electrical activity (1 each)

FDA's analysis of other cardiac arrythmias

Recent data has identified a potential risk of ventricular arrhythmias with BTKis which may signal a rare but serious class-related toxicity (Bhat, 2022). In addition to the rates of atrial fibrillation and flutter, an analysis was performed for the zanubrutinib ISS population evaluating cardiac TEAEs using the grouped term "cardiac arrhythmias". The table below displays the rates of cardiac arrhythmias in the ISS safety population.

Table 109: Breakdown of Cardiac Arrythmias (High Level Grouped Term) in the ISS Population (N = 1550) Occurring in > 1 Subject

HLGT Preferred Term	All Grades n (%)		≥ Grade 3 n (%)		Grade 5 n (%)	
Cardiac Arrhythmias	163	(11)	34	(2.2)	3	(0.2)
Atrial fibrillation or flutter	58	(3.7)	27	(1.7)	0	(0)
Sinus bradycardia	22	(1.4)	0	(0)	0	(0)
Ventricular arrhythmia HLT*	19	(1.2)	6	(0.4)	3	(0.2)
Ventricular arrhythmia HLT**	9	(0.6)	5	(0.3)	3	(0.2)
Tachycardia	13	(0.8)	1	(0.06)	0	(0)
Bradycardia^	12	(0)	3	(0.2)	0	(0)
Bundle branch block right	11	(0.7)	0	0	0	(0)
Atrioventricular block first degree	10	(0.7)	0	0	0	(0)
Supraventricular extrasystoles	9	(0.6)	0	0	0	(0)
Sinus tachycardia	7	(0.5)	0	0	0	(0)
Arrhythmia supraventricular	5	(0.3)	0	0	0	(0)
Bundle branch block left	4	(0.3)	0	0	0	(0)
Extrasystoles	3	(0.2)	0	0	0	(0)
Supraventricular tachycardia	3	(0.2)	0	(0)	0	(0)
Atrioventricular block complete	2	(0.1)	2	(0.1)	0	(0)

Source: Reviewer generated table from ADAEG dataset submitted 9/20/2022

*Grouped term including the preferred terms of ventricular tachycardia, ventricular extrasystoles, ventricular arrythmia, pulseless electrical activity, and cardiac arrest

**Grouped term as above excluding PVCs, ventricular extrasystoles

^Grouped term including bradycardia, intermittent bradycardia and bradyarrhythmia

To further evaluate the risk of cardiac arrhythmias with zanubrutinib therapy, FDA reviewed deaths with an unknown cause in patients in the ISS safety pool. Five subjects with a treatment emergent adverse event of death with an unknown cause were identified and are summarized in the Appendix (Table 127). All of the treatment emergent events with a PT of “death” and AE terms of death were unknown reason, death of unknown origin, or unexplained death occurred after discontinuation of zanubrutinib and in the setting of a recent confounding diagnosis. Although the cause of death is not definitive, these events do not appear, based on the narratives, to represent sudden cardiac deaths due to a primary cause of a cardiac arrhythmia and are not included in the numerator for ventricular arrhythmia.

Based on the analysis of the ISS population and the occurrence of ventricular arrhythmias, the existing warnings and precautions section of the label on cardiac arrhythmias will be expanded to include ventricular arrhythmias , with a 0.2% incidence of Grade 3 or higher ventricular arrhythmias based on FDA adjudication. Narratives are provided in the Appendix (Table 128).

Data:

8.2.5.3 Hypertension

Hypertension is one of the most common comorbidities in cancer patients, in particular, in the elderly (Małyszko et al 2018).Małyszko et al 2018). Longstanding hypertension ultimately leads to heart failure. In the Framingham Heart Study hypertension was noted as a preceding event in >90% of people with a new diagnosis of heart failure. After adjusting for age and heart failure risk factors, the hazard in men for developing heart failure was 2-fold higher for patients with hypertension than those who were normotensive (Lloyd-Jones 2002).

In the **All Zanubrutinib** group, all grade and ≥ Grade 3 hypertension were reported in 13.0% and 6.5% of patients, respectively; the corresponding EAIRs were 0.61 and 0.28 persons/100 person-months, respectively. Hypertension of ≥ Grade 3 severity was reported in 100 (6.5%) patients, respectively hypertension was rarely serious (0.3%) and did not lead to treatment discontinuation or death. The frequency of hypertension varied little over successive 6-month periods of zanubrutinib exposure through Month 24 and beyond. The rate of hypertension appeared to be higher in patients with a history of hypertension (15.8%) compared with those with no history of hypertension (10.8%).

The crude incidence and EAIR for hypertension among patients in the **All R/R CLL/SLL** group (14.1%, 0.76 persons/100 person-months, respectively) were comparable to the **All Zanubrutinib** group. The crude incidence and EAIR for hypertension among patients in the **All CLL/SLL** group (13.6%, 0.66 persons/100 person-months, respectively) also were similar to those in the **All Zanubrutinib** group. In Study BGB-3111-304 (cohort 1), the EAIR for hypertension was 0.61 and 0.74 persons per 100 person-months for zanubrutinib and B+R. EAIRs for hypertension were balanced between treatment groups in Study BGB-3111-305.

8.2.5.4 Second Primary Malignancies

The crude incidence of second primary malignancies among patients in the **All Zanubrutinib** group was 12.4%, and the corresponding EAIR was 0.57 persons/100 person-months. These rates were consistent in the **All R/R CLL/SLL** group (9.0%, 0.46 persons/100 person-months, respectively) and **All CLL/SLL** group (11.6%, 0.55 persons/100 person-months, respectively). Across all groups, the most common second primary malignancies were non-melanoma skin cancers (predominantly basal cell and squamous cell carcinoma), which accounted for the majority of second primary malignancies (ie, 115 of 192 patients [60.0%] in the **All Zanubrutinib** group). This finding is likely due in large part to the disproportionate representation of patients enrolled at study sites in Australia and New Zealand, where the incidence of ultraviolet light-mediated skin cancers (principally squamous and basal cell carcinomas but also melanomas) is among the highest in the world (Bray et al 2018). Skin melanoma events were reported in 16 patients (2 with past medical history) and 136 TEAEs of non-melanoma skin cancers were reported (43 with a past medical history). Other types of secondary primary malignancies occurred across varied organ systems with no apparent pattern in type.

Upon medical review, 6 of the 192 patients with second primary malignancy had transformation of the disease or disease under study. Forty-two patients had a medical history of the same type of malignancy. Forty-four of the new primary malignancy events were diagnosed within 90 days of initiating treatment with zanubrutinib, which suggests that the malignancy may have been present but undiagnosed prior to initiation of study treatment. Twenty two of these events occurred in patients with a past medical history of the same time of malignancy

Most second primary malignancies were Grade 1 or 2; Grade 3 or higher second primary malignancies were reported in 84 patients (5.4%) in the **All Zanubrutinib** group, and the events led to death in 8 patients (0.5%) (acute myeloid leukemia in 2 patients; all other were reported in 1 patient). Second primary malignancies led to treatment discontinuation in 29 patients (1.9%).

An additional analysis by MedDRA SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) is provided to support the USPI ADR Section (Module 2.7.4 Summary of Clinical Safety Appendix ADR Analysis).

The FDA's Assessment:

The Agency agrees with the rates and types of second primary malignancies presented by the Applicant. A safety signal for second primary malignancies was identified in the TN CLL/SLL population based on an increased incidence of SPM in the zanubrutinib arm of Cohort 1 compared to the BR arm and the rate of treatment emergent SPM with fatal outcomes. FDA performed an expanded analysis of second malignancies based on additional data provided by the Applicant with the safety update submitted on April 19, 2022 including updated data with a CCOD of December 1, 2021 from study BGB-3111-305. Detail regarding the rates and types of SPMs in the BGB-3111-304 and BGB-3111-305 studies are displayed in the table below. For increased sensitivity Cohort 1a (Chinese cohort) was included in this analysis for study BGB-3111-304 analysis.

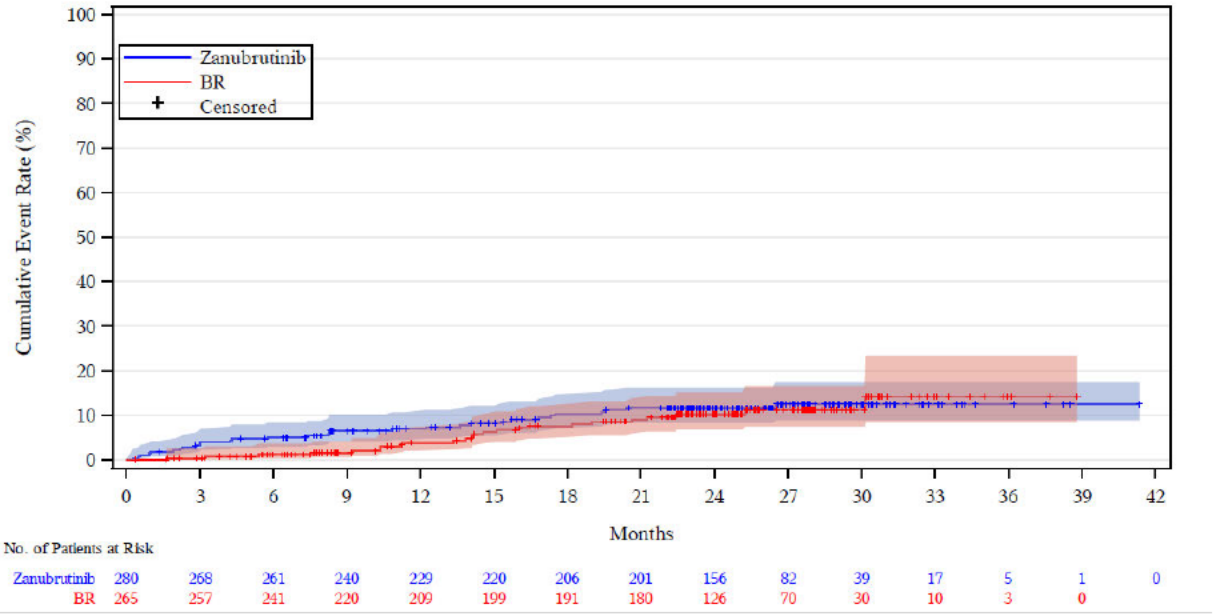
Table 110: Summary of Second Primary Malignancies in Studies BGB-3111-304 and BGB-3111-305

	BGB-3111-304 (includes Cohort 1a)			BGB-3111-305	
	Zanu N=280 n (%)	BR N=265 n (%)	Zanu 17p del N=111 n (%)	Zanu N=324 n (%)	Ibr N=324 n (%)
SPM*	31 (11)	24 (9%)	24 (22%)	31 (9.5)	32 (9.9)
Non Melanoma Skin Cancer	16 (6)	13 (4.9%)	14 (13%)	16 (4.9)	23 (7.1)
Melanoma	0	1 (1.4)	3 (2.7)	2 (0.6)	1 (0.3)
Non-Melanoma Solid Tumor	16 (6)	9 (3.4%)	7 (6%)	15 (4.6)	11 (3.4)
Breast	1 (0.4)	2 (0.8)	1 (0.9)	1 (0.3)	2 (0.6)
GI	1 (0.4)	2 (0.8)	0 (0.4)	4 (1.2)	3 (0.9)
GU	4 (1.4)	5 (1.9)	5 (4.5)	3 (0.9)	3 (0.9)
GYN	1 (0.4)	0 (0.4)	0 (0.4)	1 (0.3)	0 (0.0)
Lung	6 (2.1%)	1 (0.4%)	1 (0.9)	3 (0.9)	2 (0.6)
Other	1 (0.4)	0 (0.4)	0 (0.4)	0 (0.0)	1 (0.3)
Hematologic malignancies	1 (0.4)	1 (0.4)	0 (0.4)	1 (0.3)	1 (0.3)
Time to first SPM (days) Median (range)	251 (70, 476)	430 (51, 918)	381 (133, 966)	378 (22, 883)	247 (20, 884)

Source: Applicant submission requested by the Agency 4-4-2022 verified by fdaspm2 dataset

The estimated cumulative incidence of SPM in study BGB-3111-304 Cohort 1 is displayed in Figure 15, demonstrating an increased risk of SPM over time. Exploratory comparisons by treatment arm are limited by the greater amount of early censoring in the BR arm.

Figure 15: Cumulative Incidence of Second Primary Malignancies in Patients With TN CLL/SLL Without 17p del in Study BGB-3111-304



Source: Applicant response to FDA IR received April 4, 2022.

The FDA's Assessment:

Second primary malignancies are a known risk of zanubrutinib therapy and currently included in section 5 of the USPI. Notable in study BGB-3111-304 was the increased rates of SPM in the zanubrutinib arm compared to the BR arm to include 3 fatal TEAEs of SPMs in the zanubrutinib arm compared to none in the BR arm including those occurring early in therapy. The most common types of SPMs were non-melanoma skin cancers with no specific predominating solid tumor with the exception of lung cancer which occurred in 6 (2.1%) of the Cohort 1 zanubrutinib population. Several factors confound the analysis of SPMs, including but not limited to the small number of events, preexisting conditions and the longer duration of exposure to zanubrutinib vs. BR, in the TN CLL/SLL population; further characterization of this risk is warranted to more fully inform the benefit-risk of zanubrutinib in the TN CLL/SLL setting given alternative effective therapies. A postmarketing requirement is warranted to further evaluate this signal in the TN CLL population. Refer to section 12 for details.

Data:

8.2.5.5 Tumor Lysis Syndrome

Tumor lysis syndrome was rare, occurring in less than 1% of patients across all groups (EAIRs of 0.01 persons/100 person-months). With the exception of a single case of tumor lysis syndrome reported in the **All Zanubrutinib group** (83-year-old man with treatment-naïve MCL with

symptoms that started 1 day after discontinuation of zanubrutinib due to disease progression; refer to the brief narrative in Section 2.1.5.4.5 in Module 2.7.4), no event led to death. Among the tumor lysis syndrome events reported, none led to treatment discontinuation in any group.

8.2.5.6 Infections

As would be expected given the study populations, infections, primarily mild sinopulmonary and urinary tract infections, were consistently among the most common adverse events reported across all patient groups. In the **All Zanubrutinib** group, 1019 patients (65.7%) reported at least 1 infection (EAIR, 6.84 persons/100 person-months). Serious and ≥ Grade 3 infections were reported in 307 (19.8%) and 338 (21.8%) patients, respectively. Infections leading to death occurred in 39 patients (2.5%) (including pneumonia in 11 patients; COVID-19 in 9 patients, COVID-19 pneumonia in 3 patients, and fungal pneumonia, sepsis, and septic shock in 2 patients each). Thirty one patients (2.0%) reported at least 1 opportunistic infection.

In the **All CLL/SLL** group, 595 patients (63.4%) reported at least 1 infection (EAIR 8.46 persons/100 person-months. In the **All R/R CLL/SLL** group, 331 patients (63.0%) reported at least 1 infection (EAIR 6.30 persons/100 person-months). Thus, the rate of infection was consistent across the integrated Safety Analysis Set pools. In Study BGB-3111-304 (cohort 1), the EAIR for infection was 4.33 and 7.86 persons per 100 person-months for zanubrutinib and B+R.

8.2.5.7 Cytopenias

Anemia

In the **All Zanubrutinib** group, 37.1% of patients were anemic at baseline, and 218 (14.1%) patients had treatment-emergent anemia. Anemia events of ≥ Grade 3 events were reported in 5.2% of patients. Serious anemia adverse events were reported in 21 (1.4%), and 2 patients discontinued study treatment due to anemia. The EAIRs for all grade and ≥ Grade 3 anemia were 0.64 and 0.22 persons/100 person-months, respectively. Seventy-nine of 218 (36.2%) patients with treatment-emergent anemia received red blood cell transfusions within 30 days after onset. Anemia adverse event analyses in the **All R/R CLL/SLL** and **All CLL/SLL** groups, including the incidence of treatment-emergent events, ≥ Grade 3, and red blood cell transfusions were comparable with the **All Zanubrutinib** group.

Neutropenia

Neutrophils play a critical role in the acute inflammatory response and host-defenses against bacterial infections. Neutropenia predisposes to infection, chiefly by organism resident on body surfaces. The risk of infection is greatest with severe neutropenia.

Neutropenia, was the most common cytopenia across all integrated analysis subsets. The events were typically nonserious and effectively managed without significant compromise to the study treatment regimen. In the **All Zanubrutinib** group, 9.7% of patients were neutropenic at baseline. A total of 427 patients (27.5%) patients reported at least 1 occurrence of treatment-emergent neutropenia as a grouped term, with ≥ Grade 3 events reported in 18.5% of patients, including febrile neutropenia in 1.2% of patients. Twenty-nine patients (1.9%)

reported events that met the criteria for seriousness. The EAIRs for all grade and ≥ Grade 3 neutropenia were 1.55 and 0.93 persons/100 person-months, respectively. Rates of neutropenia were consistent across other integrated safety analysis subsets. In the **All R/R CLL/SLL** group, 172 (32.8%) patients reported at least 1 occurrence of treatment-emergent neutropenia, ≥ Grade 3 were reported in 22.1% of patients, including febrile neutropenia in 0.4%. The EAIRs for all grade and ≥ Grade 3 neutropenia were 2.39 and 1.37 persons/100 person-months, respectively. In the **All CLL/SLL** group, 241 (25.7%) patients reported at least 1 occurrence of treatment-emergent neutropenia, ≥ Grade 3 events were reported in 17.8% of patients, including febrile neutropenia in 0.6%. The EAIRs for all grade and ≥ Grade 3 neutropenia were 1.46 and 0.92 persons/100 person-months, respectively.

Neutropenia is postulated to be an on-target effect relating to the role of BTK in neutrophils and the complete BTK occupancy seen with zanubrutinib treatment versus ibrutinib treatment. Mice deficient in BTK have demonstrated a crucial role for BTK in the development and function of neutrophilic granulocytes (Fiedler et al 2011). BTK-deficient neutrophils showed defects in GM-CSF-signaling and GM-CSF–induced maturation accompanied with impaired function. Furthermore, neutrophils from these mice were found to be deficient in expression of several granule proteins including elastase, lactoferrin, and myeloperoxidase (Fiedler et al 2011). Interestingly, while BTK-deficient mice have an increase of granulopoiesis in vitro and in vivo, in patients treated with BTK inhibitors, neutropenia has been observed. These data implicate BTK in neutrophil development and function.

In an analysis of patients with neutropenia of any grade (n = 427 in the **All Zanubrutinib** arm), 34 (8.0%) patients had a ≥ Grade 3 concurrent infection which is defined as starting within 14 days after onset of neutropenia. Among the CLL/SLL patients in Phase 3 studies BGB-3111-304 and BGB-3111-305, the rate of concurrent ≥ Grade 3 infection was 4.5% and 2.9%, respectively.

Thrombocytopenia

In the All Zanubrutinib group, 24.5% of patients were thrombocytopenic at baseline, and 247 (15.9%) patients reported at least 1 occurrence of treatment-emergent thrombocytopenia as a grouped term; 1 or more ≥ Grade 3 events were reported in 5.7% of patients, and 14 (0.9%) patients reported events that met the criteria for seriousness. The EAIRs for all grades and ≥ Grade 3 thrombocytopenia were 0.76 and 0.25 persons/100 person-months, respectively. Twenty-three (9.3%) thrombocytopenic patients received platelet transfusions within 30 days of onset. These results were consistent with the incidence of thrombocytopenia in the All R/R CLL/SLL group (17.5%; EAIR: 0.99 persons/100 person-months) and All CLL/SLL group (13.0%; EAIR: 0.63 persons/100 person-months).

The Applicant's Position:

Several adverse effects have been associated with BTK inhibitors as a drug class, including atrial fibrillation/flutter, and the events were predefined for specific adverse analyses (see Section 5.2.3.5). These effects have been observed with varying frequency and severity across BTK inhibitors, in part due to differences in the specificity for BTK inhibition and off-target effects (Tam et al 2019; Levade et al 2014; Kamel et al 2015; Tang et al 2018).

Data in Section 5 (Warnings and Precautions) of the USPI reflect exposure in the 1550 patients who received zanubrutinib as a single agent (ie, monotherapy) at a dose of 160 mg twice daily or 320 mg once daily as described above in Section 5.2.1. This clinical trial experience includes substantial long-term exposure, with more than 1000 patients having received ≥ 1 year of zanubrutinib dosing and more than 100 patients having received ≥ 4 years of dosing. In total the evaluation of risks for this submission was based on an extensive 37,019.66 patient-months of zanubrutinib exposure.

The Warnings and Precautions section in the approved USPI for BRUKINSA (zanubrutinib) includes categories of risks for zanubrutinib monotherapy (b) (4) It is proposed (b) (4)

These categories include:

- Hemorrhage (USPI Section 5.1)
- Infections (USPI Section 5.2)
- Cytopenias (USPI Section 5.3)
- Second Primary Malignancies (USPI Section 5.4)
- Cardiac Arrhythmias (specifically, atrial fibrillation and atrial flutter) (USPI Section 5.5)
- Embryo-Fetal Toxicity (USPI Section 5.6)
- (b) (4)

In addition, USPI Section 7.1 (Effect of Other Drugs on BRUKINSA) describes the potential for interactions with strong or moderate CYP3A inhibitors or inducers.

Finally, Appendix 1 in Module 2.7.4, USPI Section 6.1 (Clinical Trials Experience) describes the most common adverse reactions among all patients who received zanubrutinib in clinical studies. The search criteria used for the adverse reactions are provided in Appendix 2 in Module 2.7.4.

Results of assessments of adverse reactions for zanubrutinib in Studies BGB-311-304 and BGB-311-305 and all patients with CLL/SLL, as well as the overall adverse event assessments for the pooled All Zanubrutinib Safety Analysis Set, demonstrate a safety profile in this target population that is consistent with the known safety profile previously reported for prior applications.

The FDA's Assessment:

The Agency agrees with the Applicant's position regarding the warning and precautions categories (b) (4) . The Applicant had initially proposed to (b) (4) but susequently proposed (b) (4) . The Agency did not object (b) (4) . As discussed in sections 8.2.5.2 and 8.2.5.4, the warnings and precautions sections for cardiac

arrhythmias and SPMs were revised to reflect updated information.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

COA analyses do not have impact on the safety/tolerability. Discussion is provided in Section 8.1.1 and 8.1.2.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Age

In the **All Zanubrutinib** group, ≥ 90% of patients in all age categories (< 65 years and ≥ 65 years) experienced at least 1 TEAE. Not unexpectedly, with increasing age there was a clear trend toward higher incidences of ≥ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to dose reduction, interruption, discontinuation, and death. Treatment-related TEAEs were reported at similar incidences in patients < 65 years of age and those ≥ 65 years of age.

Among patients < 65 years of age, the most commonly (≥ 20%) reported TEAEs include upper respiratory tract infection **(**36.7%) and decreased neutrophil count (23.2%). Among patients ≥ 65 years of age, common TEAEs included upper respiratory tract infection (22.3%) and contusion (21.9%).

Within the **All Zanubrutinib** group:

- Common AEs reported more frequently with increasing age included contusion (12.2% and 21.9% for patients < 65 years and ≥ 65 years, respectively), hypertension (10.0% and 13.4%), and constipation (8.0% and 15.1%).

  Additional notable differences between age groups (as defined by an approximately 10% difference or doubling from youngest to oldest age category) were observed for the system organ classes of respiratory, thoracic and mediastinal disorders (34.8% and 41.1% for patients < 65 years and ≥ 65 years, respectively), musculoskeletal and connective disorders (31.0% and 39.9%), injury, poisoning and procedural complications (25.7% and 36.7%), and vascular disorders (14.3% and 25.2%)

- Common AEs reported less frequently with increasing age included upper respiratory tract infection (36.7% and 22.3% for patients < 65 years and ≥ 65 years, respectively), decreased neutrophil count (23.2% and 10.1%), decreased platelet count (13.5% and 6.6%), decreased white blood cell count (10.5% and 2.3%), and petechiae (9.2% and 4.7%).

Additional notable differences between age groups (approximately 10% difference or doubling from oldest to youngest age category) were observed for the System Organ Class of investigations (42.8% and 27.5%).

In the **All Zanubrutinib** group, there was an age-related trend for events within the AESI category of second primary malignancies (7.0% and 15.8% for patients < 65 years and ≥ 65 years of age, respectively), including skin cancers (3.7% and 9.8%). Conversely, there was an inverse relationship between increasing age and the frequencies of neutropenia (35.2% and 22.7% for patients < 65 years and ≥ 65 years of age, respectively) and thrombocytopenia (19.3% and 13.8%).

Within the **All R/R CLL/SLL** group, common AEs reported more frequently with increasing age were contusion (12.6% versus 19.9% for patients < 65 years and ≥ 65 years, respectively) and hypertension (7.5% versus 18.2%). Common AEs reported less frequently with increasing age included upper respiratory tract infection (39.7% versus 19.9% for patients < 65 years and ≥ 65 years, respectively), decreased neutrophil count (28.0% versus 12.6%), haematuria (17.2% versus 7.7%), headache (13.4% versus 6.6%), petechiae (9.6% versus 4.5%), and decreased white blood cell count (8.8% versus 2.1%).

In the **All R/R CLL/SLL** group, there was an age-related trend for events within the AESI category of hypertension (8.8% and 18.5% for patients < 65 years and ≥ 65 years of age, respectively). Conversely, there was an inverse relationship between increasing age and the frequencies of haemorrhage (52.3% and 44.8% for patients < 65 years and ≥ 65 years of age, respectively) and neutropenia (41.4% and 25.5%).

Within the **All CLL/SLL** group, common AEs reported more frequently with increasing age included contusion (14.0% versus 20.0%, for patients < 65 years and ≥ 65 years, respectively) and hypertension (9.0% versus 14.3%). Common AEs reported less frequently with increasing age included upper respiratory tract infection (37.6% versus 18.7%, for patients < 65 years and ≥ 65 years, respectively), petechiae (10.2% versus 5.2%), decreased neutrophil count (22.0% versus 8.4%), decreased white blood cell count (6.5% versus 1.0%), headache (14.6% versus 8.0%), and haematuria (14.9% versus 7.6%).

In the **All CLL/SLL** group, there was an age-related trend for events within each of the following AESI categories: second primary malignancies (7.5% and 13.8% for patients < 65 years and ≥ 65 years of age, respectively), including skin cancers (4.0% and 8.0%). Conversely, there was an inverse relationship between increasing age and the frequencies of haemorrhage (51.2% and 45.8% for patients < 65 years and ≥ 65 years of age, respectively) and neutropenia (33.5% and 21.6%).

Sex

In the **All Zanubrutinib** group, ≥ 95% of patients of both sexes reported at least 1 TEAE. A similar proportion of male and female patients reported ≥ Grade 3 events, serious events, and TEAEs leading to treatment discontinuation, treatment interruption, and treatment reduction. The incidence of TEAEs leading to death was higher in male patients than female patients (5.7% versus 3.3%, respectively).

Upper respiratory tract infection (28.3%) was the only TEAE reported in ≥ 20% of male patients. TEAEs reported in ≥ 20% of female patients were upper respiratory tract infection (27.0%) and diarrhoea (20.1%).

Within the **All Zanubrutinib group**, events that were reported more frequently in female patients than in male patients included urinary tract infection (19.9% versus 7.3%, respectively), decreased neutrophil count (18.2% versus 13.6%), anaemia (17.0% versus 11.9%), headache (13.4% versus 8.9%), and nausea (13.0% versus 9.3%). No notables differences in the frequency of events were observed more frequently in male than in female patients.

Among the categories of AESI, more female patients than male patients reported neutropenia (31.0% versus 25.8%, respectively) and anaemia (17.6% versus 12.3%, respectively) in the **All Zanubrutinib** group. Conversely, male patients reported a slightly higher frequency of second primary malignancies (including skin cancers) than female patients (14.1% versus 9.0% for all second primary malignancies, respectively; 9.3% versus 3.8% for skin cancers).

Within the **All R/R CLL/SLL** group events that were reported more frequently in female than male patients included upper respiratory tract infection (32.8% versus 27.0%, respectively), decreased neutrophil count (23.9% versus 17.4%), urinary tract infection (22.8% versus 6.4%), anemia (20.0% versus 14.5%), hypokalaemia (14.4% versus 6.7%), and constipation (12.2% versus 8.1%). Events that were reported more frequently in male than in female patients included hypertension (15.4% versus 9.4%), rash (13.6% versus 8.3%), and fatigue (10.4% versus 5.6%).

Among the categories of AESI, more female than male patients reported infections (67.8% versus 60.6%, respectively), hemorrhage (52.8% versus 45.8%), neutropenia (38.9% versus 29.6%), and anaemia (21.7% versus 15.4%) in the **All R/R CLL/SLL** group. Conversely, male patients reported a slightly higher frequency of hypertension (15.9% versus 10.6%), second primary malignancies (including skin cancers) than female patients (11.0% versus 5.0% for all second primary malignancies, respectively; 6.1% versus 1.1% for skin cancers).

Within the **All CLL/SLL** group events that were reported more frequently in female than male patients included urinary tract infection (17.8% versus 6.6%, respectively), headache (13.0% versus 8.8%) and hypokalaemia (9.5% versus 5.0%). No notable differences in the frequency of events were observed more frequently in male than in female patients.

Among the categories of AESI, more female patients than male patients reported neutropenia (29.5% versus 23.8%, respectively) in the **All CLL/SLL** group. Conversely, male patients reported a slightly higher frequency of second primary malignancies (including skin cancers) than female patients (13.2% versus 8.6% for all second primary malignancies, respectively; 8.3% versus 3.2% for skin cancers).

Weight

In the **All Zanubrutinib** group, TEAEs were reported at approximately similar frequencies in patients below versus those at or above the median baseline weight (96.2% versus 95.2%, respectively). The frequency of ≥ Grade 3 events, serious events, and TEAEs leading to

treatment discontinuation, treatment interruption, treatment reduction, and death was similar in patients below versus those at or above the median baseline weight.

TEAEs reported in ≥ 20% of patients who had a baseline weight below the median were upper respiratory tract infection (27.3%) and decreased neutrophil count (22.2%). Upper respiratory tract infection (28.4%) and contusion (20.7%) were the only TEAEs reported in ≥ 20% of patients who had a baseline weight at or above the median.

Within the **All Zanubrutinib** group, more occurrences of the following TEAEs were reported among patients below the median baseline weight compared with those at or above the median baseline weight: decreased neutrophil count (22.2% versus 8.3%, respectively), decreased platelet count (13.1% versus 5.6%), anaemia (18.4% versus 8.9%), hypokalaemia (9.4% versus 3.7%), and hyperglycaemia (7.2% versus 2.6%). Conversely, more occurrences of the following TEAEs were reported among patients at or above the median baseline weight compared with those below the median baseline weight: contusion (20.7% versus 15.6%, respectively) and fatigue (14.4% versus 9.4%).

In the **All R/R CLL/SLL** group, more occurrences of the following TEAEs were reported among patients below the median baseline weight compared with those at or above the median baseline weight: upper respiratory tract infection (33.1% versus 25.6%, respectively), decreased neutrophil count (32.6% versus 8.8%), anaemia (23.4% versus 10.5%), haematuria (18.8% versus 6.3%), decreased platelet count (17.2% versus 4.6%), urinary tract infection (15.9% versus 8.8%), hypokalaemia (15.1% versus 4.6%), purpura (13.4% versus 4.6%), and hyperglycaemia (11.7% versus 2.5%). Conversely, more occurrences of the following TEAE was reported among patients at or above the median baseline weight compared with those below the median baseline weight: contusion (21.1% versus 11.3%, respectively).

In the **All CLL/SLL** group, more occurrences of the following TEAEs were reported among patients below the median baseline weight compared with those at or above the median baseline weight: decreased neutrophil count (21.5% versus 6.4%, respectively), haematuria (13.1% versus 7.7%), decreased platelet count (11.9% versus 3.5%), anaemia (16.9% versus 7.7%), hypokalaemia (10.3% versus 3.5%), purpura (9.3% versus 3.7%) and hyperglycaemia (8.1% versus 2.1%). Conversely, more occurrences of the following TEAE was reported among patients at or above the median baseline weight compared with those below the median baseline weight: contusion (20.5% versus 14.8%), nausea (12.7% versus 7.2%, respectively), and fatigue (12.2% versus 6.4%).

Race

To assess whether race might have an impact on the TEAE profile of zanubrutinib, an analysis of TEAEs by race was conducted. Race is presented as reported by the patient (Asian, white, black or African American, Native Hawaiian or Other Pacific Islander, multiple (patients that report two or more races), or other, as well as not reported, unknown, or missing.

As the number of patients in the Black or African American, Native Hawaiian or Other Pacific Islander, Multiple, and Other race categories was small (totaling 92 patients for the **All Zanubrutinib** group, including 39 patients for whom race was not reported the comparisons

below are mostly limited to white and Asian race categories. Furthermore, the small numbers of patients in the remaining race categories precludes any meaningful interpretation of these data.

Similar percentages of white and Asian patients reported 1 or more TEAEs, ≥ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation and death. Events that led to treatment interruption were more common in white patients than Asian in patients (46.2% versus 31.6%, respectively).

Within the **All Zanubrutinib** group, events that were reported more frequently in white than in Asian patients were contusion (23.9% versus 3.5%, respectively), diarrhoea (20.0% versus 15.1%), arthralgia (15.1% versus 6.6%), and nausea (13.3% versus 2.6%). Events that were reported more frequently in Asian than in white patients were decreased neutrophil count (45.0% versus 4.1%, respectively), upper respiratory tract infection (35.1% versus 25.4%), decreased platelet count (27.4% versus 2.5%), anaemia (24.3% versus 9.4%), pneumonia (22.4% versus 8.0%), rash (20.0% versus 13.3%), hypokalaemia (15.8% versus 2.8%), hyperglycaemia (13.9% versus 1.4%), hyperuricaemia (13.4% versus 1.9%), haematuria (16.3% versus 6.9%), and purpura (12.0% versus 2.7%).

Among the categories of AESIs more white patients than Asian patients reported haemorrhage (49.7% and 43.6%, respectively), second primary malignancies (16.6% and 2.6%), including skin cancers (10.4% and 0.0%) in the **All Zanubrutinib** group. Conversely, more Asian patients than white patients reported more frequent neutropenia (48.6% and 20.0%), thrombocytopenia (33.5% and 9.3%), and anaemia (25.9% and 9.4%).

Within the **All R/R CLL/SLL** group, events that were reported more frequently in white than in Asian patients were contusion (21.8% versus 2.7%, respectively), hypertension (14.6% versus 8.1%), arthralgia (12.3% versus 4.0%), and nausea (11.5% versus 2.0). Events that were reported more frequently in Asian than white patients were neutrophil count decreased (59.7% versus 3.7%, respectively), upper respiratory tract infection (44.3% versus 23.2%), platelet count decreased (32.9% versus 1.1%), anaemia (32.2% versus 10.0%), haematuria (32.2% versus 4.3%), pneumonia (31.5% versus 9.2%), hypokalaemia (22.8% versus 3.7%), purpura (22.1% versus 3.2%), cough (22.1% versus 15.5%), hyperglycaemia (21.5% versus 0.9%), and hyperuricaemia (20.1% versus 1.7%).

Among the categories of AESIs, more white patients than Asian patients reported second primary malignancies (11.5% and 3.4%), including skin cancers (6.0% and 0.0%), and hypertension (15.2% versus 9.4%) in the **All R/R CLL/SLL** group. Conversely, more Asian patients than white patients reported more frequent infections (79.2% versus 57.0%, respectively), neutropenia (61.1% and 22.1%), haemorrhage (56.4% and 44.7%, respectively), thrombocytopenia (41.6% and 8.0%), and anaemia (36.2% and 10.0%).

Within the **All CLL/SLL** group, events that were reported more frequently in white than in Asian patients were contusion (22.0% versus 2.6%), hypertension (12.6% versus 9.3%), arthralgia (13.9% versus 4.1%), and nausea (12.1% versus 2.1%). Events that were reported more frequently in Asian than in white patients were neutrophil count decreased (49.5% versus 3.7%, respectively), upper respiratory tract infection (39.7% versus 21.6%), platelet count decreased (28.9% versus 1.6%), anaemia (28.9% versus 7.3%), pneumonia (26.3% versus 8.2%), haematuria (25.3% versus 6.5%), hypokalaemia (20.1% versus 2.7%), purpura (18.6% versus 2.9%), hyperglycaemia (17.5% versus 1.6%), and hyperuricaemia (17.5% versus 2.0%).

Among the categories of AESIs, more white patients than Asian patients reported hypertension (13.9% versus 10.3%, respectively), second primary malignancies (14.4% and 3.1%), including skin cancers (8.5% and 0.0%) in the **All CLL/SLL Zanubrutinib** group. Conversely, more Asian patients than white patients reported more frequent infections (72.2% versus 61.6%), neutropenia (51.5% and 19.3%), thrombocytopenia (37.1% and 6.6%), and anaemia (32.0% and 7.3%).

The Applicant's Position:

Results of these subgroup analyses indicated no notable differences associated with zanubrutinib in adverse event rates by sex, body weight, race, or region. As expected, slight differences were noted in adverse event rates by age for significant events such as Grade 3 or higher adverse events, serious adverse events, and adverse events that led to discontinuation, dose reduction, or death. The differences did not appear to be a zanubrutinib-specific effect, but rather a consequence of age-related conditions.

The FDA's Assessment:
The Agency agrees with the Applicant's description of safety findings across subgroups. There were no new safety findings identified any specific subgroup.

8.2.8 Specific Safety Studies/Clinical Trials

Data:
No new information is provided in the current submission

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:

No new information is provided in the current submission

The Applicant's Position:
Not applicable

The FDA's Assessment: Not applicable.

Human Reproduction and Pregnancy
Data:
No new information is provided in the current submission

The Applicant's Position:
Not applicable

The FDA's Assessment: Not applicable.

Pediatrics and Assessment of Effects on Growth

Data:
No new information is provided in the current submission

The Applicant's Position:
Not applicable

The FDA's Assessment:
The Agency agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
None

The Applicant's Position:

There was no experience of overdose reported in the clinical studies of zanubrutinib. There is no specific antidote for zanubrutinib. If a patient experiences an overdose, he/she should be closely monitored and provided with appropriate supportive treatment, if needed.

Specific clinical studies evaluating abuse potential have not been conducted. There is no evidence that zanubrutinib produces physical or psychological dependence in patients with hematological malignancies.

No specific studies have been conducted to evaluate for withdrawal or rebound phenomena associated with discontinuation of zanubrutinib.

The FDA's Assessment:
The Agency agrees with the Applicant's position. There was no new information provided.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Zanubrutinib (BRUKINSA) has received marketing authorization in the United States for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy (14 November 2019). On 31 Aug 2021 BRUKINSA was approved in the United States for the treatment of adult patients with Waldenström's macroglobulinemia (WM) and on 14 September 2021 for adult patients with R/R MZL through the accelerated approval program. Refer to Section 1.3 of Module 2.5 Clinical Overview for global approval history.

Cumulatively, as of 24 July 2021, approximately (b) (4) capsules of zanubrutinib have been supplied to the market in Canada, China and the USA (equivalent to (b) (4) daily doses; approximately (b) (4) person months; (b) (4) person-years. Details are provided in the most recent zanubrutinib PBRER.

The Applicant's Position:

There are no safety-related issues arising from post-marketing data that need to be addressed in the current approved product labelling and no regulatory actions concerning safety have been taken since the International Birth Date of 14 November 2019.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety information collected from the post-market setting is expected to be consistent with data collected in the clinical trials.

Suggested wording:

The applicant will conduct routine pharmacovigilance activities such as safety signal detection activities within post-market surveillance and periodic safety reporting program.

The FDA's Assessment:
The Agency agrees that safety information from the postmarket setting is expected to be consistent with the current safety characterization of zanubrutinib. Additional safety signals might emerge with longer follow-up and greater exposure.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:

Substantial evidence of safety, based primarily on data from 2 large, well-controlled, randomized, pivotal Phase 3 studies (BGB-3111-304 and Study BGB-3111-305) and supported by collective data from zanubrutinib-treated patients in 7 additional studies, establishes that zanubrutinib provides a favorable safety profile compared with chemotherapy and ibrutinib in patients with TN or R/R CLL/SLL, respectively. The 2 pivotal studies allow for clear comparisons of zanubrutinib safety against the safety of standard chemotherapy (B+R) or a first-generation BTK inhibitor (ibrutinib). Patients in the pivotal studies as well as in the integrated Safety Analysis Set are representative of the general CLL/SLL population in terms of age, sex, race, geographic region, disease status, and overall health, and the sample size and treatment duration of the integrated data are adequate to allow for evaluation of safety in important subgroups. Taken together, the data package is sufficient to characterize the safety of zanubrutinib for a supplemental indication and to guide the management of risks associated with zanubrutinib as a treatment for CLL/SLL.

The safety profiles of the treatment arms in Study BGB-3111-304 were consistent with results in their approved USPIs. Consistent with their differentiated mechanisms of action, zanubrutinib had notably lower rates of cytopenias (particularly neutropenia) and gastrointestinal adverse events (particularly nausea and vomiting) compared with B+R. Zanubrutinib also had lower rates of pyrexia, rash, infusion-related reactions compared with B+R as would be expected when comparing an intravenously administered therapy versus an orally administered drug. As evidenced by the higher rates of treatment discontinuation with B+R compared with zanubrutinib (zanubrutinib 8.3%; B+R 13.7%) or delay/interruption (zanubrutinib 47.9%; B+R 70.0%) due to adverse events, some safety effects can be dose-limiting for B+R.

In Study BGB-3111-305 zanubrutinib was compared with the first-generation and less selective BTK inhibitor, ibrutinib. Notably the incidence of toxicities such as diarrhea and atrial fibrillation/flutter, appeared appreciably lower among zanubrutinib-treated patients than in patients treated with the first generation and less selective BTK inhibitor, ibrutinib. In a prespecified analysis, the superiority of zanubrutinib to ibrutinib with respect to atrial fibrillation/flutter demonstrated with a lower frequency of atrial fibrillation/flutter (difference between the 2 arms: -7.7% (95% CI: -12.3, -3.1; p = 0.0014). Rates of adverse events, serious adverse events, Grade 3 or higher adverse events, treatment-related adverse events, and adverse events leading to treatment discontinuation or modification were at least comparable, and in some cases lower, for zanubrutinib compared with ibrutinib. These data are in line with what was seen in patients with WM that compared zanubrutinib and ibrutinib where the cumulative and exposure-adjusted rates of atrial fibrillation/flutter, hemorrhage, major hemorrhage, hypertension, pneumonia, and diarrhea were all higher for ibrutinib than zanubrutinib, while neutropenia was higher with zanubrutinib, and rates of infections were similar in both arms (Tam et al 2020; BRUKINSA USPI 2021; IMBRUVICA USPI 2021).

In the integrated Safety Analysis Set, the overall zanubrutinib safety profile appeared consistent across key CLL/SLL populations. No new signals for zanubrutinib were identified when safety findings were evaluated in the larger pooled All Zanubrutinib.

Taken together these results demonstrate that zanubrutinib offers the potential for improved safety and tolerability and an improved benefit versus risk balance over existing treatment options for patients with CLL/SLL.

The FDA's Assessment:
The Agency agrees that zanubrutinib 160mg twice daily carries an acceptable safety profile in the intended population and that the safety profile of zanubrutinib observed in studies BGB-3111-304 and BGB-3111-305 was generally consistent with the safety profile of zanubrutinib observed in the expanded safety pool of 1,550 patients who received zanubrutinib at doses of either 160mg twice daily or 320mg daily. The Agency agrees, overall, that AEs with zanubrutinib tended to be manageable and can be adequately addressed with labeling.

The Agency does not agree with the Applicant's position regarding the safety profile of zanubrutinib compared to other therapies. No definitive conclusions can be made regarding the safety profile of zanubrutinib compared to other existing treatments, and the study designs included in this application were not designed for rigorous safety comparisons between arms.

As discussed in sections 8.2.4 and 8.2.5, safety signals were identified during this review in the CLL/SLL and ISS population compared to the current known profile of zanubrutinib:

- an early potential signal of increased deaths in TN CLL in recipients of zanubrutinib compared to BR primarily driven by SPMs and infections, specifically COVID-19
- a risk of SPMs in the TN CLL/SLL population (22% in patients with 17p del CLL/SLL driven primarily by skin cancers, and 14% in patients with CLL/SLL without 17p del). SPM is a known potential risk of BTK inhibitors including zanubrutinib, however the risk with zanubrutinib in a treatment-naïve setting is newly characterized.
- the potential risk of ventricular arrhythmia.

Refer to sections 8.2.4 for further discussion of these signals , and to section 13 for the recommended related post marketing requirement in the TN CLL/SLL population.

SUMMARY AND CONCLUSIONS – Section 8

8.3 Statistical Issues

The FDA's Assessment:
There were no major statistical issues identified in this submission; however, the following are important considerations when interpreting the results.

Study BGB-3111-304
The FDA notes that, the interim analysis of the primary endpoint PFS per IRC prespecified in the protocol was planned to be performed when approximately 86 PFS events were observed, the date of the approximate 86th event was to be used as the data cutoff date. However, at the time of interim analysis, May 07, 2021, there were 107 PFS events observed in Zanubrutinib and BR

arms. The actual interim analysis conducted as above were based on the data with cutoff date as of May 07, 2021, when 107 PFS events were observed in Zanubrutinib and BR arms. Based on actual number of events observed at the interim analysis (n=107), the O'Brien-Fleming boundaries were adjusted to be 0.0186 and 0.02 (1-sided) for the interim efficacy analysis and final efficacy analysis of PFS.

Study BGB-3111-305
The FDA notes that the primary endpoint considered in the submission was ORR by IRC, rather than ORR by investigator. The key secondary endpoint was PFS per IRC, rather than PFS per investigator.

The FDA disagrees with the Application's position that, using difference in response rate to demonstrate the efficacy of Zanubrutinib vs Ibrutinib. The difference in response rate (risk difference) was not planned to be estimated or tested in the SAP, and there was no prespecified alpha allocation in the SAP or protocol. Therefore, no inference should be drawn based on the estimation of difference in response rate. Instead, the prespecified measure to demonstrate efficacy of zanubrutinib was response rate ratio (risk ratio). The entire agreed-upon sample size determination and testing plan were designed based on response rate ratio as well. Thus, to demonstrate the efficacy of zanubrutinib vs ibrutinib, the estimates of the prespecified measure, response rate ratio, should be evaluated.

Across trials
No formal comparison tests should be conducted to demonstrate the similarities in the treatment effect in study BGB-3111-304 and study BGB-3111-305, and thus no statistical inference should be drawn based on the descriptive analyses across studies provided in the assessment aid.

8.4 Conclusions and Recommendations

In study BGB-3111-304 (SEQUOIA), at the prespecified interim analysis timepoint, with 107 PFS events observed by May 07, 2021, the analysis of the primary endpoint PFS per IRC demonstrated that zanubrutinib was superior to BR with a HR of 0.42 (95% CI: 0.28, 0.63), 1-sided p<0.0001 versus the boundary of 0.0186. This finding was supported by the sensitivity analyses, subgroup analyses, and the analysis of PFS by investigator prespecified in the protocol.

In study BGB-3111-305 (ALPINE), in the final analysis of ORR, the study met the primary endpoint in assessment of ORR per IRC. Superiority of zanubrutinib compared to ibrutinib was demonstrated with a response rate ratio per IRC of 1.10 (95% CI: 1.01, 1.20), with a 2-sided p-value = 0.0264 versus the prespecified 2-sided alpha of 0.047. ORR by investigator in zanubrutinib was numerically higher compared with the ibrutinib arm (79.5% vs 71.1%) with a response rate ratio of 1.12 (95% CI.: 1.02, 1.22), which was supportive to the ORR per IRC results.

The results of SEQUOIA, in isolation, support regular approval of zanubrutinib for the treatment

of adult patients with previously untreated CLL/SLL including those patients with CLL/SLL with 17p del. Additional follow-up of OS in SEQUOIA is warranted through a safety PMR. It is justifiable to extend the indication to patients with R/R CLL/SLL supported by the ALPINE trial, considering the superior ORR, with a tendency towards benefit in PFS and OS compared to the active comparator, ibrutinib. The safety profile of zanubrutinib was acceptable, and was consistent with the safety profile in an integrated analysis of 1550 patients with hematologic malignancies treated with zanubrutinib at the intended dose-schedule. The totality of the data from SEQUOIA in TN CLL/SLL coupled with the results of the ALPINE study in R/R CLL/SLL supports regular approval of zanubrutinib for the treatment of adult patients with CLL or SLL.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy concerns or new safety concerns warranting ODAC discussion.

9 Pediatrics

The Applicant's Position:

Reasons for Requesting Waiver:
Zanubrutinib was granted orphan drug designation (ODD) status by the FDA for the treatment of CLL on 20 July 2016 (#16-5275).

As ODD has been granted for CLL, under pediatric research equity act (PREA) a Pediatric Study Plan (PSP) is not required for submission.

Justification for Waiver
Under the Pediatric Research Equity Act (PREA) (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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, BeiGene requests exemption from PREA requirement for the proposed CLL/SLL indication due to ODD status.

Applicant Certification
Because zanubrutinib drug product was granted orphan drug designation (#16-5275) for this indication (CLL), BeiGene claims to be exempt from this requirement.

The FDA's Assessment:
Zanubrutinib has Orphan designation for CLL and is therefore exempt from Pediatric Research Equity Act requirements. Since this application is a supplement and not a new active ingredient, PREA as amended by FDARA is not applicable.

10 Labeling Recommendations

Data: The table below provides a high-level summary of the changes made to the USPI for Brukinsa (zanubrutinib) NDA 213217-S007. See the USPI attached to the approval letter for final labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Recommended Labeling**
Section 1: Indication and Usage	For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).	FDA agreed.
Section 2: Dosage and Administration	N/A	Table on dosage modifications for drug interactions revised to recommend increasing zanubrutinib dosage to 320 mg twice daily if moderate CYP3A inducer cannot be avoided.
Section 5: Warnings and Precautions	5.5 Cardiac Arrhythmias	Risk of ventricular arrythmias was added based on rate in the ISS population.
	(b) (4)	The Applicant proposed (b) (4) The Applicant then proposed (b) (4) FDA did not object.
Section 6: Adverse Reactions	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	For study BGB-3111-304, the population description and AR rates for Cohort 2 were separated from the originally proposed combined AR table. Rates of some ARs were revised after Agency review reflecting FDA grouping of preferred terms. For study BGB-3111-305, the Applicant's proposed (b) (4) was removed since FDA did not agree (b) (4)
Section 14: Clinical Studies	14. 4 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	For study BGB-3111-304, the Applicant proposed inclusion of the Cohort 2 (17p del population) with the randomized (Cohort 1) efficacy results. The USPI was revised to separate the Cohort 1 and Cohort 2 population descriptions and efficacy findings (b) (4) (b) (4). Duration

		of response was included in the Cohort 2 efficacy table. For study BGB-3111-305, the Applicant originally included data from the interim analysis of ORR conducted on the first 415 patients with a CCOD of 1 Dec 2020. The Agency requested updated data reflecting the final ORR analysis in the ITT total population (N= 652) with a CCOD of Dec 1, 2021. The USPI was revised to include the final ORR per IRC analysis results including DOR, (b) (4) The Applicant was informed (b) (4)

The Applicant's Position:
The USPI has been updated to include the CLL/SLL indication. Warning and Precautions was updated based on the new patient pool, and CLL/SLL Adverse reaction section was added in 6.2 for CLL/SLL studies.

The FDA's Assessment:
Significant revisions to the USPI are described above.

11 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team does not recommend a REMS. Based on the observed safety profile of zanubrutinib, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

APPEARS THIS WAY ON ORIGINAL

12 Postmarketing Requirements and Commitment

The FDA's Assessment:
The review team recommends one PMR to further evaluate the safety signal of increased deaths due to AEs, including deaths due to second primary malignancy, in the zanubrutinib arm compared to the control arm in Study BGB-3111-304. Refer to the action letter for milestone dates.

PMR: Conduct an integrated safety analysis of patients enrolled in Study BGB-3111-304 to further characterize the risk of second primary malignancies, including incidence and types, and other serious risks with extended follow-up in patients receiving zanubrutinib as first-line treatment for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Include incidence rates of second primary malignancies, including after receipt of subsequent anticancer therapy, types, time to onset, potential predisposing factors, and outcomes in patients who received zanubrutinib or bendamustine plus rituximab in Study BGB-3111-304, and an analysis of post-marketing reports of second primary malignancies in recipients of zanubrutinib as first-line treatment for CLL/SLL. Evaluate overall survival in each treatment arm in Study BGB-3111-304, and include causes of death and narratives for death in the absence of treated disease progression, at least 8 years after randomization of the first subject in Cohort 1.

Rationale: In study BGB-3111-304 evaluating zanubrutinib vs. BR in patients with previously untreated CLL or SLL, an early analysis of OS revealed a numerically higher rate of deaths in the zanubrutinib arm (6.6%, vs. 5.9% in the control arm), with a HR of 1.07 (95% CI 0.51, 2.22) favoring the control arm. The leading causes of fatal AEs were SPMs and infections, which are important considerations particularly in this first-line setting. Longer-term data are needed to characterize the risk and types of SPM and other fatal AEs, to evaluate the impact on OS and to guide mitigation recommendations.

13 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

14 Division Director (OB)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (Clinical)

X

APPEARS THIS WAY ON ORIGINAL

16 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

APPEARS THIS WAY ON ORIGINAL

17 Appendices

17.1 References

The Applicant's References:

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukemia (CLL14): follow-up results from a multicentre, open-label, randomized, phase 3 trial. Lancet Oncol. 2020;21:1188-1200.
Bauer K, Rancea M, Roloff V, et al. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. Cochrane Database Syst Rev. 2012:CD008079.
Boriani G, Corradini P, Cuneo A, et al. Practical management of ibrutinib in the real life: Focus on atrial fibrillation and bleeding. Hematol Oncol . 2018 Oct;36(4):624-632. doi: 10.1002/hon.2503. Epub 2018.
Brannath W, Bauer P, Maurer W, et al. Sequential tests for noninferiority and superiority. Biometrics. 2003;59(1):106-14.
Bray F, Ferlay J, Soerjomataram I, Siegel RL, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424
BRUKINSA (zanubrutinib) [US Prescribing Information]. Cambridge, Massachusetts. BeiGene; 2021.
Bryan J, Borthakur G. Role of rituximab in first-line treatment of chronic lymphocytic leukemia. Ther Clin Risk Manag. 2010;22;7:1-11.
Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373: 2425-37.
Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical endpoints in chronic lymphocytic leukemia. J Clin Oncol. 2012;30(23):2820-2.
Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014;32:3059-68.
Fiedler K, Sindrilaru A, Terszowksi G, et al. Neutrophil development and function critically depend on Bruton tyrosine kinase in a mouse model of X-linked agammaglobulinemia. Blood. 2011;117(4):1329-39.
Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380:2225-36.
Global Burden of Disease Cancer collaboration Fitzmaurice C, Allen C, Barber RM. Et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease study. JAMA Oncol. 2017;3(4):524-48.
Goede V, Fischer K, Bosch F, et al. Updated Survival Analysis from the CLL11 Study: Obinutuzumab Versus Rituximab in Chemoimmunotherapy-Treated Patients with Chronic Lymphocytic Leukemia. Blood. 2015;126:1733.

Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. J Clin Oncol. 2020 Sep 1;38(25):2849-2861.
Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. Am J Hematol. 2019;94:1266–1287.
IMBRUVICA (ibrutinib) [US prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; Horsham, PA: Janssen Biotech, Inc. 2021.
Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. Leukaemia. 2015;29(4):783-7.
Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations driving CLL and their evolution in progression and relapse. Nature. 2015;526(7574):525-30.
Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014;124(26):3991-5.
Lloyd-Jones DM, Larson MG, Leip EP, et al. Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106:3068-72.
Mallinckrodt CH, Lane PW, Schnell D, et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Information Journal. 2008. 42:303-319.
Małyszko J, Małyszko M, Kozlowski L, et al. Hypertension in malignancy-an underappreciated problem. Oncotarget. 2018;9:20855-71.
McMullen JR, Boey EJ, Ooi JY et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829-30.
National cancer institute (2020) Cancer Stat facts: leukemia — chronic lymphocytic leukemia (CLL). https://seer.cancer.gov/statfacts/html/clyl.html.
National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). Chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 4.2021, April 29, 2021.
Ou YC, Tang Z, Novotny W, et al. Rationale for once-daily or twice-daily dosing of zanubrutinib in patients with mantle cell lymphoma. Leuk Lymphoma. 2021.
doi:10.1080/10428194.2021.1929961. Epub ahead of print. PMID: 34159878.
Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukaemia. N Engl J Med. 2000;343(24):1750-57.
Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994;83(2):435-45.
Sharman J, Egyed M, Wojciech J, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395(10232):1278-1291.
Siegel R, Miller KD, Fuchs H, et al. Cancer Statistics, 2021. Cancer J Clin. 2021;71(1):7.

Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432-443.
Swerdlow S, Campo E, Harris NL, et al. WHO classification of tumors of Hematopoetic and Lymphoid Tissues. IARC, Lyon. 2008.
Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood. 2019;134:851-859.
Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment-naïve chronic lymphocytic leukemia and 17p deletion. Haematologica 2020; epub ahead of print.
Tang CPS, McMullen J, Tam C. Cardiac side effects of Bruton tyrosine kinase (BTK) inhibitors. Leuk Lymphoma. 2018;59(7):1554-64.
Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemotherapy in older patients with untreated CLL. N Engl J Med. 2018;379:2517-2528.
Xiao L, Salem JE, Clauss S, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-terminal Src kinase. Circulation. 2020;142:2443-55.
Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002. Cancer Causes Control. 2008;19(4):379.

The FDA's References:
Bhat SA, Gambril J. Ventricular arrhythmias and sudden death events following acalabrutinib initiation. Blood. 2022; 140(20):2142-2145.

17.2 Financial Disclosure

The Applicant's Position:
See Section 8.1.1 and Section 8.1.2 for Financial Disclosure information from the Applicant.

The FDA's Assessment:
All investigators participating in study BGB-3111-304 and BGB-3111-305 were assessed for equity interest, significant payments, proprietary interests and other compensation. Thirty three of the investigators out of 2938 total investigators had financial interests to disclose. Statements of due diligence in cases where the applicant was unable to obtain a signed financial disclosure form from the investigator are included in the FDA Form 3454 provided in this sNDA submission.

Covered Clinical Study:* BGB 3111-304 and BGB 3111-305

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2938		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 33		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: No Significant payments of other sorts: 33 (Investigators overlap in BGB 3111-304 and BGB 3111-305 studies) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

17.3 OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

8.17.1 Pharmacometric Review

8.17.1.2 Review Summary

The PopPK analysis evaluated data from 6 Phase 1 (103, 104, 105, 106, AU-003, 1002, and 205), 2 Phase 2 (205 and 206), and 3 Phase 3 (302, 304, and 305) studies. The final PopPK analysis dataset consisted of 6500 plasma concentrations from 1291 subjects including 90 healthy volunteers and 1201 patients with B-Cell malignancies. A 2-compartment model with sequential 0-order then 1st-order absorption and 1st-order elimination described zanubrutinib PK. Health status, baseline ALT, and age were identified as statistically significant covariates on the PK of zanubrutinib. The population PK model remained the same with previous submissions where patients showed higher clearance than healthy volunteers. No clinically meaningful covariates were identified in patients.

No exposure response relationship was identified for ORR or PFS from efficacy perspectives. No exposure-response relationship was identified for safety endpoints, including AEs leading to treatment discontinuation and AEs of interest (grade ≥3 neutropenia, grade ≥3 thrombocytopenia, grade ≥ 3 anemia, grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and any bleeding events).

8.17.1.3 Applicant PPK Analysis

Title: Population Pharmacokinetic Analysis of the BTK Inhibitor Zanubrutinib in Healthy Volunteers and Patients with B-Cell Malignancies.
Objectives: To describe zanubrutinib PK, variability, and covariate effect in healthy subjects and cancer patients.
Data: This population pharmacokinetics (PopPK) analysis evaluated data from 6 Phase 1 (103, 104, 105, 106, AU-003, 1002, and 205), 2 Phase 2 (205 and 206), and 3 Phase 3 (302, 304, and 305) studies (**Table 111**).

Table 111 : Summary of Studies Included in the Population Pharmacokinetics Analysis

Study	Oral Dose Regimen	Comment
BGB-3111-AU-003, A Phase 1, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients with B-Cell Lymphoid Malignancies	40, 80, 160, and 320 mg QD. 160 mg BID	PK and PD. Ongoing study 04 November-2019 data cut

Study	Oral Dose Regimen	Comment
BGB-3111-1002, A Phase 1 clinical study to investigate the safety, tolerability and pharmacokinetics/ pharmacodynamics of the BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma	320 mg QD. 160 mg BID	PK and PD. 14 Dec 2017 data cut
BGB-3111-205, A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)	160 mg BID	Sparse PK. 15 Jun 2018 data cut
BGB-3111-206, A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate the Efficacy and Safety of BGB-3111, a BTK Inhibitor, in Patients with Relapsed or Refractory MCL	160 mg BID	Sparse PK. 27 Mar 2018 data cut
BGB-3111-103, A Single-Center, Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of a Single Dose of 320 mg BGB-3111 Given Orally to Healthy Adult Subjects	320 mg QD	PK and food effects
BGB-3111-104, A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of BGB-3111 in Healthy Subjects	320 mg (Part A). 20 mg (Part B)	PK and DDI
BGB-3111-105, A Phase 1 Study to investigate the absorption, metabolism, and excretion of [^{14}C]-BGB-3111 following a single oral administration in healthy male subjects	320 mg	PK and ADME
BGB-3111-106, A Phase 1 Two-Part Study Consisting of a Randomized, Placebo-Controlled, Single Dose Safety and Tolerability Study (Part A) Evaluating a Supratherapeutic Dose of Zanubrutinib Followed by a Randomized, Placebo- and Positive-Controlled, Crossover Study (Part B) to Evaluate the Effect of Zanubrutinib on Cardiac Repolarization in Healthy Volunteers	160, 480 mg	PK and QTc
BGB-3111-302, A Phase 3 Study Comparing BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)	160 mg BID	Sparse PK Ongoing study. 09 Dec-2019 data cut
BGB-3111-304, An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	160 mg BID	Sparse PK 21 June 2021 data cut
BGB-3111-305, A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with	160 mg BID	Sparse PK 21 June 2021

Study	Oral Dose Regimen	Comment
Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma		data cut
Source: Table 2 of Applicant's PopPK Report for This Supplement.		

A summary of the demographics of the PopPK dataset is provided in **Table 112** and **Table 113**.

APPEARS THIS WAY ON ORIGINAL

Table 112: Mean (SD) of Baseline Continuous Covariates in the PopPK Dataset								
Study (N of Subjects)	**ALB (g/L)**	**ALT (IU/L)**	**AST (IU/L)**	**BIL (μmol/L)**	**CRCL (mL/min)**	**Creatine (μmol/L)**	**Weight (kg)**	**Age (year)**
103 (18)	40.7 (3.08)	20.5 (6.64)	19.9 (4.46)	10.0 (5.79)	117 (26.6)	72.7 (11.9)	75.2 (11.7)	45.2 (13.8)
104 (38)	44.6 (2.80)	25.8 (12.5)	23.0 (5.49)	10.6 (4.15)	154 (45.4)	64.4 (18.1)	78.8 (13.0)	40.2 (10.1)
105 (6)	44.2 (1.94)	23.3 (11.4)	20.3 (5.68)	9.98 (9.52)	123 (21.2)	86.9 (10.3)	78.3 (11.1)	29.8 (4.79)
106 (28)	46.2 (2.15)	23.9 (8.87)	20.4 (4.77)	8.80 (3.51)	121 (27.7)	86.9 (10.3)	87.1 (12.9)	42.4 (8.87)
205 (13)	44.7 (5.24)	15.5 (4.79)	23.7 (4.20)	15.9 (6.51)	80.1 (18.4)	71.1 (13.6)	61.3 (9.71)	61.5 (8.30)
206 (20)	42.7 (4.52)	16.5 (12.5)	24.1 (8.08)	11.7 (3.30)	92.1 (30.3)	76.9 (20.0)	71.1 (12.1)	61.4 (7.21)
1002 (44)	43.3 (5.05)	15.6 (9.13)	24.6 (8.30)	13.1 (4.18)	103 (25.9)	70.3 (16.6)	68.1 (13.6)	50.1 (11.2)
AU003 (337)	38.3 (5.10)	25.9 (20.1)	26.6 (17.4)	11.3 (5.97)	86.0 (33.6)	85.2 (27.1)	78.3 (17.9)	66.4 (11.1)
302 (127)	34.4 (5.74)	15.9 (8.52)	20.4 (10.2)	9.63 (4.71)	78.6 (31.8)	85.8 (32.3)	74.4 (17.0)	69.3 (11.1)
304 (389)	44.3 (3.74)	16.6 (9.78)	22.3 (10.0)	9.83 (6.15)	72.8 (21.5)	90.3 (21.4)	76.5 (16.4)	69.1 (8.32)
305 (271)	45.4 (3.52)	19.0 (11.6)	22.5 (10.3)	11.0 (6.32)	76.9 (26.6)	89.0 (21.1)	76.5 (17.4)	66.5 (10.1)
Total (1291)	41.9 (5.71)	19.9 (14.1)	23.3 (12.3)	10.6 (5.91)	83.4 (32.7)	86.1 (24.3)	76.5 (16.9)	65.1 (12.5)
Total (1291), median(range)	43.0 (20.0-53.0)	16.9 (4.00-197)	21.0 (5.00-190)	9.00 (2.00-54.0)	77.9 (13.5-241)	83.0 (35.4-278)	74.8 (36.0-149)	67.0 (19.0-90.0)

Source: Table 5 of Applicant's PopPK Report for This Supplement.

Table 113: Baseline Categorical Covariate Information in the PopPK Dataset					
Study	**Sex (M/F)**	**Race (Missing/Asian/White/ Other/Black)**	**TUMTP (HV/CLL-SLL/MCL/WM/Other B-cell malignancies)**	**Use of PPI (No/Yes)**	**Use of H2RA (No/Yes)**
103	13/5	1/0/17/0/0	18/0/0/0/0	18/0	18/0
104	29/9	0/16/16/1/5	38/0/0/0/0	38/0	38/0
105	6/0	0/2/2/0/2	6/0/0/0/0	6/0	6/0
106	27/1	0/0/12/0/16	28/0/0/0/0	28/0	28/0
205	8/5	0/13/0/0/0	0/13/0/0/0	12/1	13/0
206	16/4	0/20/0/0/0	0/0/20/0/0	18/2	19/1
1002	24/20	0/44/0/0/0	0/9/2/2/31	43/1	44/0
AU003	239/98	1/48/267/18/3	0/113/48/66/110	295/42	321/16
302	81/46	11/4/112/0/0	0/0/0/127/0	116/11	124/3
304	258/131	16/45/323/1/4	0/389/0/0/0	336/53	373/16
305	171/100	6/45/215/5/0	0/271/0/0/0	246/25	267/4
Total	872/419	35/237/964/25/30	90/795/70/195/141	1156/135	1251/40
Source: Table 6 of Applicant's PopPK for This Supplement.					

Methods: A nonlinear mixed-effects modelling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4.3 (b) (4) was used for the PopPK analysis. The impact of baseline age, body weight (WT), sex, race (Asian, White, Black, and Other), creatinine clearance (CRCL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (BIL), tumor type (TUMTP, mantle cell lymphoma [MCL], chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL], Waldenström macroglobulinemia [WM], and other B-cell malignancies), health status (healthy volunteers [HV] and patients with B-cell malignancies), and use of acid- reducing agents (proton-pump inhibitors [PPI], H2-Receptor Antagonists [H2RA], and Other) on the PK of zanubrutinib were investigated during PopPK model development. Covariates were selected using a stepwise forward selection and backward elimination method (based on a significance level of $p < 0.01$ for the forward steps and $p < 0.001$ for the backward steps).

RESULTS

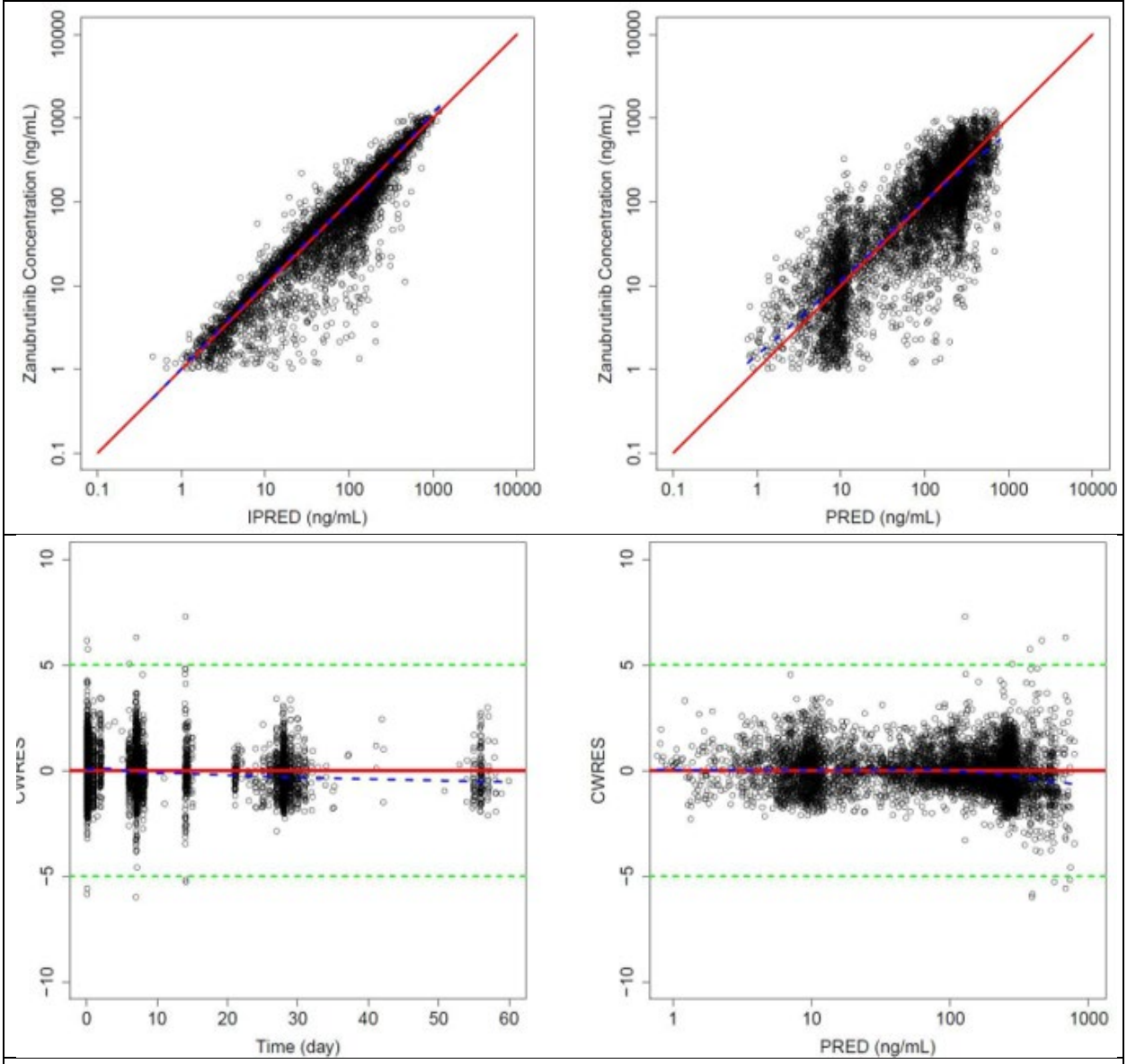
The final PopPK analysis dataset consisted of 6500 plasma concentrations from 1291 subjects including 90 healthy volunteers and 1201 patients with B-Cell malignancies. A 2-compartment model with sequential 0-order then 1st-order absorption and 1st-order elimination described zanubrutinib PK (**Figure 16**). Health status, baseline ALT, and age were identified as statistically significant covariates on the PK of zanubrutinib. The parameter-covariate relations in the final PopPK model are described by the following equations:

$$CL/F_i(L/hr) = exp\left(4.57 + 0.478 \times (PATi = Patient) - 0.123 \times ln\left(\frac{ALT_i}{17}\right) - 0.463 \times ln\left(\frac{Age_i}{67}\right) + \eta_{CL/F,i}\right)$$

$$Vc/F_i(L) = exp\left(4.30 - 0.788 \times ln\left(\frac{Age_i}{67}\right) + \eta_{Vc/F,i}\right)$$

where CL/F_i and V_c/F_i represent the clearance from the central compartment (CL/F) and volume of distribution of the central compartment (V_c/F); CL/F_i and V_c/F_i are the interindividual random effects of CL/F and V_c/F of the i^{th} individual; PAT_i, ALT_i, and Age_i represents health status, baseline ALT, and age of the i^{th} individual, respectively.

Figure 16: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figures 37 and 38 of Applicant's PopPK Analysis Report

For a typical patient with ALT of 17 U/L and age of 67 year, the estimated CL/F was 155 L/hr, V_c/F was 73.6 L, Q/F was 15.5 L/hr, V_p/F was 472 L, k_a was 0.477 hr^{-1}, and D_1 was 1.26 hr. Interindividual variability on CL/F, V_c/F, Q/F, V_p/F, and D_1 were 37.0%, 55.1%, 123%, 70.0%, and 55.2%, respectively. The geometric mean elimination half- life was 2.52 hours with a CV of 47.6%. Parameter estimates for the final PopPK model are listed in **Table 114**. The covariate effects are presented in **Table 115.**

Table 114: Parameter Estimates of the Final Population Pharmacokinetic Model

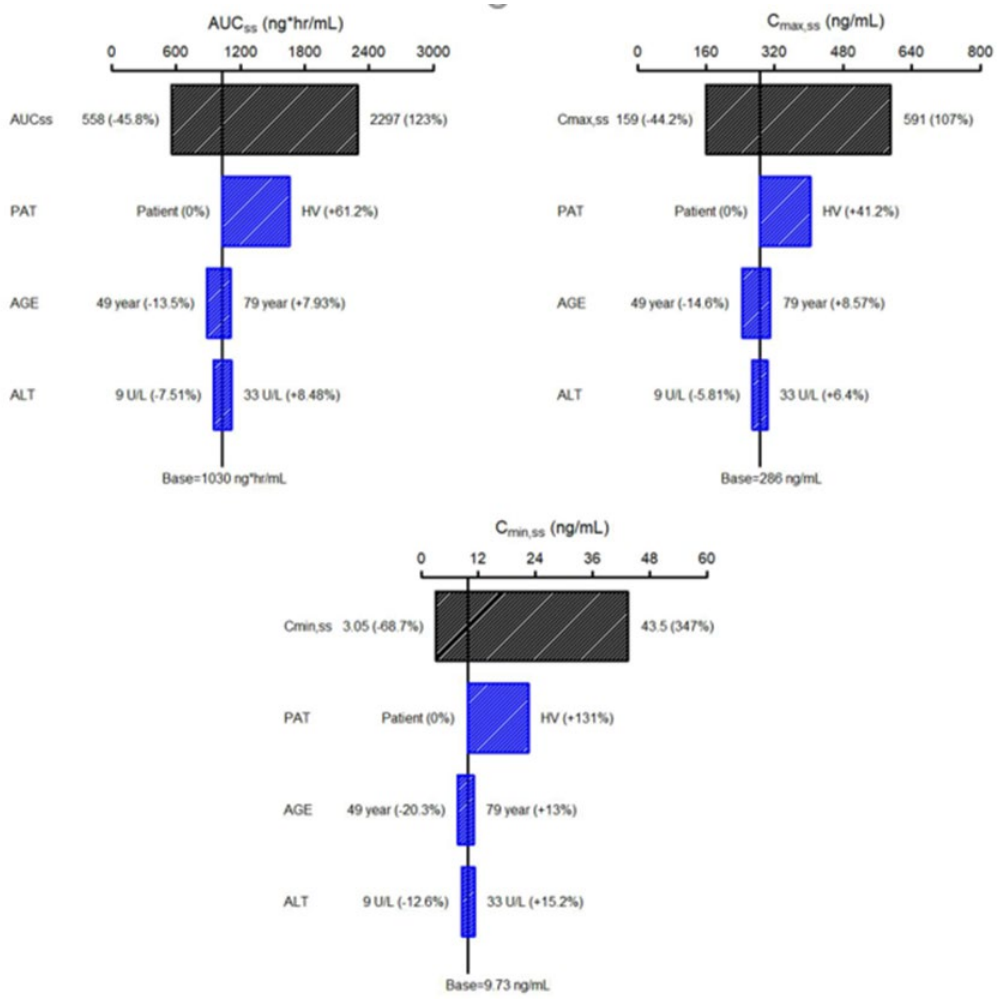
Parameter	Parameter Description		Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
$exp(\theta_1+\theta_{10})$	Apparent oral clearance, CL/F (L/hr)	Patient	155 (19.5 %)	157 (124, 199)	—
$exp(\theta_1)$		HV	96.4 (19.5%)	95.8 (84.5, 107)	—
θ_{11}	Influence of ALT on CL/F		-0.123 (1.34%)	-0.130 (-0.189, -0.0769)	—
θ_{12}	Influence of age on CL/F		-0.463 (0.302%)	-0.455 (-0.608, -0.300)	—
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		73.6 (0.819%)	71.3 (58.7, 85.2)	—
θ_{13}	Influence of age on V_c/F		-0.788 (0.0482%)	-0.762 (-0.963, -0.455)	—
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)		15.5 (2.67%)	15.6 (13.6, 18.3)	—
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)		472 (9.48%)	487 (410, 585)	—
$exp(\theta_5)$	Absorption rate constant, k_a (hr^{-1})		0.477 (1.59%)	0.480 (0.462, 0.501)	—
$exp(\theta_6)$	Duration, D_1 (hr)		1.26 (1.32%)	1.27 (1.16, 1.38)	—
ω^2	Covariance (CL/F,V_c/F)		0.147 (31.7%)	0.142 (0.0681, 0.200)	—
θ_9	Additive residual error (ng/mL, TFDS<5 hr)		72.4 (0.659%)	72.4 (65.1, 80.0)	—
θ_7	Additive residual error (ng/mL, TFDS≥5 hr)		0.730 (2.33%)	0.719 (0.411, 1.10)	—
θ_8	Proportional residual error (%)		45.6 (0.664%)	45.2 (42.7, 47.2)	20.9
IIV (%RSE)	CL/F		37.0 (10.5%)	37.0 (33.8, 40.1)	29.2
	V_c/F		55.1 (26.5%)	55.1 (36.1, 76.6)	44.1
	Q/F		123 (27.9%)	125 (114, 138)	36.5
	V_p/F		70.0 (3.32%)	70.3 (58.9, 85.7)	73.7
	D_1		55.2 (2.18%)	55.4 (48.3, 61.5)	56.7
IOV (%RSE)	CL/F		33.7 (13.2%)	34.0 (30.8, 37.6)	44.3
	V_c/F		61.7 (0.490%)	63.3 (51.4, 79.2)	71.2

Source: Table 8 of Applicant's PopPK Report

Table 115: Covariate Effects on Key Pharmacokinetics Parameters			
PK Parameters and Baseline Covariates		**Estimate**	**Change from Typical**
Typical CL/F (L/hr, ALT=17 U/L, 67 years, patient)		155	—
Health status	HV	96.4	-38.0%
ALT (U/L)	10^{th} percentile (9 U/L)	168	+8.12%
	90^{th} percentile (33 U/L)	143	-7.82%
Age (year)	10^{th} percentile (49 years)	180	+15.6%
	90^{th} percentile (79 years)	144	-7.34%
Typical V_c/F (L, 67 years)		73.6	—
Age (year)	10^{th} percentile (49 years)	94.2	+27.9%
	90^{th} percentile (79 years)	64.7	-12.2%
Typical Q/F (L/hr)		15.5	—
Typical V_p/F (L)		472	—
Typical k_a (hr^{-1})		0.477	—
Typical D_1 (hr)		1.26	—
Source: Table 1 of Applicant's PopPK Report			

Covariate effects on steady-state exposure are shown in **Figure 17**, where the black vertical line refers to the predicted exposure (AUCss and Cmax,ss) of zanubrutinib in a typical subject after 160 mg BID for 10 days, which serve as the reference values. All percentage values shown in each plot are the relative changes in exposure relative to the reference value. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the study population. Each blue shaded bar represents the magnitude of influence of the respective covariate on the exposure. The length of each bar represents the range of predicted zanubrutinib exposure between the high/low or possible values of the covariate (indicated at each end of the bar). The covariates shown in each plot are ordered from the most influential covariate at the top to the least influential covariate at the bottom.

Figure 17: Covariate Effect on Steady-State Exposure AUCss, Cmax,ss, and Cmin,ss



Source: Figure 10 of Applicant's PopPK Analysis Report

The FDA's Assessment:

Although there were some overprediction for zanubrutinib concentrations under 20 ng/mL, the PopPK analysis is acceptable in general for describing the PK of zanubrutinib and deriving exposure metrics for subsequent exposure-response analyses.

8.17.1.4 Applicant's Exposure-Response Analysis

Title: Population Exposure-Response Analysis of Zanubrutinib in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL).
Objectives: Using data from studies 304 and 305 to explore whether there is an exposure-response (E-R) relationship between zanubrutinib exposure metrics (Cmin,ss, Cmax,ss, and AUCss) and efficacy endpoints (PFS, ORR, and ORR including partial response with lymphocytosis PR-L), and whether there is an E-R relationship between those exposure metrics and adverse

event (AE) leading to treatment discontinuation or AEs of interest (grade ≥3 neutropenia, grade ≥3 thrombocytopenia, grade ≥ 3 anemia, grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and any bleeding events).

Method: R 4.1.1 was used for the E-R analysis.

Result:

E-R Relationship for Efficacy

The E-R relationship for PFS was explored by Kaplan- Meier estimates based on the data from patients without del17p (Arm A, n=278) and patients with del17p (Arm C, n=110) in Study 304.

The E-R relationships for efficacy endpoints of ORR (PR or higher) and ORR (PR-L or higher) were explored based on Arms A of Study 304, Arm C of Study 304, and Study 305 (n=173), respectively. **Table 116** summarizes the key baseline characteristics of the E-R analysis dataset and **Table 117** lists the efficacy endpoints**.**

Table 116: Baseline Population Characteristics in the Exposure Efficacy Analysis Dataset

Characteristics		BGB-3111-304		BGB-3111-305 (n=173)
		Arm A (n=278)	Arm C (n=110)	
Continuous Variable, median [min, max]				
Age (year)		70.0 [32.0, 86.0]	70.0 [42.0, 86.0]	67.0 [35.0, 86.0]
Weight (kg)		74.0 [42.5, 147]	75.9 [44.7, 124]	75.8 [47.0, 149]
Creatinine (μmol/L)		84.5 [39.9, 161]	91.5 [56.0, 163]	88.0 [51.0, 166]
Creatinine clearance (CRCL, mL/min)		71.5 [36.2, 154]	69.2 [27.7, 140]	74.8 [36.2, 193]
Total bilirubin (BIL, μmol/L)		8.00 [3.00, 54.0]	9.00 [3.00, 35.0]	10.0 [3.00, 41.0]
Aspartate aminotransferase (AST, U/L)		20.0 [10.0, 156]	22.0 [5.00, 55.0]	20.0 [10.0, 50.0]
Alanine aminotransferase (ALT, U/L)		14.0 [4.00, 132]	16.0 [5.00, 67.0]	16.0 [4.00, 59.0]
Albumin (ALB, g/L)		45.0 [28.0, 51.1]	45.0 [33.0, 52.0]	46.0 [35.0, 53.0]
Categorical Variable, N (%)				
Race	Asian	44 (15.8%)	1 (0.900%)	23 (13.3%)
	White	218 (78.4%)	104 (94.5%)	143 (82.7%)
	Other	1 (0.400%)	—	5 (2.90%)
	Black	4 (1.40%)	—	—
	Missing	11 (4.00%)	5 (4.50%)	2 (1.20%)
Sex	Male	179 (64.4%)	78 (70.9%)	115 (66.5%)
	Female	99 (35.6%)	32 (29.1%)	58 (33.5%)
Use of proton-pump inhibitors (PPI)	No	243 (87.4%)	92 (83.6%)	152 (87.9%)
	Yes	35 (12.6%)	18 (16.4%)	21 (12.1%)
Use of H_2-receptor antagonists (H2RA)	No	265 (95.3%)	107 (97.3%)	171 (98.8%)
	Yes	13 (4.70%)	3 (2.70%)	2 (1.20%)
Source: Table 1 of Applicant's Exposure-Response Analysis Report				

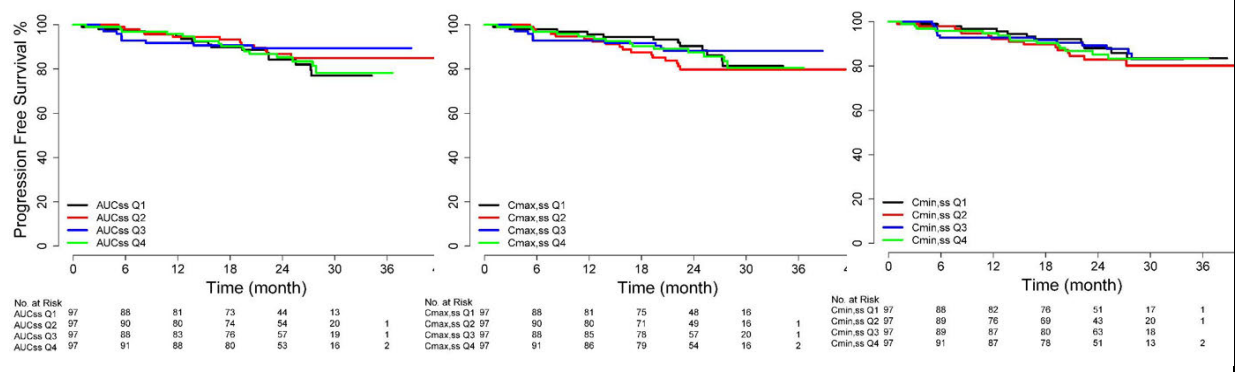
Table 117: Summary of Efficacy Endpoints in the Exposure Efficacy Analysis Dataset				
Efficacy Endpoint		**BGB-3111-304**		**BGB-3111-305**
		Arm A (n=278)	**Arm C (n=110)**	**(n=173)**
ORR (PR or higher)				
Non-responder		31 (11.2%)	13 (11.8%)	40 (23.1%)
Responder		247 (88.8%)	97 (88.2%)	133 (76.9%)
ORR (PR-L or higher)				
Non-responder		23 (8.30%)	11 (10.0%)	25 (14.5%)
Responder		255 (91.7%)	99 (90.0%)	148 (85.5%)
PFS				
PFS (month)	Mean (SD)	21.5 (8.21)	26.2 (7.45)	—
	Min~Max	0.0329~41.4	0.986~38.8	—
Censored	No	39 (14.0%)	15 (13.6%)	—
	Yes	239 (86.0%)	95 (86.4%)	—

Abbreviations: ORR, overall response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis
Source: Table 2 of Applicant's Exposure-Response Analysis Report

E-R analysis for PFS: The plots of Kaplan-Meier PFS curve stratified by quartiles of model-predicted AUCss, Cmax,ss, and Cmin,ss suggested that PFS was not different among zanubrutinib exposure quartiles based on the data from 388 patients in Study 304. There was no apparent relationship between PFS and any of the zanubrutinib exposure metrics in the zanubrutinib treated patients in Study 304 (**Figure 18**).

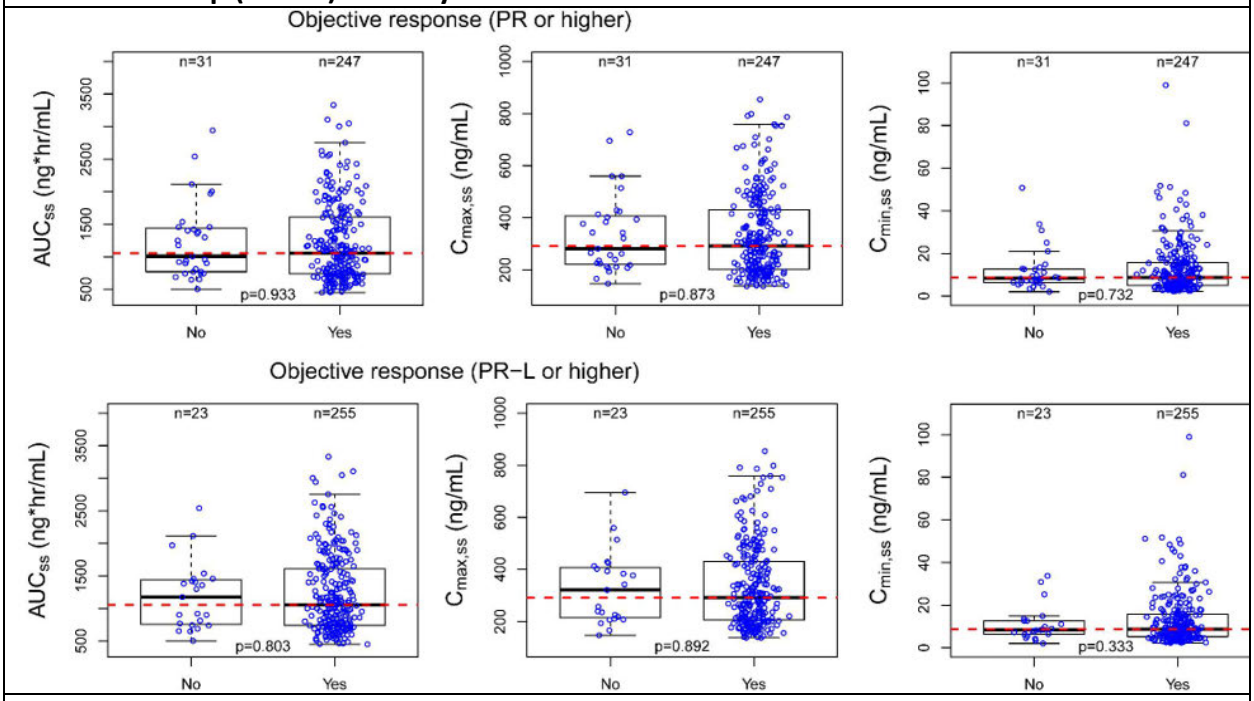
E-R analysis for ORR: The median exposure values were similar between responders and non-responders based on separate analyses in 278 patients without del17p (Arm A) in Study 304, 110 patients with del17p (Arm C) in Study 304, and 173 patients in Study 305. The probability of response plots and logistic regression models for ORR (PR or higher, or PR-L or higher) indicated none of the zanubrutinib exposure metrics had a significant effect on E-R relationship for this endpoint (**Figure 19**, **Figure 20**, and **Figure 21**).

Figure 18: Kaplan–Meier PFS Curves Stratified by Median and Quartiles of AUCss for Study BGB-3111-304 (N=388)



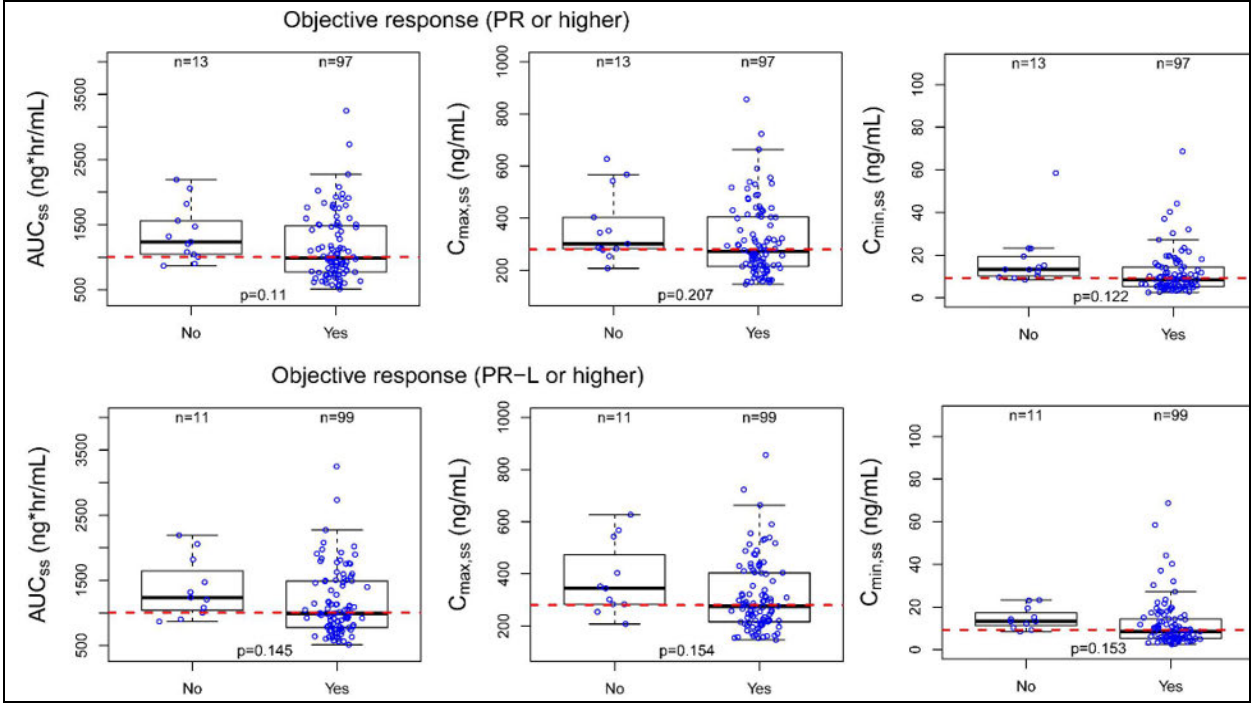
Source: Figures 2-4 of Applicant's Exposure-Response Report

Figure 19: The Relationship Between Exposure Metrics and Objective Response for Patients Without del17p (Arm A) in Study BGB-3111-304



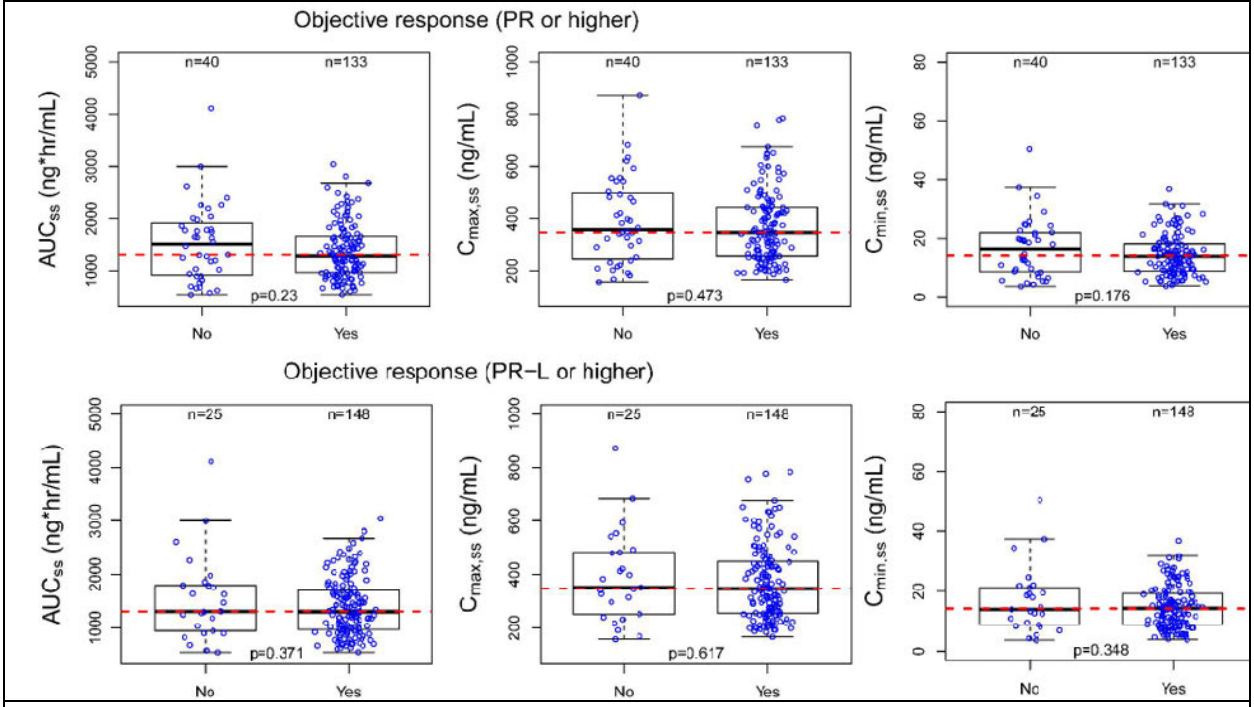
Source: Figures 5 and 11 of Applicant's Exposure-Response Report

Figure 20: The Relationship Between Exposure Metrics and Objective Response for Patients with del17p (Arm C) in Study BGB-3111-304



Source: Figures 7 and 13 of Applicant's Exposure-Response Report

Figure 21: The Relationship Between Exposure Metrics and Objective Response for Patients in Study BGB-3111-305



Source: Figures 9 and 15 of Applicant's Exposure-Response Report

E-R Relationship for Safety

A total of 660 patients from studies 304 (n=389) and BGB-311-305 (n=271) were included in the exposure-safety analyses. The E-R relationship was assessed between zanubrutinib exposure metrics (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) and safety endpoints, including AEs leading to treatment discontinuation and AEs of interest (grade ≥3 neutropenia, grade ≥3 thrombocytopenia, grade ≥ 3 anemia, grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and any bleeding events). **Table 118** summarizes the key baseline characteristics of the E-R analysis dataset. The summary of the safety endpoints is shown in **Table 119**.

Table 118: Baseline population characteristics in the exposure safety analysis dataset

Characteristics	BGB-3111-304 (n=389)	BGB-3111-305 (n=271)	Total (N=660)
Continuous Variable, median [min, max]			
Age (year)	70.0 [32.0, 86.0]	67.0 [35.0, 89.0]	69.0 [32.0, 89.0]
Weight (kg)	74.5 [42.5, 147]	75.0 [42.5, 149]	74.8 [42.5, 149]
Creatinine (μmol/L)	88.0 [39.9, 163]	87.0 [48.0, 166]	87.5 [39.9, 166]
CRCL (mL/min)	70.5 [27.7, 154]	73.3 [31.5, 193]	71.5 [27.7, 193]

BIL (μmol/L)		8.00 [3.00, 54.0]	10.0 [2.00, 41.0]	9.00 [2.00, 54.0]
AST (U/L)		21.0 [5.00, 156]	21.0 [10.0, 125]	21.0 [5.00, 156]
ALT(U/L)		14.8 [4.00, 132]	16.0 [4.00, 120]	15.0 [4.00, 132]
ALB (g/L)		45.0 [28.0, 52.0]	46.0 [35.0, 53.0]	45.0 [28.0, 53.0]
Categorical Variable, N (%)				
Race	Asian	45 (11.6%)	45 (16.6%)	90 (13.6%)
	White	323 (83.0%)	215 (79.3%)	538 (81.5%)
	Other	1 (0.300%)	5 (1.80%)	6 (0.900%)
	Black	4 (1.00%)	—	4 (0.600%)
	Missing	16 (4.1%)	6 (2.20%)	22 (3.30%)
Sex	Male	258 (66.3%)	171 (63.1%)	429 (65.0%)
	Female	131 (33.7%)	100 (36.9%)	231 (35.0%)
Use of PPI	No	336 (86.4%)	246 (90.8%)	582 (88.2%)
	Yes	53 (13.6%)	25 (9.20%)	78 (11.8%)
Use of H2RA	No	373 (95.9%)	267 (98.5%)	640 (97.0%)
	Yes	16 (4.10%)	4 (1.50%)	20 (3.00%)

Source: Table 3 of Applicant's Exposure-Response Report

Table 119: Summary of safety endpoints in the exposure safety analysis dataset

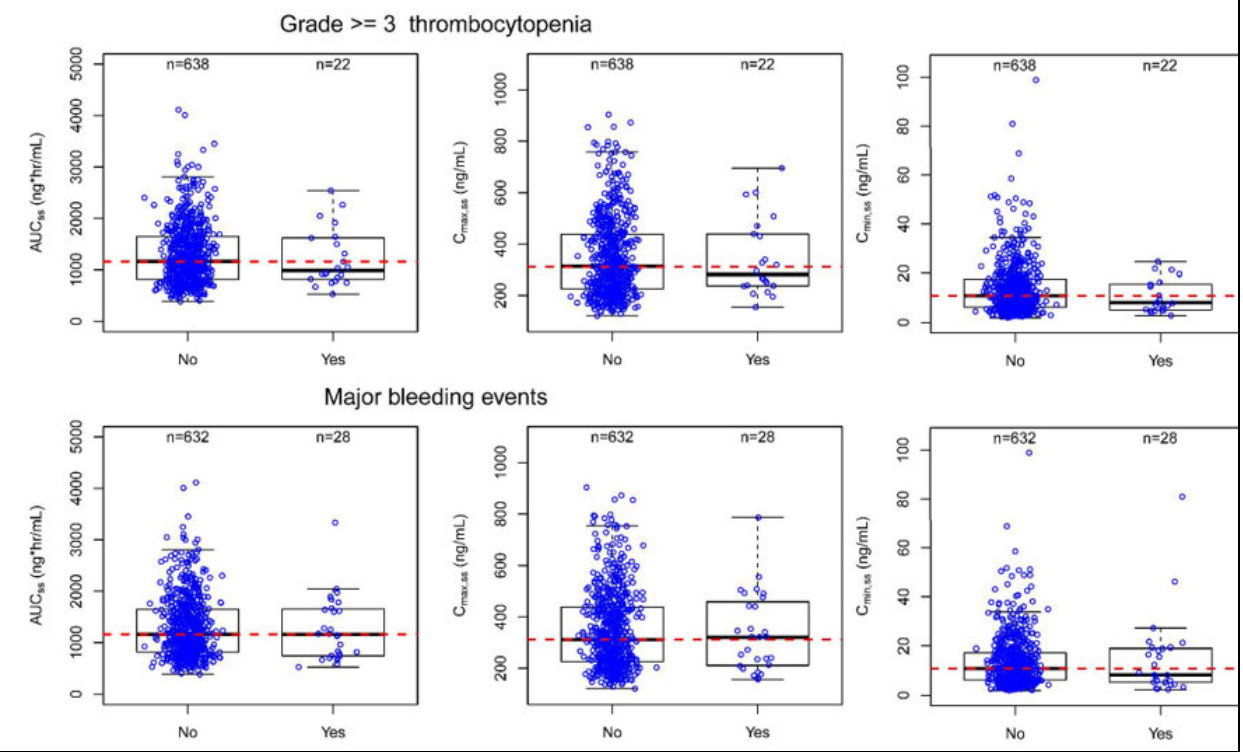
Safety Endpoints	The percentage of patients having AE [%(Yes/No)]		
	BGB-3111-304 (n=389)	BGB-3111-305 (n=271)	Total (n=660)
Grade≥3 neutropenia	17.0% (66/323)	14.0% (38/233)	15.8% (104/556)
Grade≥3 thrombocytopenia	2.57% (10/379)	4.43% (12/259)	3.33% (22/638)
Grade≥3 anemia	5.14% (20/369)	5.54% (15/256)	5.30% (35/625)
Grade≥3 infections/infestations	16.2% (63/326)	11.8% (32/239)	14.4% (95/565)
All events of secondary primary malignancies	14.1% (55/334)	5.54% (15/256)	10.6% (70/590)
All events of atrial fibrillation and flutter	3.08% (12/377)	1.11% (3/268)	2.27% (15/645)
Major bleeding events	5.66% (22/367)	2.21% (6/265)	4.24% (28/632)
Any bleeding events	46.0% (179/210)	32.1% (87/184)	40.3% (266/394)
AE leading to treatment discontinuation	7.46% (29/360)	7.38% (20/251)	7.42% (49/611)

Source: Table 4 of Applicant's Exposure-Response Report

The exposure ranges appeared to be similar in patients who experienced AEs of interest relative to those who were not based on 660 patients from studies 304 (n=389) and 305 (n=271). The probability of response plots and logistic regression models showed that there were no evident E–R relationships between exposure metrics (AUCss, Cmax,ss, or Cmin,ss) and the probability of occurrence of AEs leading to treatment discontinuation or specified AEs of interest, including grade ≥ Grade 3 neutropenia, grade ≥Grade 3 thrombocytopenia, grade ≥ Grade 3 anemia, grade

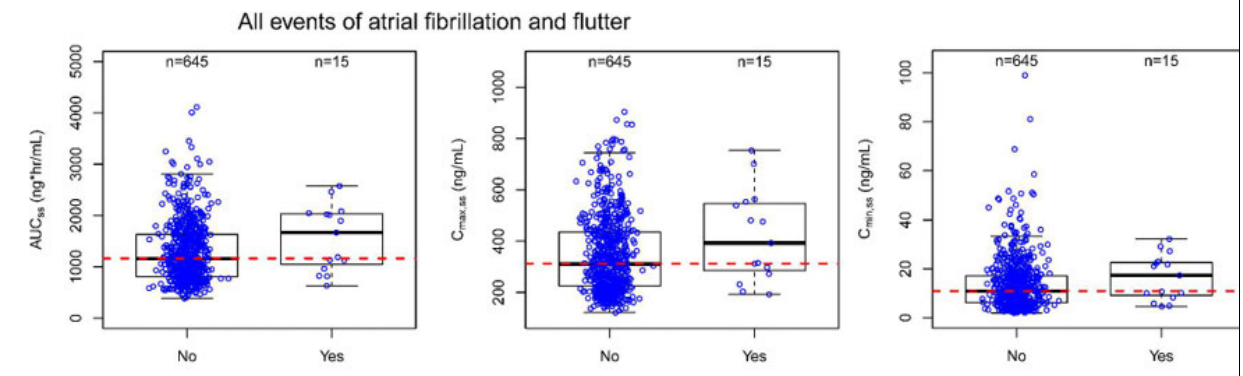
≥ Grade 3 infections/infestations, all events of secondary primary malignancies, all events of atrial

Figure 22: ER Relationship for Grade ≥ 3 Thrombocytopenia and Major Bleeding Events



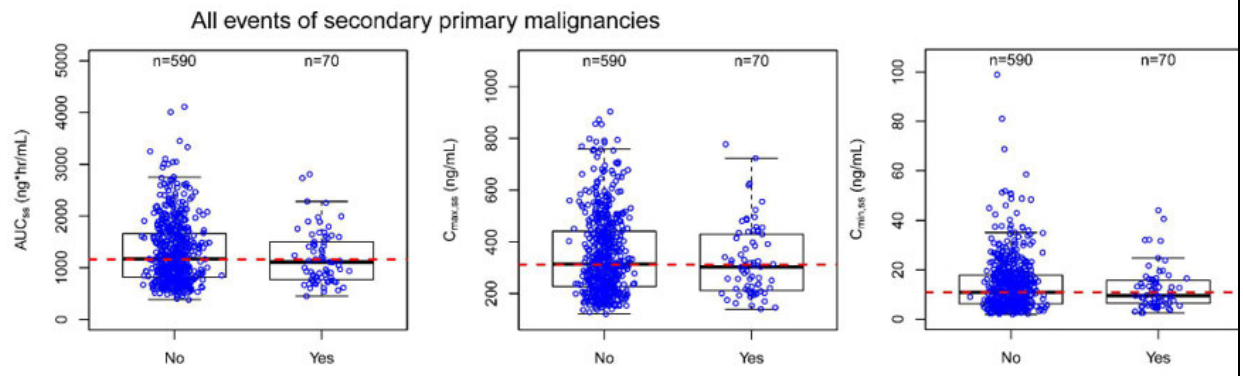
Source: Figures 19 and 29 of Applicant's Exposure-Response Report

Figure 23: ER Relationship for All Events of Atrial Fibrillation and Flutter



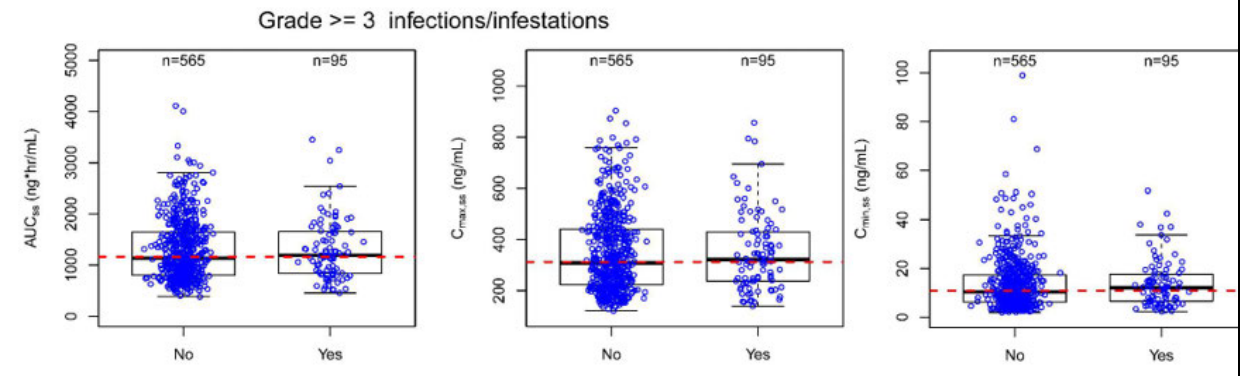
Source: Figure 27 of Applicant's Exposure-Response Report

Figure 24: ER Relationship for All Events of Secondary Primary Malignancies



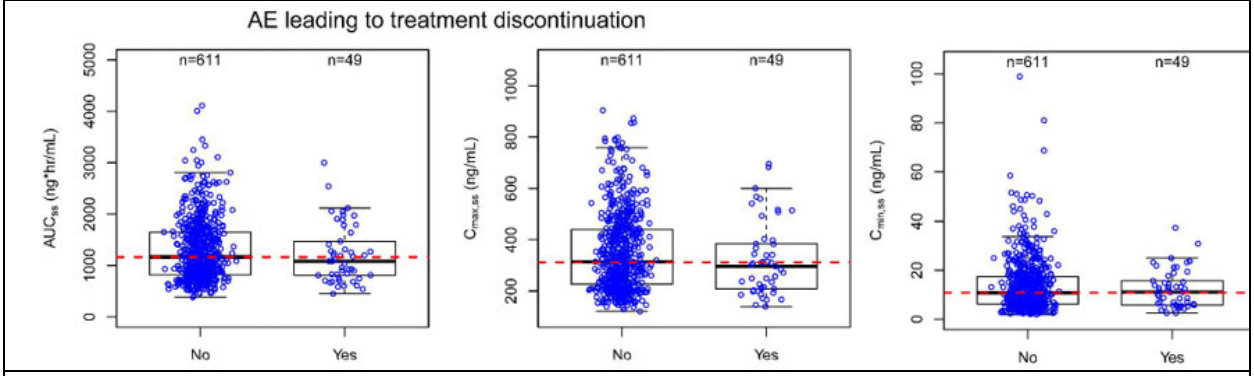
Source: Figure 25 of Applicant's Exposure-Response Report

Figure 25: ER Relationship for Grade ≥ 3 Infections/Infestations



Source: Figure 23 of Applicant's Exposure-Response Report

Figure 26: ER Relationship for AE Leading to Treatment Discontinuation



Source: Figure 33 of Applicant's Exposure-Response Report for This Supplement.

The FDA's Assessment

Exposure-response analyses from applicant appears to be acceptable. However, the current results could be limited by data from one dose level.

17.4 Additional Efficacy Data

17.4.1 Study BGB-3111-304: Additional PFS Analysis

The FDA's Assessment:
The following table provides an updated PFS analysis per investigator in Cohort 1, after an estimated median follow-up of 33.5 months. The OS data for this CCOD are discussed in Section 8.1.1.2.

Table 120: Updated PFS per Investigator (ITT) in Cohort 1 Based on CCOD of March 07, 2022

Progression-Free Survival	Zanubrutinib (N=241)	BR (N=238)
Events, n (%)	37 (15.4)	86 (36.1)
Progressive disease, n (%)	21 (8.7)	69 (29.0)
Death, n (%)	16 (6.6)	17 (7.1)
Censored, n (%)	204 (84.6)	152 (63.9)
Hazard Ratio (95% CI)	0.33 (0.22, 0.48)	
1-sided p-value*	< 0.0001	
Median PFS (95% CI), months	NE (NE, NE)	
PFS rate at 2 years	89.0 (84.3, 92.4)	78.3 (72.1, 83.3)

*nominal p-value
Source: Applicant's analysis received May 23, 2022

17.4.2 Study BGB-3111-304: Additional OS Analyses

The FDA's Assessment:
FDA requested additional simulated OS results, with different data cut-off dates, for Study BGB-3111-304. Per the Applicant's response, the simulation study with follow-up until October 2025 suggested that, when the true HR=1 or < 1, the probability of the point estimate exceeding 1 is < 42%. This simulation helped to inform the milestone dates for the PMR involving longer-term safety and OS follow-up described in Section 12.

Table 121: Summary of Simulated OS Results, with Different Data Cut-Off Dates in Study BGB-3111-304

DCO Date	31 October 2023	31 October 2024	31 October 2025	31 OCT 2032
	Probability of Upper Bound / Point Estimate Exceeding 1			
HR=1.1	99.8% / 49.3%	99.5% / 53.2%	99.6% / 57%	99.5% / 66.8%
HR=1.0	99.4% / 39.1%	98.9% / 41.4%	98.7% / 41.9%	98.2% / 48.6%
HR=0.9	98.7% / 29.8%	97.4% / 30.1%	96.6% / 29.5%	94.3% / 29.1%
HR=0.8	97.9% / 21.7%	95.3% / 19.7%	93.0% / 18.0%	85.8% / 14.0%
	Probability of Upper Bound / Point Estimate Exceeding 1.1			
HR=1.1	98% / 26.1%	96.9% / 28.8%	96.2% / 29.4%	95.5% / 32.4%
HR=1.0	96.5% / 18.5%	94.4% / 19.1%	92.5% / 18.8%	88.9% / 17.4%
HR=0.9	93.6% / 12.4%	90.0% / 11.5%	86.8% / 11.1%	76.0% / 7.8%
HR=0.8	91.2% / 7.6%	84.1% / 6.4%	78.2% / 5.4%	57.2% / 2.6%
	Probability of Upper Bound / Point Estimate Exceeding 1.2			
HR=1.1	92.2% / 11.4%	89.2% / 12.2%	87.7% / 12.2%	80.7% / 10.4%
HR=1.0	88.8% / 7.0%	83.4% / 6.7%	79.4% / 6.5%	65.1% / 4.0%
HR=0.9	83.1% / 4.0%	75.0% / 3.7%	68.3% / 3.0%	45.8% / 1.2%
HR=0.8	77.8% / 2.2%	65.5% / 1.7%	55.5% / 1.1%	26.7% / 0.3%
	Probability of Upper Bound / Point Estimate Exceeding 1.3			
HR=1.1	81.2% / 4.0%	75.7% / 4.6%	71.7% / 4.1%	54.3% / 2.3%
HR=1.0	75.0% / 2.0%	66.1% / 1.9%	59.5% / 1.9%	36.2% / 0.6%
HR=0.9	67.1% / 0.9%	55.2% / 1.0%	46.7% / 0.7%	19.7% / 0.2%
HR=0.8	58.1% / 0.6%	43.5% / 0.4%	32.6% / 0.3%	8.6% / 0.03%

Source: Applicant's IR dated June 3, 2022 and received June 10, 2022

17.4.3 Efficacy Summary: Studies BGB-3111-304 and BGB-3111-305

The FDA's Assessment:

Table 122: Summary of PFS and ORR Results in Studies BGB-3111-304 and BGB-3111-305

	BGB-3111-304 (Treatment-Naïve CLL/SLL)			BGB-3111-305 (Relapsed or Refractory CLL/SLL)	
	Zanubrutinib Arm A N = 241	**Bendamustine + Rituximab Arm B N = 238**	**Zanubrutinib del(17p)+ N = 110**	**Zanubrutinib Arm A N = 327**	**Ibrutinib Arm B N = 325**
Progression Free Survival	**Primary Endpoint**		Exploratory	CCOD Dec 1, 2021 (secondary endpoint, descriptive analysis)	
PFS events	**36 (15%)**	**71 (30%)**	17 (16%)	60 (18.3%)	87
Median PFS (95% CI)	**NE (NE, NE)**	**33.7 (28.1, NE)**	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Hazard Ratio	**0.42**		--	0.61	
	95% CI (0.28, 0.63)			95% CI (0.44, 0.86)	
	P value < 0.0001			P value 0.0264	
Median follow-up for PFS (mo)	25.0		28 mo	22	
	Secondary Endpoint		**Primary Endpoint**	**Primary Endpoint**	
Overall Response Rate	225 (93%)	203 (85%)	**97 (88)**	**263 (80%)**	**237 (73%)**
95% CI	89,96	80,90	**(81, 94)**	**76,85**	**68,78**
				Response Ratio 1.10 (95% CI 1.01, 1.20) P 0.0264	
Complete Response (CR)	16 (7)	36 (15)	**7 (6)**	13 (4)	8 (2.5)
Nodular Partial Response (nPR)	3 (1.2)	14 (6)	**2 (1.8)**	1 (0.5)	0 (0.0)
Partial Response (PR)	206 (85)	153 (64)	**88 (80.0)**	249(76)	229 (70)
Median DOR (95% CI)			**NE (NE, NE)**	NE (NE, NE)	NE (NE, NE)
Median follow-up for DOR (mo)			**25.1 mo**	14.1	

Source: FDA summary

17.5 Additional Safety Data

17.5.1 Cardiac Arrhythmias

USUBJID	Abbreviated Narrative
BGB-3111-206-(b) (6)	66 year old with R/R MCL treated in China died on study day 56, 2 days after the last dose of zanubrutinib was taken. The patient had a history of a recent hospitalization for a UTI and new fevers, thrombocytopenia and neutropenia. The patient was instructed to go to hospital but did not and died at home due to unknown causes, suspected infection based on the history. No autopsy was performed.
BGB-3111-206-(b) (6)	61 year old with R/R MCL who died on study day 300, 20 days after discontinuing zanubrutinib for thrombocytopenia. The patient died at home after being discharged after treatment for pneumonia and anemia. No specific cause of death was reported and no additional information was available.
BGB-3111-210-(b) (6)	60 year old male with R/R WM who died on study day 98, 30 days after taking the last dose of zanubrutinib. The patient was recently diagnosed with a new pulmonary mass after discontinuing zanubrutinib for PD. The patient also was diagnosed with a recent upper gastrointestinal hemorrhage possibly contributing to death according to the investigator.
BGB-3111-305-(b) (6)	89 year old female with CLL who died on study day 469, 5 days after stopping zanubrutinib. The patient died at home while sleeping. No other information was available and no autopsy was performed.
BGB-3111-AU-003-(b) (6)	87 year old male with R/R DLBCL who died on study day 221, 25 days after stopping zanubrutinib per investigator choice. The patient was hospitalized on day 216 for grade 3 fatigue and then released, and subsequently died at home. No information was available and no autopsy was performed.

Table 123: Summary of Ventricular Arrhythmias with Fatal Outcomes in the ISS (N=1550) population

USUBJID	Brief Narrative	Reviewer Assessment
BGB-3111-302-(b) (6)	74 year old male with Waldenström macroglobulinemia who was treated with zanubrutinib 160mg twice day on study BGB-3111-302 who had a grade 5 cardiac arrest (HLT ventricular arrhythmia and cardiac arrest) on study day 889. Previously, the patient had developed the grade 2 peripheral edema on day 814 which worsened to grade 3 peripheral edema requiring hospitalization on study day 815. The peripheral edema resolved with sequelae on day 825 and the patient was discharged. On study day 883 the patient was hospitalized for Grade 3 atrial fibrillation and grade 3 peripheral edema. Zanubrutinib was held at that time. He received medical management for the atrial fibrillation and while hospitalized was exposed to another patient with COVID -19 (days 886-887). Initially the patient tested negative for COVID-19, however on day 888, he developed cough and mild hypoxia and tested positive for COVID-19 on study day 889. Chest Xray at that time had showed bilateral pleural effusions with cardiomegaly. Fatal AE: On the same day (SD 889) was found unconscious on the floor and resuscitation was unsuccessful. No other details were provided.	Although COVID-19 is a confounding factor in this grade 5 event of cardiac arrest, this patient had recently (2 months prior) been diagnosed with new pulmonary edema and subsequently atrial fibrillation requiring medical management. At the time of his sudden death, he was reported to have mild cough and hypoxia due to COVID-19. Given that per the report that this patient had mild COVID symptoms at time of the event and the recent history of other symptoms consistent with cardiac toxicity (pulmonary edema and atrial fibrillation), it is possible that zanubrutinib contributed to cardiac toxicity and the event of cardiac arrest. The reviewer considers this event possibly related to zanubrutinib cardiac toxicity.

USUBJID	Brief Narrative	Reviewer Assessment
BGB-3111-304-(b) (6):	This was a 78 year old male who was treated on cohort 2 (17pdel) of study BGB-311-304 and who had a grade 5 pulseless electrical activity on study day 773. History: The patient had previously been diagnosed with grade 3 atrial fibrillation on day 276, during a hospitalization which was complicated by grade 4 sepsis and grade 3 intrabdominal hematoma. The patients resumed zanubrutinib at a reduced dose (80mg) on day 312 after resolution and medical management of the atrial fibrillation and abdominal infections. The patient developed grade 3 pneumonia which resulting in zanubrutinib interruption which was restarted on day 541. Fatal AE: Preferred Term: Pulseless electrical activity. On day 723 the patient presented to the ER with severe chest and back pain. The last zanubrutinib dose was one day prior CT scan showed aortic dissection and pericardial tamponade. EKG showed atrial fibrillation with non-specific ST-T wave changes. The patient had a pericardial drain placed, and was noted to have severely reduced left ventricular systolic function (EF 15%), persistent arrhythmias were associated with ventricular dyssynchrony. The patient underwent emergent pericardiocentesis, and suffered pulseless electrical activity, cardiac activity was briefly restored but deteriorated to ventricular fibrillation twice without durable recovery. Resuscitation was stopped and the patient died.	Reviewer assessment: This patient died after suffering aortic dissection. Although this patient had a history of atrial fibrillation that had developed while receiving zanubrutinib, the patient had continued zanubrutinib therapy at a reduced dose for over one year after medical management. The patients cardiac arrest, preceded by ventricular arrhythmias, based on the narrative was in the context of an acute aortic dissection with pericardial tamponade. While certain factors that are associated with zanubrutinib (bleeding and hypertension) may have contributed to the event of aortic dissection, it is not conclusive that the ventricular arrhythmia was primarily associated with zanubrutinib given the timing of the event and alternative contributing factors.
BGB-3111-304-(b) (6):	This was a 73 year old male with CLL treated with zanubrutinib 160mg twice daily on study BGB-3111-304 cohort 1. He was treated for grade 3 pneumonia on day 190 requiring interruption of zanubrutinib therapy, zanubrutinib 160mg twice daily was resumed on day 195. On day 620, he was evaluated in the	Reviewer assessment: This patient had a diagnosis of COVID-19 and was symptomatic with worsening COVID symptoms indication pulmonary deterioration and collapse associated with worsening

USUBJID	Brief Narrative	Reviewer Assessment
	emergency department for fever and tested positive for COVID-19. Chest X-ray was negative, he was treated with doxycycline and discharged the same day. He continued to receive zanubrutinib. Fatal AE: On day 624, he woke at home with dyspnea, pallor and cyanosis. His family contacted emergency services, the patient collapsed, and resuscitation was attempted but was unsuccessful. The patient died soon after entering the emergency room.	hypoxia on the day of death. This event appears related to COVID-19 and there is no indication of a primarily cardiac event or cardiac arrhythmia as the primary cause of the patient's death.

APPEARS THIS WAY ON ORIGINAL

17.5.1 FDA Grouping of Preferred Terms for Safety Analysis

The FDA's Assessment:

The following grouping of terms was adopted for the primary safety analyses for SEQUOIA and ASPEN studies as well as the FDA integrated safety analysis (N = 1550) performed subsequently using ISS datasets. Underlined terms were added upon review of the ISS.

Table 124: FDA Grouping of Preferred Terms for Primary Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort	
Anemia	All PTs containing "anemia", RBC count decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias"	
Cardiac failure	All PTs containing "cardiac failure", Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cardiopulmonary failure Added with ISS: Cardiogenic shock, Ischemic cardiomyopathy	ISS: Cardiomegaly, Hypertrophic cardiomyopathy, Ejection fraction decreased
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic	Enteritis ISS: colitis ischemic, infectious colitis (e.g. C difficile)
Cough	All PTs containing "Cough"	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Post procedural diarrhea
Colitis	All PTs containing "colitis"	
COVID-19	COVID-19, COVID-19 pneumonia	
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnea	All PTs containing "Dyspnea"	

FDA Grouped PT	Included in Grouping	Not Included
Edema	Edema, Generalized edema, Face edema, Swelling face, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion	Edema blister, Localized sites of edema (e.g. Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye swelling) With ISS: Angioedema, Gravitational edema, Soft tissue swelling
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enteritis	Gastroenteritis radiation, Gastritis, Duodenitis
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing "headache", Migraine With ISS: Head discomfort	
Hemorrhage	All PTs containing "hemorrhage", "hemorrhagic", or "hematoma", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis ISS: Blood urine present, Extravasation blood, Hematospermia, Hematotympanum, Scrotal Hematocoele	Petechiae, Purpura, FDA's grouping for "Bruising"
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy

FDA Grouped PT	Included in Grouping	Not Included
Herpesvirus infection	High-level group term, "Herpes viral infection"	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased. ISS: hypertensive crisis, Malignant hypertension	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis [a]	Leukocytosis, White blood cell count increase	
Lower respiratory tract infection	All PTs containing "bronchitis" or "lower respiratory tract infection", Bronchiolitis, Tracheitis, Lung infection. ISS: Infective exacerbation of bronchiectasis	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain, Bone pain	Arthralgia, Musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction	Angina pectoris
Nausea	Nausea, Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	ISS: Neuroendocrine carcinoma of the skin
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation Included AEs of COVID-19 pneumonia which were also included in the COVID-19 grouping.	Lung infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease	
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Erythema, Erythema multiforme, Generalized erythema, Palmoplantar Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, ISS: acute febrile neutrophilic dermatosis	All PTs containing "Eczema", Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis, contact dermatitis, stasis dermatitis ISS: Erythema nodosum, Erythema annulare, Dermatitis infected

FDA Grouped PT	Included in Grouping	Not Included
Renal insufficiency	All PTs containing "renal failure" or "nephropathy", Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease. ISS: Renal injury	
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection, influenza, Haemophilus infection), Influenza like illness, Sinobronchitis [b]	Upper respiratory tract infection, Lower respiratory tract infection [b]
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g. urosepsis), Septic shock *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection, Human rhinovirus test positive	Rhinitis allergic ISS: Allergic sinusitis, Reflux laryngitis, Epiglossitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", Pyelonephritis, Kidney infection	Cystitis non infective cystitis
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest"	

Source: FDA analysis

[a] Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, lymphopenia = lymphopenia + lymphocyte count decreased

[b] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

17.5.2 Laboratory Data from the ISS Safety Pool

The FDA's Assessment:

Table 125: Summary of Hematologic Abnormalities in the ISS (N=1550) Safety Pool

Laboratory Value	All Grades (%)*		Grade 3 and 4 (%)*		Grade 4 (%)*	
Neutrophils decreased	620	46.8%	270	20.4%	126	9.5%
Hemoglobin decreased	449	33.9%	77	5.8%	0	0.0%
Platelets decreased	412	31.1%	90	6.8%	30	2.3%
Leukocytes decreased	325	24.5%	58	4.4%	9	0.7%
Leukocytes increased	191	14.4%	191	14.4%	0	0.0%
Lymphocytes decreased	265	20.0%	77	5.8%	13	1.0%
Lymphocytes increased	308	23.2%	188	14.2%	0	0.0%

Source: FDA reviewer analysis from Applicant's updated ADLB dataset submitted 1-5-2022
*Denominator varied between 1325 and 1326 based on the number of patients with baseline and post-baseline assessments.

APPEARS THIS WAY ON ORIGINAL

Table 126: Summary of Laboratory Chemistry Abnormalities in the ISS (N=1550) Safety Pool

Laboratory Value	All Grades n (%)		Grade 3 and 4 n (%)		Grade 4 n (%)	
Alkaline Phosphatase increased	211	15.9%	5	0.4%	0	0.0%
ALT increased	286	21.6%	15	1.1%	4	0.3%
AST increased	187	14.1%	13	1.0%	1	0.1%
Creatinine increased	315	23.7%	10	0.8%	4	0.3%
Hemoglobin decreased	449	33.9%	77	5.8%	0	0.0%
Hyperbilirubinemia	214	16.1%	7	0.5%	2	0.2%
Hypercalcemia	75	5.7%	7	0.5%	5	0.4%
Hyperglycemia	690	52.6%	60	4.6%	2	0.2%
Hyperkalemia	135	10.2%	10	0.8%	4	0.3%
Hypermagnesemia	173	13.1%	9	0.7%	0	0.0%
Hypernatremia	139	10.5%	1	0.1%	0	0.0%
Hyperuricemia	125	23.0%	16	2.9%	16	2.9%
Hypoalbuminemia	187	14.1%	5	0.4%	0	0.0%
Hypocalcemia	269	20.3%	10	0.8%	6	0.5%
Hypoglycemia	136	10.4%	6	0.5%	3	0.2%
Hypokalemia	195	14.7%	23	1.7%	2	0.2%
Hypomagnesemia	97	7.3%	1	0.1%	1	0.1%
Hyponatremia	194	14.6%	38	2.9%	4	0.3%
Hypophosphatemia	294	22.9%	38	3.0%	1	0.1%

Source: FDA reviewer analysis from Applicant's updated ADLB dataset submitted 1-5-2022
*Denominator varied between 544 and 1326 based on the number of patients with baseline and post-baseline assessments.

17.5.3 Safety Narratives

The FDA's Assessment

Narratives are provided for fatal AEs of unknown cause and for fatal ventricular arrhythmias in the zanubrutinib ISS population.

Table 127: Summary of Fatal AEs with Unknown Cause of Death in the Zanubrutinib ISS Population (N = 1550)

USUBJID	Abbreviated Narrative
BGB-3111-206-(b) (6)	66 year old with R/R MCL treated in China died on study day 56, 2 days after the last dose of zanubrutinib was taken. The patient had a history of a recent hospitalization for a UTI and new fevers, thrombocytopenia and neutropenia. The patient was instructed to go to hospital but did not and died at home due to unknown causes, suspected infection based on the history. No autopsy was performed.
BGB-3111-206-(b) (6)	61 year old with R/R MCL who died on study day 300, 20 days after discontinuing zanubrutinib for thrombocytopenia. The patient died at home after being discharged after treatment for pneumonia and anemia. No specific cause of death was reported and no additional information was available.
BGB-3111-210-(b) (6)	60 year old male with R/R WM who died on study day 98, 30 days after taking the last dose of zanubrutinib. The patient was recently diagnosed with a new pulmonary mass after discontinuing zanubrutinib for PD. The patient also was diagnosed with a recent upper gastrointestinal hemorrhage possibly contributing to death according to the investigator.
BGB-3111-305-(b) (6)	89 year old female with CLL who died on study day 469, 5 days after stopping zanubrutinib. The patient died at home while sleeping. No other information was available and no autopsy was performed.
BGB-3111-AU-003-(b) (6)	87 year old male with R/R DLBCL who died on study day 221, 25 days after stopping zanubrutinib per investigator choice. The patient was hospitalized on day 216 for grade 3 fatigue and then released, and subsequently died at home. No information was available and no autopsy was performed.

Source: FDA analysis

Table 128: Summary of Ventricular Arrhythmias with Fatal Outcomes in the ISS Population (N=1550)

BGB-3111-302-[redacted] (b) (6): 74 year old male with Waldenström macroglobulinemia who was treated with zanubrutinib 160mg twice day on study BGB-3111-302 who had a grade 5 cardiac arrest (HLT ventricular arrhythmia and cardiac arrest) on study day 889. Previously, the patient had developed the grade 2 peripheral edema on day 814 which worsened to grade 3 peripheral edema requiring hospitalization on study day 815. The peripheral edema resolved with sequelae on day 825 and the patient was discharged. On study day 883 the patient was hospitalized for Grade 3 atrial fibrillation and grade 3 peripheral edema. Zanubrutinib was held at that time. He received medical management for the atrial fibrillation and while hospitalized was exposed to another patient with COVID -19 (days 886-887). Initially the patient tested negative for COVID-19, however on day 888, he developed cough and mild hypoxia and tested positive for COVID-19 on study day 889. Chest Xray at that time had showed bilateral pleural effusions with cardiomegaly. Fatal AE: On the same day the patient was found unconscious on the floor and resuscitation was unsuccessful. No other details were provided. Reviewer assessment: Although COVID-19 is a confounding factor in this grade 5 event of cardiac arrest, this patient had recently (2 months prior) been diagnosed with new pulmonary edema and subsequently atrial fibrillation requiring medical management. At the time of his sudden death, he was reported to have mild cough and hypoxia due to COVID-19. Given that per the report that this patient had mild COVID symptoms at time of the event and the recent history of other symptoms consistent with cardiac toxicity (pulmonary edema and atrial fibrillation), it is possible that zanubrutinib contributed to cardiac toxicity and the event of cardiac arrest. The reviewer considers this event possibly related to zanubrutinib cardiac toxicity.
BGB-3111-304-[redacted] (b) (6): This was a 78 year old male who was treated on cohort 2 (17pdel) of study BGB-311-304 and who had a grade 5 pulseless electrical activity on study day 773. History: The patient had previously been diagnosed with grade 3 atrial fibrillation on day 276, during a hospitalization which was complicated by grade 4 sepsis and grade 3 intrabdominal hematoma. The patients resumed zanubrutinib at a reduced dose (80mg) on day 312 after resolution and medical management of the atrial fibrillation and abdominal infections. The patient developed grade 3 pneumonia which resulting in zanubrutinib interruption which was restarted on day 541. Fatal AE: Preferred Term: Pulseless electrical activity. On day 723 the patient presented to the ER with severe chest and back pain. The last zanubrutinib dose was one day prior CT scan showed aortic dissection and pericardial tamponade. EKG showed atrial fibrillation with non-specific ST-T wave changes. The patient had a pericardial drain placed, and was noted to have severely reduced left ventricular systolic function (EF 15%), persistent arrhythmias were associated with ventricular dyssynchrony. The patient underwent emergent pericardiocentesis, and suffered pulseless electrical activity, cardiac activity was briefly restored but deteriorated to ventricular fibrillation twice without durable recovery. Resuscitation was stopped and the patient died.

Reviewer assessment: This patient died after suffering aortic dissection. Although this patient had a history of atrial fibrillation that had developed while receiving zanubrutinib, the patient had continued zanubrutinib therapy at a reduced dose for over one year after medical management. The patients cardiac arrest, preceded by ventricular arrhythmias, based on the narrative was in the context of an acute aortic dissection with pericardial tamponade. While certain factors that are associated with zanubrutinib (bleeding and hypertension) may have contributed to the event of aortic dissection, it is not conclusive that the ventricular arrhythmia was primarily associated with zanubrutinib given the timing of the event and alternative contributing factors.
BGB-3111-304-(b) (6): This was a 73 year old male with CLL treated with zanubrutinib 160mg twice daily on study BGB-3111-304 cohort 1. He was treated for grade 3 pneumonia on day 190 requiring interruption of zanubrutinib therapy, zanubrutinib 160mg twice daily was resumed on day 195. On day 620, he was evaluated in the emergency department for fever and tested positive for COVID-19. Chest X-ray was negative, he was treated with doxycycline and discharged the same day. He continued to receive zanubrutinib. Fatal AE: On day 624, he woke at home with dyspnea, pallor and cyanosis. His family contacted emergency services, the patient collapsed, and resuscitation was attempted but was unsuccessful. The patient died soon after entering the emergency room. Reviewer assessment: This patient had a diagnosis of COVID-19 and was symptomatic with worsening COVID symptoms indication pulmonary deterioration and collapse associated with worsening hypoxia on the day of death. This event appears related to COVID-19 and there is no indication of a primarily cardiac event or cardiac arrhythmia as the primary cause of the patient's death.

Source: FDA analysis

Multi-Disciplinary Review Signature Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yue Xiang, PhD	OCP/DCPI	Sections: 5, 17.3	Select one: ☑ Authored ☐ Approved
	Signature: Yue Xiang -S			
Clinical Pharmacology Team Leader	Vicky Hsu, PhD	OCP/DCPI	Sections: 5, 17.3	Select one: ☐ Authored ☑ Approved
	Signature: Wenchi Hsu -S			
Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections: 5, 17.3	Select one: ☑ Authored ☐ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2023.01.17 15:51:29 -05'00'			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 5, 17.3	Select one: ☐ Authored ☑ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S			
Statistical Reviewer	Kun Wang, PhD	OB/DBIX	Sections: 8	Select one: ☑ Authored ☐ Approved
	Signature: Kun Wang -S			
Statistical Reviewer	Mingyu Xi, PhD	OB/DBIX	Sections: 8	Select one: ☑ Authored ☐ Approved
	Signature: Mingyu Xi -S Digitally signed by Mingyu Xi -S Date: 2023.01.18 08:56:03 -05'00'			
Statistical Team Leader	Lola Lu, PhD	OB/DBIX	Sections: 8	Select one: ☑ Authored ☐ Approved
	Signature: Lola Luo -S Digitally signed by Lola Luo -S Date: 2023.01.18 09:23:46 -05'00'			

NDA 213217 S-007 Brukinsa (zanubrutinib)
Beigene USA, Inc.

Statistical Deputy Division Director	Lisa Rodriguez, PhD	OB/DBIX	Sections: 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S Date: 2023.01.13 16:35:57 -05'00'			
Clinical Reviewer	Margret Merino, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Margret Merino -S Digitally signed by Margret Merino -S Date: 2023.01.13 23:26:07 -05'00'			
Clinical Team Leader	Yvette Kasamon, MD	OOD/DHM2	Sections: All	**Select one:** ☑ Authored ☐ Approved
	Signature: Yvette L. Kasamon -S Digitally signed by Yvette L. Kasamon -S Date: 2023.01.13 15:05:54 -05'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ☑ Authored ☐ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2023.01.10 13:41:01 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Yvette Kasamon, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Yvette L. Kasamon -S Digitally signed by Yvette L. Kasamon -S Date: 2023.01.13 15:06:50 -05'00'			
Division Director (Statistics)	Mark Levenson, PhD	OB/DBIX	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Mark S. Levenson -S Digitally signed by Mark S. Levenson -S Date: 2023.01.18 08:52:35 -05'00'			
Division Director (OCP)	Brian Booth, PhD	OCP/DCPI	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S Date: 2023.01.18 13:04:15 -05'00'			
Division Director (Clinical)	Nicole Gormley, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicole J. Gormley -S Digitally signed by Nicole J. Gormley -S Date: 2023.01.18 11:04:22 -05'00'			

DCPI = Division of Cancer Pharmacology I
DPM = Division of Pharmacometrics
OB = Office of Biostatistics
DBIX = Division of Biometrics IX
OOD = Office of Oncologic Diseases
DHM2 = Division of Hematologic Malignancies II

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/

MARGRET E MERINO
01/19/2023 09:08:49 AM

NICOLE J GORMLEY
01/19/2023 01:35:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s007

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 20, 2022
To:	Denise Felluca, PharmD, MBA Regulatory Health Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Valerie Guerrier, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BRUKINSA (zanubrutinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 213217
Supplement Number:	S-007
Applicant:	BeiGene USA, Inc.

1 INTRODUCTION

On December 20, 2021, BeiGene USA, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 213217/S-007 for BRUKINSA (zanubrutinib) capsules. With this supplement, the Applicant proposes a new indication for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies II (DHM2) on January 24, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRUKINSA (zanubrutinib) capsules.

2 MATERIAL REVIEWED

- Draft BRUKINSA (zanubrutinib) capsules PPI received on December 20, 2021, and received by DMPP and OPDP on December 12, 2022.
- Draft BRUKINSA (zanubrutinib) capsules Prescribing Information (PI) received on December 20, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 12, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/

JESSICA M CHUNG
12/20/2022 11:37:04 AM

VALERIE GUERRIER
12/20/2022 11:44:34 AM

RUTH I MAYROSH
12/20/2022 11:49:02 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 20, 2022

To: Denise Felluca, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Elizabeth Everhart, Associate Director for Labeling, DMH2

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRUKINSA® (zanubrutinib) capsules, for oral use

NDA: 213217/S-007

Background:

In response to DHM2's consult request dated January 24, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement 007 for BRUKINSA® (zanubrutinib) capsules, for oral use. This supplement provides for a new indication for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 15, 2022, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on December 20, 2022.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

35 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/

VALERIE GUERRIER
12/20/2022 05:14:47 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 27, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 213217/S-007
Product Name, Dosage Form, and Strength:	Brukinsa (zanubrutinib) capsules, 80 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BeiGene USA, Inc.
FDA Received Date:	December 20, 2021 and February 24, 2022
OSE RCM #:	2022-156
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

BeiGene USA, Inc. submitted supplemental NDA 213217/S-007 for Brukinsa (zanubrutinib) capsules to update the Prescribing Information (PI) to support the addition of a new indication for Brukinsa for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). We reviewed the proposed Brukinsa Prescribing Information and Patient Information for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Brukinsa is a kinase inhibitor that was approved on November 14, 2019.

Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, waldenström's macroglobulinemia (WM), and relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

It is available as 80 mg capsules in a 120 count bottle.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

BeiGene USA, Inc. is proposing the addition of a new indication for Brukinsa for the treatment of adult patients with CLL/SLL. We performed a risk assessment of the proposed PI and Patient Information to determine if they are acceptable from a medication error perspective. We note

the review team plans to recommend BieGene, USA to include dosage adjustment of Brukinsa when co-administered with moderate CYP3A inducers (e.g. 320 mg twice daily or 640 mg once daily) based upon drug-drug interaction study results. Brukinsa is currently available as 80 mg capsules. The dosage of Brukinsa when co-administered with moderate CYP3A inducers would require 4 capsules twice daily or 8 capsules once daily. We find that requirement of 4 to 8 capsules to achieve the dosage adjustment described above enhances the pill burden and medication error risk for patients. We recommend that the review team consider asking the Applicant to develop additional strengths post-marketing.

We find the proposed PI and Patient Information acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We note the review team plans to recommend BieGene, USA to include dosage adjustment in the PI of Brukinsa when co-administered with moderate CYP3A inducers (e.g. 320 mg twice daily or 640 mg once daily), which would require 4 capsules twice daily or 8 capsules once daily. The requirement of 4 to 8 capsules to achieve the dosage adjustment of 320 mg twice daily or 640 mg once daily enhances the pill burden and medication error risk for patients. We recommend that the review team consider requesting the Applicant develop additional strengths of Brukinsa post-marketing to minimize the risk of medication errors.

We find the proposed PI and Patient Information acceptable from a medication error perspective and have no additional recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brukinsa received on February 24, 2022 from BeiGene USA, Inc..

Table 2. Relevant Product Information for Brukinsa	
Initial Approval Date	November 14, 2019
Active Ingredient	zanubrutinib
Indication	• For the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. • Waldenstrom's Macroglobulinemia (WM) • Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. • *Chronic lymphocytic leukemia (CLL) or Small lymphocytic lymphoma (SLL). (proposed)*
Route of Administration	Oral
Dosage Form	capsules
Strength	80 mg
Dose and Frequency	The recommended dose is 160 mg orally twice daily or 320 mg orally once daily.
How Supplied	Bottle with a child-resistant cap containing 120 capsules
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 29, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Brukinsa. Our search identified three previous reviews[a,b,c] , and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[a] Garrison, N. Label and Labeling Review for Brukinsa (zanubrutinib) (NDA 213217). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 04. RCM No.: 2019-1364.

[b] Mehta, H. Label and Labeling Review for Brukinsa (zanubrutinib) (NDA 213217). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 18. RCM No.: 2019-1364-1.

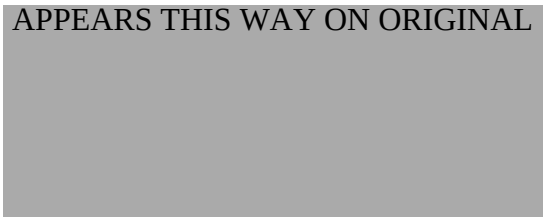
[c] Iverson, N. Label and Labeling Review for Brukinsa (zanubrutinib) (NDA 213217/S-004 and S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 02. RCM No.: 2021-578.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Brukinsa labels and labeling submitted by BeiGene USA, Inc..

- Prescribing Information (Image not shown) received on February 24, 2022, available from \\CDSESUB1\evsprod\nda213217\0118\m1\us\redlined-uspi.docx.
- Patient Information received on January 24, 2022, available from \\CDSESUB1\evsprod\nda213217\0110\m1\us\draft-labeling-text-ppi-redline.docx.



[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE F IVERSON
09/27/2022 03:26:38 PM

HINA S MEHTA
09/28/2022 09:28:37 AM

CLINICAL INSPECTION SUMMARY

Date	May 17, 2022
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/Division Director Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Margret Merino, M.D., Medical Officer Yvette Kasamon, M.D., Ph.D., Medical Team Leader Nicole Gormley, M.D., Division Director Denise Felluca, Senior Regulatory Health Project Manager Division of Hematologic Malignancies II Office of Oncology Drugs (OOD)
NDA	NDA 213217 S-007
Applicant	BeiGene USA, Inc.
Drug	zanubrutinib [Brukinsa®]
NME	No
Division Classification	Bruton's tyrosine kinase (BTK) inhibitor
Proposed Indication	Treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.
Review Type	Priority
Consultation Request Date	February 18, 2022
Summary Goal Date	July 1, 2022
PDUFA Date	October 22, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study BGB-3111-304 (SEQUOIA) and Study BGB-3111-305 were submitted to the Agency in support of a New Drug Application supplement for zanubrutinib, proposed as treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). A single clinical investigator (Mazyar Shadman, M.D.) and the sponsor, BeiGene USA, Inc., were inspected in support of this supplemental NDA 213217 S-007 and covering Study Protocol BGB-3111-304 (SEQUOIA) and Study Protocol BGB-3111-305.

The study appears to have been conducted adequately and the study data derived from the above clinical investigator site appear reliable. BeiGene USA, Inc.'s oversight of the above studies as the sponsor appears adequate. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Zanubrutinib [BGB-3111, BRUKINSA®] is classified as a Bruton's tyrosine kinase (BTK) inhibitor. The original NDA 213217 under 505(b)(1) for zanubrutinib was submitted on June 27, 2019, for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL) and approved on November 14, 2019.

Two additional clinical studies were submitted in support of the current applicant's NDA supplement, proposed for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Study BGB-3111-304

Study BGB-3111-304 (SEQUOIA) was a Phase 3, open-label randomized study of zanubrutinib versus bendamustine plus rituximab (B+R) in patients with previously untreated chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL).

For the study populations who were treatment naive, there were two cohorts studied:
Cohort 1 (randomized 1:1 to Treatment arm A or B): Patients without 17p deletion.
Cohort 2 (non-randomized to Treatment arm C): Patients with 17p deletion per central testing.

The treatment arms for Cohort 1 were as follows:
Arm A: Zanubrutinib 160mg twice daily until disease progression or unacceptable toxicity.
Arm B: Bendamustine 90mg/m^2/day on the first 2 days of each cycle for 6 cycles.
Rituximab IV 375mg/m^2 for Cycle 1 and 500mg/m^2 Cycles 2-6

Arm C for Cohort 2 (non-random assignment): Zanubrutinib 160mg twice daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint for Cohort 1 was progression free survival (PFS) based on independent central review. Response was assessed by independent review committee in a blinded manner and was also assessed by investigator. Response parameters included assessment of lymphadenopathy, hepatomegaly, splenomegaly, blood lymphocyte count, bone marrow aspirate/biopsy, platelet count, hemoglobin level, and neutrophil count. The primary efficacy endpoint for Cohort 2 was Objective Response Rate (ORR) per Independent Review Committee.

The study was conducted at 153 study centers in 14 countries. The calendar date of first patient randomization was on October 31, 2017. The data cutoff was May 7, 2021. The study is currently ongoing.

In Cohort 1, of the 479 patients were randomized; 241 patients were randomized to the zanubrutinib arm, and 238 patients were randomized to the B+R (bendamustine and rituximab) arm. In Cohort 2, 111 patients were enrolled to receive zanubrutinib.

Study BGB-3111-305

Study BGB-3111-305 was an ongoing, Phase 3, randomized study of zanubrutinib compared with ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Patients with CLL/SLL who have relapsed or refractory disease after at least 1 prior systemic therapy for CLL/SLL, received either treatment:

Zanubrutinib: 160mg orally twice daily until disease progression or unacceptable toxicity.
Ibrutinib: 420mg orally once daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall response rate determined by investigator assessment. The chronic lymphocytic leukemia efficacy endpoint was determined by the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria (Hallek et al 2008) with addition of treatment-related lymphocytosis (Cheson et al 2012). The small cell lymphoma efficacy endpoint was determined by the Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) using CT-based response.

The study was conducted at 117 study centers in 15 countries. The date of first patient randomization was on November 1, 2018. The data cutoff date for the submission was on December 31, 2020. The study is ongoing. Of the 652 patients were randomized; 327 patients were randomized to the zanubrutinib arm, and 325 patients were randomized to the ibrutinib arm.

III. RESULTS (by site)

1. Mazyar Shadman, M.D.

1100 Fairview Avenue N
Seattle, WA 98109

Inspection dates: March 28 to April 5, 2022

For Study BGB-3111-304, 27 subjects were screened, and 19 subjects were enrolled. Of the enrolled study subjects who participated in the treatment phase, five subjects discontinued treatment due to the following reasons: neutropenia, aortic dissection, unspecified progressive disease, respiratory infection and failure, and intracranial hemorrhage. Source records were reviewed for 15 enrolled study subjects.

For Study BGB-3111-305, 9 patients were screened and enrolled. Six study patients received drug treatment. Three subjects discontinued due to disease progression, adverse event or both. Source records were reviewed for 9 enrolled study patients.

Study administrative files were reviewed and evaluated including FDA 1572 (Statement of Investigator) completion, financial disclosure forms, IRB approvals, clinical site training documentation, and monitoring reports. The sponsor had pre-designated vendors for central

laboratory analysis ([redacted]), clinical pathology, biomarkers ([redacted]), central imaging ([redacted] study management and monitoring.

The site audit involved review of the electronic medical record printouts, electronic data capture for study subject enrollment per inclusion and exclusion criteria, informed consent, treatment assignment, adverse events reporting, concomitant medications, vitals, and study drug accountability and disposition.

Source records for the enrolled study patients were examined. The primary efficacy data were verified against the data line listings, including the investigator's response assessment and independent review committee as part of the endpoint data. Adverse and serious adverse event were assessed for reporting adequacy. No discrepancies were noted.

2. BeiGene USA, Inc.

2955 Campus Drive, Suite 200
San Mateo, CA 94403

Inspection dates: April 4 to 8, 2022

The inspection assessed the application sponsor's oversight responsibilities for Study BGB-3111-304 (SEQUOIA) and Study BGB-3111-305.

The inspection included review of the trial master files, organizational charts, standard operating procedures, operational manuals, contracts, transfers of obligations, site monitoring, case report forms, handling of adverse events, data collection, and how the sponsor brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, monitoring procedures and frequency, and other monitoring-related activities, test articles, test accountability records.

Oversight activities and monitoring in 10 clinical study sites for Study BGB-3111-304 (Sites 146, 165, 185, 186, 137) and Study BGB-3111-305 (Sites 1059, 1111, 1131, 1145, 1182) were reviewed during this sponsor audit.

The FDA inspection found that sponsor provided adequate oversight, monitored these study sites and performed its responsibilities according to the FDA regulatory requirements. No evidence of comprehensive under-reporting of adverse events to the Agency was found.

In general, the oversight and monitoring of Study BGB-3111-304 (SEQUOIA) and Study BGB-3111-305 appeared adequate.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/

ANTHONY J ORENCIA
05/20/2022 11:22:29 AM

MIN LU
05/20/2022 11:24:49 AM

KASSA AYALEW
05/20/2022 11:46:02 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s007

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 125326

MEETING MINUTES

BeiGene USA, Inc.
Attention: Tania Bekerman, BSc
Associate Director, Regulatory Affairs
2955 Campus Drive, Suite 200
San Mateo, CA 94403

Dear Ms. Bekerman:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for zanubrutinib.

We also refer to the teleconference between representatives of your firm and the FDA on September 17, 2021. The purpose of the Pre-sNDA meeting was to discuss the data from the pivotal studies BGB-3111-304 (SEQUOIA) in treatment-naïve (T/N) CLL/SLL patients, and BGB-3111-305 (ALPINE) in relapsed/refractory (R/R) CLL/SLL patients.

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

If you have any questions, please contact Denise Felluca, Regulatory Project Manager, via email at denise.felluca@fda.hhs.gov or at 301-796-4574.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting 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.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	September 17, 2021 10:00 AM to 11:00 AM ET
Meeting Location:	Teleconference
Application Number:	IND 126325
Product Name	zanubrutinib
Indication:	Treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
Sponsor Name:	BeiGene USA, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Yvette Kasamon, MD
Meeting Recorder:	Denise Felluca, PharmD, MBA

FDA ATTENDEES

Oncology Center of Excellence
Marc Theoret, MD, Deputy Office Director

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, *Director*
Yvette Kasamon, MD, *Clinical Team Leader*
Nicholas Richardson, DO, MPH, *Clinical Team Leader*
Bindu Kanapuru, MD, *Clinical Team Leader*
Margret Merino, MD, *Clinical Reviewer*

Office of Biostatistics/Division of Biometrics IX
Qing Xu, PhD, *Team Leader (Acting)*
Kung Wang, PhD, *Statistical Reviewer*

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Vicky Hsu, PhD, *Clinical Pharmacology Team Leader (Acting)*
Yue Xiang, PhD, *Clinical Pharmacology Reviewer*

Office of Regulatory Operations for Oncologic Diseases/Division of Regulatory Operations
Theresa Carioti, MPH, *Chief, Project Management Staff*
Denise Felluca, PharmD, MBA, *Regulatory Health Project Manager*

Office of Oncologic Diseases/Division of Safety
Shan Pradhan, MD, *Associate Director for Safety (Acting)*
Felicia Diggs, RN, BSN, MSN, *Senior Regulatory Health Project Manager*

SPONSOR ATTENDEES

Jane Huang, MD, *Chief Medical Officer, Hematology*
William Novotny, MD, *Senior VP, Clinical Development Hematology*
Aileen Cohen, MD, PhD, *VP, Clinical Development Hematology*
Alan Wu, PhD, *Executive Director, Global Statistics*
Ken Wu, PhD, *Director, Biostatistics*
Meng Zhang, PhD, *Senior Director, Global Product Safety*
Sanjeeve Bala, MD, MPH, *VP, US Regulatory Affairs*
Benny Tan, *Senior Director, Regulatory Affairs*
Himani Parikh, *Director, Regulatory Affairs*
Tania Bekerman, MSc, *Director, Regulatory Affairs*
Tony Xu, MSc, *Senior Manager, Regulatory Affairs*

1.0 BACKGROUND

BeiGene plans to submit a supplemental new drug application (sNDA) for zanubrutinib for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) using efficacy data from the randomized study BGB-3111-304 in treatment-naive CLL, with additional data in relapsed/refractory CLL/SLL from BGB-3111-305. The purpose of this meeting is to provide a summary of these data for zanubrutinib in adult patients with CLL/SLL, and to seek agreement from seek the Agency on the regulatory pathway for the approval of zanubrutinib in this patient population.

FDA sent Preliminary Comments to Beigene USA, Inc. on September 13, 2021.

2.0 DISCUSSION

Question 1: *BeiGene plans to submit a supplemental New Drug Application (sNDA) in Q4 2021 to seek approval of zanubrutinib for the treatment of adult patients with CLL/SLL. Does the Agency agree that the study design and data from the pivotal Studies BGB-3111-304 (SEQUOIA) in treatment-naïve (TN) CLL/SLL patients, and BGB-3111-305 (ALPINE) in relapsed/refractory (RR) CLL/SLL patients, can support an sNDA in the proposed indication of treatment of adult patients with CLL/SLL?*

FDA Response to Question 1: No. We note that the PFS advantage with zanubrutinib in Study BGB-3111-304 may not translate into an OS advantage and in fact, may be associated with a detriment compared to the BR arm. Although the OS data from study

BGB-3111-304 are immature and the study is not powered for OS, we consider this finding an important issue that will need to be addressed in any submission, particularly for a proposed first-line indication. We strongly recommend delaying the sNDA submission until more mature OS data are available from study BGB-3111-304, in order to inform benefit/risk.

The adequacy of the data to support the proposed sNDA and the wording of the indication statement will be review issues.

Discussion: The Sponsor presented additional overall survival (OS) data from study BGB-3111-304, stated that the KM survival curves are largely overlapping, and described possible confounding factors. The Sponsor also cited regulatory precedent in approving therapies for CLL based on PFS superiority in the absence of an OS benefit or inclusion of OS data in labeling.

The Agency reiterated concerns regarding the immature OS data from study BGB-3111-304 that may signal a survival detriment in the treatment naïve CLL population. The Agency conveyed that OS data, while immature, are still considered an important aspect of the benefit risk analysis, regardless of whether the data are included in the label.

The Agency noted that when OS findings do not appear consistent with favorable PFS findings, this may be due to a safety issue, an efficacy issue such as relapse with more resistant disease, or immaturity of the data. This is an important issue particularly for an indication in the treatment-naive setting. The Agency acknowledged that confounding issues, such as COVID and alternative therapies to include crossover, may apply, however those issues would be considered during the review.

The Agency recommended that the Sponsor wait and submit their sNDA with a more mature OS analysis, such as pre-specified in the statistical analysis plan (SAP), which would occur 5 years after the study initiation or November 2022. The current PFS analysis represents an interim analysis that occurred later than prespecified, and no further OS updates are prespecified apart from the final analysis. The Agency is open to the possibility of an additional, exploratory OS update to be added to the SAP. The timing of this update would need to be adequately justified and agreed upon prior to sNDA submission.

Question 2: *Does the Agency agree with the Sponsor's proposed content of the ISE/SCE?*

FDA Response to Question 2: This question is premature, based on the concern described in the response to Question 1. It is acceptable for the ISE to reference the SCE, provided the appropriate data can be included within the space limitations of the SCE.

Discussion: **No discussion occurred.**

Question 3: *Does the Agency agree with the Sponsor's proposed content of ISS/SCS including providing safety-only SDTM and ADAM datasets for all supportive safety studies included in the SCS?*

FDA Response to Question 3: See the response to Question 1.

The following are general recommendations for a future sNDA submission: Your proposal for the ISS and SCS appears reasonable provided that a) you include full integrated safety datasets for the ISS in module 5, and that b) the narrative portion of the ISS that references the SCS fits within the space limitations of the SCS and includes a comprehensive analysis of safety, to include AESIs across zanubrutinib clinical trials. The adequacy of the ISS would be a review issue.

Discussion: **No discussion occurred.**

Question 4: *Does the Agency agree with the Sponsor's proposal for safety narratives and CRFs?*

FDA Response to Question 4: In addition to your proposed safety narratives and CRFs, safety narratives and CRFs should be included for all SAEs within the cardiac SOC rather than only cardiac arrhythmias. Additional CRFs and/or narratives may be requested during the review.

Discussion: **No discussion occurred.**

Question 5: *The Sponsor plans to submit a safety update report following the submission of this sNDA.*

5a. *In the sNDA safety update, the Sponsor proposes to provide an additional 4 months' safety data from the zanubrutinib arms of Study BGB-3111-304 and additional 6 months safety data from the zanubrutinib arm of Study BGB-3111-305. Does the Agency agree with the Sponsor's proposal?*

FDA Response to Question 5a: See the response to Question 1. In general, a safety update report should have at least 4 months of updated data relative to the primary data cut-off.

5b. *According to 21 CFR 314.50, the Sponsor is requesting* (b) (4) [redacted]. *Does the Agency agree?*

FDA Response to Question 5b: No, [redacted] (b) (4) Provide justification for why these cannot be provided with the safety update.

Discussion: **No discussion occurred.**

ADDITIONAL COMMENTS

Clinical Pharmacology

Please see the following recommendations below regarding our general expectations for your proposed supplemental NDA submissions.

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application?
2. What is the exposure-response relationships for efficacy, safety and biomarkers in the proposed patient populations of previously untreated and relapsed/refractory CLL and SLL?
3. How do intrinsic factors (such as race, disease) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the sNDA submission:

1. Assess race and ethnicity in addition to other covariates known to affect zanubrutinib PK and PD to facilitate exposure-response analyses to inform safe and effective dosing regimens across the intended patient population that should be reflective of the ethnic and racial diversity of the US. The adequacy of the assessment, which should include a sufficient number of patients reflective of the ethnic and racial diversity of the US patient population, will be a review issue.

2. Submit bioanalytical methods and validation reports for PK data in all clinical trials.

3. 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.

4. 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.

5. Submit the following for the population pharmacokinetic analysis reports:
   - Standard model diagnostic plots
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
   - Model parameter names and units in tables.
   - Summary of the report describing the clinical application of modeling results.

   Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

6. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation
   - 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
   - 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). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)

7. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK and for exposure-response relationships.

Statistics

1. The submission should include following:
   - The data safety monitoring board (DSMB) meeting minutes/reports.
   - Documentation of any correspondence (written documents or meeting minutes) with FDA in regard to SAP Study BGB-3111-305 and BGB-3111-304.
   - All raw as well as derived variables in .xpt format. FDA strongly recommendssubmission of datasets using CDISC standards.

Discussion: **No discussion occurred regarding the additional comments.**

3.0 OTHER IMPORTANT INFORMATION

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 an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) 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 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 Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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 FDA.gov.[3]

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 Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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.

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.[6]

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.[7]

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

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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,* and the associated conformance guide, *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*.[10]

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

[10] https://www.fda.gov/media/85061/download

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[11]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[12]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted during the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster appropriate prospective use of "decentralized" aspects of clinical trials in the post-COVID era. For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the preliminary comments will be appended.

8 Pages have been Withheld in Full as CCI/TS immediately following this page.

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/

YVETTE L KASAMON
09/20/2021 09:25:08 AM