CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213217Orig1s004

Trade Name:	BRUKINSA
Generic or Proper Name:	(zanubrutinib)
Sponsor:	BeiGene USA LLC.
Approval Date:	March 22, 2021
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).

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213217Orig1s004

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)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s004

APPROVAL LETTER

NDA 213217/S-004

SUPPLEMENT APPROVAL

BeiGene, Ltd.
Attention: Tania Bekerman
Associate Director, Regulatory Affairs
2955 Campus Drive, Suite 200
San Mateo, CA 94403

Dear Ms. Bekerman:

Please refer to your supplemental new drug application (sNDA) dated December 18, 2020, received December 18, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRUKINSA (zanubrutinib) capsules.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

APPROVAL & LABELING

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.

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 Food and Drug Administration (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, 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]

[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.

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.

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.

Since Brukinsa (zanubrutinib) was approved on November 14, 2019, we have become aware through clinical trials of an increased risk of second primary malignancies in patients with Waldenström's macroglobulinemia receiving zanubrutinib. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the 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 the known serious risk of second primary malignancies.

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

4130-1 Conduct an integrated safety analysis of patients with lymphoid malignancies and Waldenström's Macroglobulinemia enrolled in clinical trials and from post-marketing reports to further characterize the risk of second primary malignancies with extended follow-up in patients receiving zanubrutinib. Submit interim reports after 2 years and 3 years containing cumulative safety updates. Include incidence rates, time to onset, predisposing factors including coexisting mutations and outcomes in the interim and final reports.

The timetable you submitted on August 27, 2021 states that you will conduct this study according to the following schedule:

Draft Analysis Protocol Submission:	03/2022
Final Analysis Protocol Submission:	09/2022
Interim Report #1 Submission:	12/2024
Interim Report #2 Submission:	12/2025
Trial Completion:	12/2026
Final Report Submission:	06/2027

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 the protocol(s) to your IND 125326, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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

[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.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4130-2 Conduct a study to further characterize the clinical benefit and safety of zanubrutinib for the treatment of patients with newly diagnosed Waldenström's Macroglobulinemia with MYD88 mutation. This should include an assessment of the CXCR4 mutation status. In addition, the study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2025
Final Report Submission: 03/2026

4130-3 Conduct a study to further characterize the clinical benefit and safety of zanubrutinib in patients with newly diagnosed and relapsed/refractory Waldenström's Macroglobulinemia with MYD88^{wt}. This study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022

Study Completion: 08/2025
Final Report Submission: 03/2026

4130-4 Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of zanubrutinib in racial and ethnic minorities with Waldenström's Macroglobulinemia.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2023
Study Completion: 01/2028
Final Report Submission: 06/2028

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 125326 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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 information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety 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).

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, call Bernetta Lane, Regulatory Health Project Manager, at (301) 796-0937.

Sincerely,

{See appended electronic signature page}

Nicole 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 or Medication Guide

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

APPEARS THIS WAY ON ORIGINAL

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
08/31/2021 08:42:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s004

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)	8/2021
Dosage and Administration (2)	8/2021
Warnings and Precautions (5)	8/2021

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)

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 occurred in patients including skin cancers. Advise patients to use sun protection. (5.4)
- Cardiac Arrhythmias: Monitor for atrial fibrillation and atrial flutter and manage appropriately. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy. (5.6)

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, (≥ 20%) are neutrophil count decreased, upper respiratory tract infection, platelet count decreased, rash, hemorrhage, musculoskeletal pain, hemoglobin decreased, bruising, diarrhea, pneumonia, and cough. (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 co-administration with moderate or strong CYP3A inducers. (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: 8/2021

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).

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 *[see Drug Interactions (7.1)]*.

Table 1: Dose Modifications for Use With CYP3A Inhibitors or Inducers

Co-administered Drug	Recommended BRUKINSA Dose
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)]*.
Moderate or strong CYP3A inducer	Avoid concomitant use.

After discontinuation of a CYP3A inhibitor, 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

Event	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 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	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
	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)]*		
Grade 3 or 4 non-hematological toxicities *	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^

Event	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities *[see Warnings and Precautions (5.3)]*		
	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

*Evaluate the benefit-risk before resuming treatment for a Grade 4 non-hematological toxicity.

^ Evaluate the benefit-risk before resuming treatment at the same dose 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 hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 3.0% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration 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) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 28% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred *[see Adverse Reactions (6.1)]*.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci 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 (28%), thrombocytopenia (11%), and anemia (7%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 4% 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 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 (4%), melanoma (1.4%), and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 2.8% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events of atrial fibrillation and atrial flutter were reported in 0.8% of patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate *[see Dosage and Administration (2.4)]*.

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 in seven clinical trials, administered as a single agent at 160 mg twice daily in 662 patients, in patients with hematologic malignancies in clinical trials at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily (0.125 to 0.5 times the recommended dosage) in 12 patients. Among 779 patients receiving BRUKINSA, 74% were exposed for at least 1 year, 55% were exposed for at least 2 years, and 16% were exposed for at least 3 years.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥ 20% of patients who received BRUKINSA were neutrophil count decreased (56%), upper respiratory tract infection (49%), platelet count decreased (44%), rash (35%), hemorrhage (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), bruising (25%), diarrhea (23%), pneumonia (22%), and cough (21%).

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 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total

bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x 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 %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection ¶	39	0
	Pneumonia §	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash ‖	36	0
	Bruising *	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage †	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction

* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis

† Hemorrhage includes all related terms containing hemorrhage, hematoma

‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis

§ 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

‖ Rash includes all related terms containing rash

¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

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%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 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 (%)**
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis †	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† 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 and 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) and 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 ¶	44	0	40	2
	Pneumonia §	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 and administration site conditions	Fatigue[#]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising *	20	0	34	0
	Rash	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ‡	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 †	42	4	43	9
	Hypertension	14	9	19	14

* Bruising includes all related terms containing "bruise," "contusion," or "ecchymosis"
† 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 and subarachnoid hemorrhage.
# Fatigue includes asthenia, fatigue, lethargy
‡ Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis and musculoskeletal discomfort.
§ Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
‖ Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatosis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, and skin toxicity.
¶ 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

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* (20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	**BRUKINSA[1]**		**Ibrutinib[1]**	
	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				
Bilirubin increased	12	1.0	33	1.0
Calcium decreased	27	2.0	26	0
Creatinine increased	31	1.0	21	1.0
Glucose increased	45	2.3	33	2.3

Laboratory Abnormality	BRUKINSA[1]		Ibrutinib[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Potassium increased	24	2.0	12	0
Urate increased	16	3.2	34	6
Phosphate decreased	20	3.1	18	0

* Based on laboratory measurements.

[1]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.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 7: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration 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 co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration 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 co-administration of BRUKINSA with moderate or strong CYP3A inducers *[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 post-natal 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 779 patients in clinical studies with BRUKINSA, 52% were ≥ 65 years of age, while 20% were ≥ 75 years of age. No overall differences in safety or 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

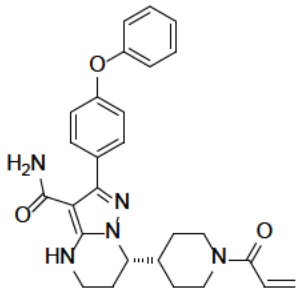
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic 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: Co-administration of multiple doses of CYP3A inhibitors increases zanubrutinib C_{max} and AUC (Table 8).

Table 8: Observed or Predicted Increase in Zanubrutinib Exposure After Co-Administration of CYP3A Inhibitors

Co-administered 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: Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92% and AUC by 93%.

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

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

CYP2C19 Substrates: Co-administration 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 co-administered with zanubrutinib.

Transporter Systems: Co-administration 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 co-administered with zanubrutinib.

Gastric Acid Reducing Agents: No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered 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 9: 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%*
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

* 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 pre-specified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN.

Table 10 shows the response rates in ASPEN based on IRC assessment.

Table 10: Response Rate and Duration of Response Based on IRC Assessment in ASPEN

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

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).

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. 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 avoid becoming pregnant 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)]*.

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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)

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 not become 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 your 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)** that 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.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with BRUKINSA, but can also be severe. 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. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Tell your healthcare provider if you have any of the following signs or symptoms:
  - o your heartbeat is fast or irregular
  - o feel lightheaded or dizzy
  - o pass out (faint)
  - o shortness of breath
  - o chest discomfort

The most common side effects of BRUKINSA include:

- decreased white blood cells
- upper respiratory tract infection
- decreased platelet count
- rash
- bleeding
- muscle or bone pain
- decreased red blood cells (anemia)
- bruising
- diarrhea
- pneumonia
- cough

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.

Distributed and Marketed by: BeiGene USA, Inc. San Mateo, CA 94403
BRUKINSA® is a registered trademark owned by BeiGene, Ltd.
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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: 8/2021

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
08/31/2021 08:42:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s004

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

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Application Type	505(b)(1)
Application Number(s)	NDA 213217, S-004
Priority or Standard	Standard
Submit Date(s)	December 18, 2020
Received Date(s)	December 18, 2020
PDUFA Goal Date	October 18, 2021
Division/Office	Division of Hematologic Malignancies 2/OOD
Review Completion Date	August 20, 2021
Established Name	Zanubrutinib
(Proposed) Trade Name	BRUKINSA
Pharmacologic Class	Kinase inhibitor
Code name	BGB-3111
Applicant	BeiGene USA
Formulation(s)	Capsules
Dosing Regimen	160 mg orally twice daily or 320 mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of Waldenström's Macroglobulinemia
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Waldenström's Macroglobulinemia

Table of Contents

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Reference ID: 4850271

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Table of FDA Tables

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Table of Applicant Tables

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Reference ID: 4850271

Table of FDA Figures

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Reference ID: 4850271

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Bernetta Lane, DHSc, MBA, RN
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Office of Clinical Pharmacology Team Leader	Xiling Jiang, PhD
Office of Clinical Pharmacology (Pharmacometrics) Reviewer	Hongshan Li, PhD
Office of Clinical Pharmacology (Pharmacometrics) Team Leader	Lian Ma, PhD
Office of Clinical Pharmacology (Genomics) Reviewer	Oluseyi Adeniyi, PhD
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Statistical Team Leader	Lisa Rodriguez, PhD
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Division Director (OB)	Thomas Gwise, PhD
Division Director (DHM2)	Nicole Gormley, MD

Additional Reviewers of Application

OPDP	Nisha Patel. PharmD
PLT	Ruth Mayrosh, BSN

OPDP=Office of Prescription Drug Promotion
PLT=Patient Labeling Team

Glossary

AC advisory committee

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Reference ID: 4850271

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology

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Reference ID: 4850271

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VGPR	very good partial response
WM	Waldenström's macroglobulinemia.

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Reference ID: 4850271

1 Executive Summary

1.1. Product Introduction

Established Name: Zanubrutinib, BGB-3111
Proprietary Name: BRUKINSA
Therapeutic Class: Antineoplastic
Chemical Class: Small Molecule
Pharmacologic Class: Bruton's Tyrosine Kinase (BTK) Inhibitor
Dosage Form: Capsules: 80 mg

Mechanism of Action: Irreversible inhibitor of Bruton's tyrosine kinase, disrupting B-cell signaling, inducing apoptosis and inhibiting proliferation

Approved Indication: Accelerated approval for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy in November 2019.

Proposed Indication: Treatment of adult patients with Waldenström's macroglobulinemia (WM)

Proposed Dosage and Administration: 160 mg orally twice daily or 320 mg orally once daily (b) (4) until disease progression or unacceptable toxicity.

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Reference ID: 4850271

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of BRUKINSA (zanubrutinib) for the following indication:

BRUKINSA is indicated for the treatment of adult patients with Waldenström's Macroglobulinemia (WM).

Approval of zanubrutinib for the above indication is based on the totality of evidence from Study BGB-3111-302 (ASPEN), which demonstrated a favorable benefit-risk profile for the indicated patient population.

Study BGB-3111-302 was a phase 3, randomized, open-label study in patients with both newly diagnosed and relapsed/refractory Waldenström's Macroglobulinemia. Patients were assigned to either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT}$), based on MYD88 mutational status. Patients were randomized 1:1 to receive either zanubrutinib (n=102) or ibrutinib (n=98) until disease progression or unacceptable toxicity in Cohort 1. Patients in Cohort 2 (n=28) received zanubrutinib until disease progression or unacceptable toxicity. Subjects in Cohort 1 were stratified by CXCR4 mutational status as assessed by the Sanger assay ($CXCR4^{WHIM}$ vs. $CXCR4^{WT}$) and number of prior lines of therapy (0 vs. 1-3 vs. more than 3).

Efficacy

- The primary endpoint of Study BGB-3111-302 was to demonstrate superiority of zanubrutinib relative to ibrutinib based on CR+VGPR rates assessed by IRC with adaptation of the response criteria updated at the Sixth IWWM in the relapsed/refractory patient population in Cohort 1. If the obtained one-sided p-value was ≤0.025, it would be concluded that single agent zanubrutinib statistically significantly increases CR+VGPR rate compared to ibrutinib.
- The study did not meet the primary endpoint. As of the pre-specified data cutoff of August 31, 2019, CR+VGPR in the relapsed/refractory patient population based on the modified response criteria was 28.9% in the zanubrutinib arm and 19.8% in the ibrutinib arm, as assessed by IRC. Using the stratified CMH method, the risk difference was 10.7 with 95% CI of (-2.5, 23.9), p-value 0.116.
- FDA assessment of benefit was based on major response rate (defined as ≥PR) in the ITT population in Cohort 1, which included 18% treatment naïve patients, supported by the durability of response and response rates in Cohort 2 $MYD88^{WT}$ population.
- The major response rate (defined as ≥PR) assessed using standard consensus criteria for the ITT population was 77.5% (95% Confidence Interval (CI): 68.1, 85.1) in the zanubrutinib arm and 77.8% (95% CI: 68.3, 85.5) in the ibrutinib arm.
- The median duration of response for patients who achieved major response per IRC had not

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Reference ID: 4850271

been reached for both treatment arms. The USPI will include duration of response event free rates at 12 months, as follows: zanubrutinib: 94.4% (95% CI: 85.8, 97.9); ibrutinib: 87.9% (95% CI: 77.0, 93.8).

Cohort 2 enrolled patients with MYD88 wildtype (*MYD88^{WT}*) or MYD88 mutation unknown WM (N=26 and N=2, respectively). All patients in Cohort 2 received BRUKINSA 160 mg twice daily. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease. Major response rate (PR or better) in Cohort 2 was seen in 50% (13/26 patients).

Although Study BGB-3111-302 failed to meet its primary endpoint, the efficacy results from Cohort 1 and Cohort 2 provides substantial evidence of effectiveness for zanubrutinib for patients with WM.

Safety

- In general, the overall safety profile of zanubrutinib in Study BGB-3111-302 was similar to the known safety profile of zanubrutinib. There were no new safety concerns identified.
- The most common adverse events in both treatment arms of Cohort 1 included musculoskeletal pain (zanubrutinib: 44.6%; ibrutinib: 38.8%), upper respiratory tract infection (zanubrutinib: 43.6%; ibrutinib: 39.8%), hemorrhage (zanubrutinib: 40.6%; ibrutinib: 42.9%), fatigue (zanubrutinib: 30.7%; ibrutinib: 24.5%), neutropenia (zanubrutinib: 30.7%; ibrutinib: 16.3%), and rash (zanubrutinib: 26.5%; ibrutinib: 30.6%),
- Serious adverse events occurred in 43.6% of patients in the zanubrutinib arm and 46.9% of patients in the ibrutinib arm.
- More patients discontinued treatment due to an adverse event in the ibrutinib arm (15% vs. 4%).

Adverse events of special interest included hemorrhage (zanubrutinib: 40.6%; ibrutinib: 42.9%), atrial fibrillation (zanubrutinib 3.9%; ibrutinib: 17.2%), infections and second primary malignancies.

Overall, the efficacy and safety results from Study BGB-3111-302 demonstrate an acceptable benefit-risk profile for zanubrutinib in patients with Waldenström's Macroglobulinemia. All disciplines agreed with the approval recommendation. Approval was based on a non-comparative assessment of major response rate and DOR from the zanubrutinib arm. The regular approval based on Major response rate is consistent with the original approval for ibrutinib, which was based on a single arm trial for patients with Waldenström's Macroglobulinemia in January 2015.

In Study BGB-3111-302, a total of 37 patients with treatment naïve WM were randomized in Cohort 1 (MYD88^{MUT}). Of these, 19 received zanubrutinib. Cohort 2 (MYD88^{WT}) included 5 patients with newly diagnosed WM. A Post Marketing Commitment (PMC) will be issued with

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Reference ID: 4850271

this application to obtain additional safety and efficacy data in treatment naïve patients with WM.

Although Cohort 1 enrolled patients selected for $MYD88^{MUT}$ and only a small number of patients enrolled had $MYD88^{WT}$ (Cohort 2), the efficacy results from Cohort 2 support approval for zanubrutinib, regardless of mutation status. A companion diagnostic assay is not needed for the safe and effective use of zanubrutinib in patients with WM. A PMC will be issued with this application to obtain additional safety and efficacy data in patients with both treatment naïve and relapsed/refractory $MYD88^{WT}$ WM.

Underrepresentation of Racial and Ethnic Subgroups

Study BGB-3111-302 included 101 patients in Cohort 1 who were randomized to receive zanubrutinib. Of these, 87 (86%) were Caucasian, four (4%) were Asian and 10 (10%) were "not reported/unknown". In addition, in Cohort 1, four (4%) patients were Hispanic or Latino and 16 (15.7%) had unknown or not reported ethnicity. In Cohort 2, 27/28 (96%) patients were Caucasian and one (4%) was race "not reported/unknown". A PMC will be issued to obtain additional safety and efficacy data with zanubrutinib in racial and ethnic minorities with WM.

Second Primary Malignancies

Second primary malignancies is an identified risk with zanubrutinib therapy. In Study BGB-3111-302, a total of 19/129 (14.7%) of patients with WM developed a second primary malignancy. Of these, the majority were non-melanoma skin cancer. In the pooled zanubrutinib safety population, approximately 13.5% of patients developed second primary malignancies. A Post Marketing Requirement (PMR) will be issued to further characterize the risk of second primary malignancies in patients receiving zanubrutinib with longer follow up.

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Reference ID: 4850271

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Waldenström macroglobulinemia (WM) is a rare B-cell disorder characterized by bone marrow infiltration by lymphocytic cell population along with immunoglobulin M (IgM) monoclonal gammopathy. Approximately 1000 to 1500 new cases are reported every year in the United States. MYD88 (L265P) mutations are present in greater than 90% of patients. Recurrent mutations in the CXCR4 gene are found in up to 40% of the patients and may impact response to therapy. Patients can have long periods of asymptomatic disease (may exceed 5-10 years), and treatment is recommended for symptoms and complications related to tumor burden such as hyperviscosity, neuropathy, anemia, and constitutional symptoms. (Dimopoulos MA, 2019).

The benefit-risk assessment for this supplemental new drug application (sNDA) is based on the totality of evidence from the pivotal study BGB-3111-302 (ASPEN), a phase 3, randomized, open-label study comparing the safety and efficacy of zanubrutinib and ibrutinib in patients with both newly diagnosed and relapsed/refractory Waldenström's Macroglobulinemia. Patients were assigned to either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT}$) based on MYD88 mutational status. Subjects in Cohort 1 were randomized 1:1 to receive either zanubrutinib (N=102) 160 mg PO twice daily or ibrutinib 420 mg PO once daily (N=99) until disease progression or unacceptable toxicity. Cohort 1 included total of 37 patients (Zanubrutinib n=19, ibrutinib n=18) who were treatment naïve (newly diagnosed). Cohort 2 enrolled patients with MYD88 wildtype (MYD88W*T*) or MYD88 mutation unknown WM (N=26 and N=2, respectively). All patients in Cohort 2 received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease.

The primary endpoint of the ASPEN study was superiority of CR+VGPR in the relapsed/refractory patient population in Cohort 1. The study did not meet the primary endpoint. All other endpoints are descriptive. The FDA's assessment of efficacy was based on the major response rate, defined as PR+VGPR+CR, as assessed by the IRC, per standard response criteria from IWWM-6 in the Zanubrutinib arm in Cohort 1 and Cohort 2. The major response rate was 77.5% (95% Confidence Interval (CI): 68.1, 85.1) in the zanubrutinib arm and 77.8% (95% CI: 68.3, 85.5) in the ibrutinib arm in the ITT population. The median duration of response for patients who achieved major response per IRC had not been reached for both the treatment arms. The duration of response event free rates at 12 months were as follows: zanubrutinib: 94.4% (95% CI: 85.8, 97.9); ibrutinib: 87.9% (95% CI: 77.0, 93.8). Major response rate (PR or better) in Cohort 2 was reported in 50% of patients with $MYD88^{WT}$.

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The safety of zanubrutinib in patients with Waldenström's Macroglobulinemia was assessed primarily in Study BGB-3111-302. In general, the overall safety profile of zanubrutinib in Study BGB-3111-302 was similar to the known safety profile of zanubrutinib, and no new safety concerns were identified. The most common adverse events in both treatment arms of Cohort 1 included musculoskeletal pain (zanubrutinib: 44.6%; ibrutinib: 38.8%), upper respiratory tract infection (zanubrutinib: 43.6%; ibrutinib: 39.8%), hemorrhage (zanubrutinib: 40.6%; ibrutinib: 42.9%), fatigue (zanubrutinib: 30.7%; ibrutinib: 24.5%), neutropenia (zanubrutinib: 30.7%; ibrutinib: 16.3%), and rash (zanubrutinib: 26.5%; ibrutinib: 30.6%). Serious adverse events occurred in 43.6% of patients in the zanubrutinib arm and 46.9% of patients in the ibrutinib arm. Second primary malignancies (SPM) is an important safety risk with zanubrutinib. SPMs were reported in 14.7% of patients in the zanubrutinib arm in Study BGB-3111-302. A Postmarketing requirement will be issued to further characterize SPMs with zanubrutinib with long term follow up.

The safe use of zanubrutinib in this patient population can be managed through labeling, monitoring and routine hematology and oncology care.

In summary, the totality of the evidence from Cohort 1 ($MYD88^{MUT}$) and Cohort 2 ($MYD88^{WT}$) in the Study BGB-3111-302, supports a positive benefit-risk assessment for granting regular approval of zanubrutinib for the treatment of adult patients with Waldenström's Macroglobulinemia. The approval is consistent with the original approval for ibrutinib in January 2015. Ibrutinib was granted regular approval based on Major response rates in a single arm trial in patients with Waldenström's Macroglobulinemia.

Several Postmarketing commitments (PMCs) will be issued with this application to obtain additional safety and efficacy data in treatment naïve patients with $MYD88^{MUT}$ WM and patients with $MYD88^{WT}$ (treatment naïve and relapsed/refractory). In addition, racial and ethnic subgroups were underrepresented in the ASPEN study. In Cohort 1, only 4% of patients enrolled were Asian and no Black patients were enrolled; 4% patients were Hispanic or Latino and 15.7% were unknown or not reported ethnicity. In Cohort 2, 27/28 (96%) patients were Caucasian and one (4%) was race "not reported/unknown". A PMC will be issued to obtain additional safety and efficacy data with zanubrutinib in racial and ethnic subgroups with WM.

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Reference ID: 4850271

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Waldenström's Macroglobulinemia (WM) is a rare B-cell malignancy characterized by bone marrow infiltration by lymphocytic cell population along with immunoglobulin M (IgM) monoclonal gammopathy • Patients suffer from organ damage related to infiltration or hyperviscosity and cytopenias related to bone marrow infiltrations • WM is considered incurable.	WM is a serious and life-threatening disease
Current Treatment Options	• There are currently two FDA approved therapies for WM, ibrutinib monotherapy and ibrutinib+rituximab combination therapy. • Additional therapies for WM include alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies, corticosteroids, and proteasome inhibitors.	There continues to remain an unmet medical need for new therapies for the treatment of WM.
Benefit	• The primary clinical benefit of zanubrutinib for the treatment of patients with WM was established by the efficacy results from Study BGB-3111-302. • In Study BGB-3111-302, 201 patients with either treatment naïve (N=37) or relapsed WM (N=164) with $MYD88^{MUT}$ were randomized 1:1 to receive either zanubrutinib (N=102) or ibrutinib	The response rates from Cohort 1 and Cohort 2 in Study BGB-3111-302 and the durability of response support the efficacy of zanubrutinib for patients with WM. PMCs will be issued with this application to conduct a study to further characterize the clinical benefit of zanubrutinib in patients with treatment naïve WM, as well as in patients with $MYD88^{WT}$ disease, including both treatment-naïve and

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(N=99). • The Study did not meet the primary endpoint of VGPR/CR rate in the relapsed patient population, as assessed by modified consensus response criteria, was 28.9% in the zanubrutinib arm, compared to 19.8% in the ibrutinib arm. Using stratified CMH method, the risk difference was 10.7; 95% CI:-2.5, 23.9; p=0.116. • The major response rate (defined as PR+VGPR+CR) was 77.5% (95% CI: 68.1, 85.1)in the zanubrutinib arm and 77.8% (95% CI: 68.3, 85.5) in the ibrutinib arm. • The duration of response event free rates at 12 months; zanubrutinib: 94.4% (85.8, 97.9); ibrutinib: 87.9% (77.0, 93.8). • In Cohort 2, responses (PR or better) was reported in 13/26 patients with MYD88 ^{WT}	relapsed/refractory disease. Racial and ethnic minority subgroups were underrepresented in Study BGB-3111-302. A PMC for additional safety and efficacy data in the underrepresented racial and ethnic subgroups will be issued.
Risk and Risk Management	• Safety of zanubrutinib in patients with WM is consistent with the known safety profile of zanubrutinib. • Potential risks associated with zanubrutinib, as well as other BTK inhibitors include hemorrhage, infections, cytopenias, second primary malignancies, cardiac arrhythmias, and embryo-fetal toxicity. • In Study BGB-3111-302 the most common adverse events in both treatment arms were	The safety profile of zanubrutinib is acceptable for the intended patient population. Toxicities were manageable with appropriate treatment interruption and/or dose modifications, which are clearly delineated in labeling and can be managed with routine clinical care. The Warnings and Precautions section of the label details the potential risks with zanubrutinib use. A PMR will be issued with this application to conduct an integrated safety analysis of patients with lymphoid

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	musculoskeletal pain (zanubrutinib: 44.6%; ibrutinib: 38.8%), upper respiratory tract infection (zanubrutinib: 43.6%; ibrutinib: 39.8%), hemorrhage (zanubrutinib: 40.6%; ibrutinib: 42.9%), fatigue (zanubrutinib: 30.7%; ibrutinib: 24.5%), neutropenia (zanubrutinib: 30.7%; ibrutinib: 16.3%), and rash (zanubrutinib: 26.5%; ibrutinib: 30.6%). SPMs were reported in 14.7% of patients in the zanubrutinib arm in Study BGB-3111-302.	malignancies and WM to further characterize the risk of second primary malignancies with extended follow-up in patients receiving zanubrutinib.

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1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	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		[e.g., Section 2.1 Analysis of Condition]
	□	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

Bindu Kanapuru, MD
Cross-Disciplinary Team Leader

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Reference ID: 4850271

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

WM is a rare hematologic malignancy characterized by overproduction and bone marrow infiltration of monoclonal, IgM-secreting, lymphoplasmacytoid B-cells. The presence of elevated monoclonal IgM protein adds a unique dimension to the disorder and is the primary driver of morbidity, because it can result in hyperviscosity syndrome, peripheral neuropathy, hemolytic anemia, and immune complex vasculitis (Gertz 2017, Ghobrial et al 2003), and detection of IgM forms the basis of response assessment (Owen et al 2013). WM has an overall incidence of 1 in 260,000 persons per year in the USA (ACS 2016). WM is primarily a disease of the elderly, with a median age at diagnosis of 63 to 68 years. There is a male predominance, with an incidence twice as high in men than in women, and higher in whites than blacks and other races (Gertz 2017; Leukemia and Lymphoma Society 2020).

Evidence has shown that certain factors, such as the number of lines of prior therapy and MYD88/CXCR4 mutational status can significantly impact response (Treon SP et al 2015 (a), Treon SP et al 2015 (b), Treon SP et al 2020b). Regardless of these factors, the goal of WM therapy is to achieve rapid, deep, and sustained reduction in IgM in order to minimize the direct pathologic effects of IgM. The greater the decrease in serum IgM over time, the better the response (Owen RG at al 2013, Treon SP et all 2011).

Response to therapy in Waldenström's macroglobulinemia (WM) is based upon guidelines developed by the IWWM, with somewhat arbitrary categorizations: A decrease of ≥ 25% in serum IgM is categorized as a minor response, a ≥ 50% reduction as a partial response (PR), and a normal post-treatment IgM level (with undetectable serum monoclonal IgM) a CR (Weber et al 2003). At the sixth meeting of the IWWM, a new category of response, VGPR, defined as a ≥ 90% reduction in serum IgM with a reduction in the extent of extramedullary disease, was adopted (Owen et al 2013). This addition recognized the predictive value of VGPR for progression-free survival, and the distinction between VGPR(≥ 90% IgM reduction) and PR (≥ 50% but < 90% IgM reduction) in regard to PFS (Owen et al 2013). With chemoimmunotherapy in Waldenström's macroglobulinemia, patients with VGPR have PFS outcomes indistinguishable from complete response (Treon et al 2011). Recent data show that patients who achieve a PR or VGPR demonstrated a longer PFS and time to next treatment (TTNT) than those who had minor response or stable disease (Paludo et al 2018). This is further supported by data in ibrutinib treated patients that showed that MRR at 6 months appears to be a surrogate for PFS (Castillo et al 2019). These findings are consistent with the distinct predictive value of VGPR versus partial response in other diseases associated with

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Reference ID: 4850271

gammopathy, such as multiple myeloma (Moreau et al 2011). Overall, these data suggest a clinical benefit of depth of response and support the use of VGPR and CR rate as a meaningful clinical endpoint in assessing treatment success in Waldenström's macroglobulinemia.

Although WM is described as an indolent disease, it poses a major clinical challenge for the treating physician, as it often causes considerable morbidity in the mostly elderly patients, who often carry significant comorbidities that can impact treatment options. Moreover, despite substantial progress in treating WM patients, current therapies provide only a few patients with complete remission, and relapse has not been preventable despite improved therapeutic tools, such as the BTK inhibitor ibrutinib.

Ibrutinib was granted regular approval for the treatment of patients with WM in 2015 based on a single-arm study in 63 patients, in which response rates and durations compared favourably with historical reports of the safety and effectiveness of intensive combination chemoimmunotherapy regimens. Responses were limited to patients harboring a *MYD88*^{L265P} mutation, with all 5 patients with wild-type MYD88 disease failing to have a major response (PR and above) (Treon 2015b). In the studies of ibrutinib for WM, adverse events were frequently seen to be treatment limiting: atrial fibrillation, hypertension, bleeding, diarrhea, and arthralgia are frequently related to treatment discontinuation or disruption, compromising ibrutinib's achievable benefit since continuous administration is required for efficacy. A recent report of 189 patients confirms the frequency of treatment discontinuation with ibrutinib in WM (22% at 12 months, 35% at 36 months) and highlights the impact of the toxicity profile in maintaining successful BTK inhibitor treatment in patients with WM (Gustine et al, 2018). Studies of ibrutinib point to safety considerations around its cardiovascular toxicity. The safety profile of ibrutinib in older adults reveals the unmet medical need for additional options for treatment individualization based on, for example, cardiovascular comorbidities.

BeiGene is seeking approval for BRUKINSA (zanubrutinib), a Bruton Tyrosine Kinase (BTK) inhibitor, for the treatment of patients with WM. FDA first approved zanubrutinib in November 2019 for second-line therapy in mantle cell lymphoma under the accelerated approval pathway. BeiGene has been developing zanubrutinib for WM and now has efficacy data from an ongoing pivotal Phase 3 study, as well as ongoing Phase 2 and Phase 1 studies, in this indication. In July 2018, FDA granted zanubrutinib fast track status for the WM indication.

BeiGene's supplemental new drug application (sNDA) for zanubrutinib for the treatment of WM is based on the data from the pivotal Phase 3 study (the BGB-3111-302 Study), as well as supportive evidence from the BGB-3111-AU-003 Study and the BGB-3111-210 Study. These data, when considered in their totality, demonstrate that zanubrutinib meets the statutory standard for approval for the treatment of WM under the Federal Food, Drug, and Cosmetic Act (FDCA). Our studies have demonstrated that the efficacy of zanubrutinib in WM is at least comparable to the current standard of care in this disease (ibrutinib); shows improvements

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Reference ID: 4850271

over ibrutinib on several safety parameters; and has an overall positive benefit-risk profile in this patient population. Zanubrutinib provides an important treatment option for patients with WM, and FDA has the authority to approve the product based on the evidence developed to date.

Originally, Study BGB-3111-302 (ASPEN) was designed to assess both the non-inferiority and superiority of zanubrutinib to ibrutinib. FDA subsequently recommended that BeiGene modify the study design to focus on the superiority of zanubrutinib to ibrutinib, which the company incorporated. While the 302 Study did not demonstrate superiority of zanubrutinib over ibrutinib on the primary endpoint of complete response (CR) + very good partial response (VGPR) at the timepoint selected, the study demonstrated several key findings in support of a positive benefit-risk analysis for zanubrutinib in this indication:

- In the cohort that was randomized to either ibrutinib or zanubrutinib (cohort 1), zanubrutinib demonstrated a major response rate (MRR) comparable to ibrutinib, with numerically higher very good partial response (VGPR) rates as assessed by the Independent Review Committee (data cutoff date 31Aug2019):

    - 79 patients in the zanubrutinib arm achieved major responses, compared to 77 patients in the ibrutinib arm (77.5% of the 102 zanubrutinib patients and 77.8% of the 99 ibrutinib patients);
    - 29 patients in the zanubrutinib arm achieved VGPR, compared to 19 patients in the ibrutinib arm (28.4% of the 102 zanubrutinib patients and 19.2% of the 99 ibrutinib patients);
    - The concordance rates between Independent Review Committee and investigator assessments for the zanubrutinib and ibrutinib arms were 100% and 98.0% for VGPR/CR, and 94.1% and 94.9% for best overall response, respectively.

- Zanubrutinib-treated patients showed consistent trends in progression-free survival (PFS) and overall survival (OS);
- Zanubrutinib demonstrated a greater sustained reduction in IgM than ibrutinib, which is an important marker used in the treatment of WM patients; and
- Zanubrutinib is safe for the treatment of this vulnerable patient population, with a lower overall proportional incidence of adverse events and a markedly lower atrial fibrillation/flutter rate compared to ibrutinib.

As discussed with and proposed by FDA, BeiGene proceeded to review the data with a longer follow-up. This subsequent analysis (data cutoff date 31Mar2020) has demonstrated key findings continued to support a positive benefit-risk analysis for zanubrutinib in this indication:

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Reference ID: 4850271

- In cohort 1 , zanubrutinib demonstrated a major response rate (MRR) comparable to ibrutinib, with numerically higher very good partial response (VGPR) rates:
    - 80 patients in the zanubrutinib arm achieved major responses, compared to 77 patients in the ibrutinib arm (78.4% of the 102 zanubrutinib patients and 77.8% of the 99 ibrutinib patients);
    - 33 patients in the zanubrutinib arm achieved VGPR, compared to 19 patients in the ibrutinib arm (32.4% of the 102 zanubrutinib patients and 19.2% of the 99 ibrutinib patients), nominal p-value 0.0206;
    - Zanubrutinib-treated patients showed consistent trends in progression-free survival (PFS) and overall survival (OS);
    - Zanubrutinib demonstrated a greater sustained reduction in IgM than ibrutinib, which is an important marker used in the treatment of WM patients.

- Compared with the ibrutinib arm, the zanubrutinib arm had lower incidences of Grade 3 or higher adverse events (64.4% versus 67.3%), adverse events leading to death (1.0% versus 4.1%), adverse events leading to treatment discontinuation (4.0% versus 15.3%), adverse events leading to dose reduction (14.9% versus 25.5%), adverse events leading to dose hold (51.5% versus 59.2), and treatment-related adverse events (82.2% versus 87.8%).
- With zanubrutinib treatment (compared to ibrutinib treatment), there was a reduction in the risk of specific events known to be associated with ibrutinib therapy: atrial fibrillation and flutter (4.0% versus 18.4%), hypertension (13.9% versus 20.4%), major bleeding (5.9% versus 10.2%), and diarrhoea (21.8% versus 33.7%).
- Zanubrutinib is safe for the treatment of this vulnerable patient population, with a lower overall proportional incidence of adverse events, a markedly lower atrial fibrillation/flutter rate and treatment discontinuation rate due to AE compared to ibrutinib.
- The safety analyses of the ASPEN study demonstrated that treatment with zanubrutinib was associated with marked toxicity and tolerability advantages over treatment with ibrutinib.
- BeiGene concludes that the ASPEN study, with clear efficacy in WM independent of MYD88 mutational status and good tolerability, supported by additional clinical studies, pre-clinical evidence, well defined target engagement and mechanism of action, demonstrates that zanubrutinib represents an improved overall benefit/risk profile over existing approved therapies.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of Waldenström's Macroglobulinemia (WM). WM is a serious and life-threatening condition that is characterized by abnormal B lymphocytes that infiltrate the bone marrow and are associated with a production of monoclonal IgM protein. According to the SEER database, there are 1000-1500 new cases of WM diagnosed annually in the United States (Sekhar, 2012). The median age of diagnosis is 63-68 with a predominance in males and Caucasians. Mutations of the toll-like receptor 4 adaptor protein, MYD88, and the C-X-C chemokine receptor type 4 WHIM ($CXCR4^{WHIM}$) are found in

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Reference ID: 4850271

approximately 90% and 30% of patients with WM, respectively.

Clinical manifestations of WM are related to organ infiltration of lymphocytes and include hepatomegaly, splenomegaly, and lymphadenopathy, as well cytopenias and symptoms related to elevated IgM levels, which include hyperviscosity and peripheral neuropathy. At diagnosis, WM is often considered indolent, and most patients do not meet accepted criteria for treatment. Treatment is indicated for patients who develop IgM related complications, cytopenias and constitutional symptoms or bulky disease. Invariably, patients with WM progress and WM is considered an incurable disease. The historic median overall survival for patients with WM from SEER data is 6-8 years, though this is likely improving with novel treatment combinations. Ten-year overall survival rates have been reported to be 81-95% (Castillo, 2018).

FDA does not agree with the Applicant's inclusion of information regarding the approval of ibrutinib or discussion of Study BGB-3111-302 in this section. In addition, FDA notes that some of the language used by the Applicant in this section is promotional. For discussion regarding current therapies for WM, Study BGB-3111-302 (ASPEN), responses observed with zanubrutinib, the safety of zanubrutinib in WM, and the FDA's assessment of overall benefit/risk, refer to the corresponding sections in this review.

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Reference ID: 4850271

2.2. Analysis of Current Treatment Options

The Applicant's Position

FDA approved treatment options for patients with WM (NCCN 2020) are summarized below.

BeiGene Table 1 Summary of NCCN Preferred Regimens for Primary Therapy

Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Ibrutinib	WM	2015 Full approval	420 mg taken orally once daily	Study 1118 (NCT01614821): open-label, multi-center, single-arm trial in previously treated patients (n=63). Response rate (CR +VGPR+PR) was 61.9%; VGPR was 11.1% and PR 50.8%. None of the patients achieved CR. Median duration of response was not evaluable	Hemorrhage, infections, cytopenias, Cardiac Arrhythmias and Cardiac Failure, Hypertension, Second Primary Malignancies, Tumor Lysis Syndrome, Embryo-Fetal Toxicity	Single-arm trial results granted regular approval by FDA.

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Adminis-tration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				(range, 2.8+, 18.8+ months) and The median time to response was 1.2 months (range, 0.7-13.4 months). <u>Innovate monotherapy:</u> 31 patients with previously treated WM who failed prior rituximab-containing therapy. Overall follow-up of 61 months, the response rate per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR); median duration of response was 33 months (range, 2.4 to 60.2+ months).		

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Ibrutinib / rituximab	WM	2018 Full approval	Ibrutinib: 420 mg daily Rituximab: 375 mg/m^2 weeks 1-4; followed by a second course of weekly rituximab weeks 17-20	Innovate (NCT02165397): randomized, double-blind, placebo-controlled, phase 3 study in combination with rituximab. treatment naïve or previously treated patients. PFS. With an overall follow-up of 63 months, median PFS in ibrutinib+R was NE vs 20.3 months in placebo+R. Response rate (CR+VGPR+PR) was 76% ibrutinib+R) vs 31% (Placebo+R) (P<0.0001). Median DOR was NE in both groups.	most common adverse reactions (occurring in 20% or more of patients) of all grades in patients treated with ibrutinib plus rituximab in the iNNOVATE study were bruising (37%), musculoskeletal pain (35%), hemorrhage (32%), diarrhea (28%), rash (24%), arthralgia (24%), nausea (21%), and hypertension (20%).	Based on the totality of the evidence, addition of rituximab to ibrutinib appears to add toxicity without clinically meaningful efficacy benefit.
Other Treatments						

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Bendamustine/Rituximab (BR)	WM	Not approved by FDA	Bendamustine: 120 mg/m2 IV over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles Rituximab: 375 mg/m^2 on day 1 every 28 days for 4 cycles; single rituximab doses were also	A large, randomized, multicenter phase 3 trial of previously untreated patients with indolent NHL with BR vs CHOP-R. 41 patients with WM/LPL were Included in this study, 40 of whom were available for response assessment. After a median follow-up of 45 months, the median PFS was significantly longer with BR treatment, 69.5 months versus 28.5 months with CHOP-R.	BR was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. These results suggest that BR may be a preferable option to CHOP-R as primary therapy for WM	NCCN Guidelines Version 1.2021- Preferred Regimens for Primary Therapy

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			administered 1 week prior to the first cycle and 4 weeks after the last cycles (for a total of 6 rituximab doses)			
Bortezomib/Dexamethasone/Rituximab (BDR)	WM	Not approved by FDA	Bortezomib: using a twice-a-week schedule	A study by WMCTG reported an ORR of 96%, including 83% with PR in newly diagnosed patients with WM. With a median follow-up of 2 years, 80% of patients remained free of	Grade 3 peripheral neuropathy was observed in 30% of patients in the study that utilized twice-a-week bortezomib. Peripheral neuropathy led to premature discontinuation of bortezomib in 61% of patients in this study	NCCN Guidelines Version 1.2021- Preferred Regimens for Primary Therapy

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				disease progression, including all patients achieving a VGPR or better.		
			Bortezomib was used once weekly	Another multicenter phase 2 trial, the activity of BDR was evaluated in 59 newly diagnosed symptomatic patients with WM. The ORR was 85% (3% complete response [CR], 7% VGPR, and 58% PR). In 11% of patients, an increase of IgM (≥25%) was observed after administration of rituximab. After 32 months of follow-up, median PFS was 42 months and 3-year OS	Peripheral neuropathy was observed in 46% (grade ≥3 in 7%) of patients; 8% discontinued bortezomib due to neuropathy. The high rate of peripheral neuropathy could be attributed to the intravenous administration of bortezomib in the trial.	NCCN Guidelines Version 1.2021- Preferred Regimens for Primary Therapy

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				was 81%.		
Rituximab/Cyclophosphamide/Dexamethasone (R-CD)	WM	Not approved by FDA		In a prospective study of untreated WM patients (n = 72), treatment with R-CD resulted in an ORR of 83% that included a 7% CR and a 67% PR. The 2-year PFS was 67% for all evaluable patients and 80% for responders. The 59 In a retrospective analysis of outcomes after treatment with R-CD in 50 patients with untreated WM, the ORR was 96% and the median PFS was 34 months. The response rate and duration of response were	R-CD regimen was well-tolerated, with 9% of patients experiencing grade 3 or 4 neutropenia and approximately 20% of patients experiencing some form of toxicity related to rituximab. The 8-year OS based on the IPSS risk status for WM was 100%, 55%, and 27% for low-, intermediate-, or high-risk disease, respectively (P = .005).	

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Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				independent of MYD88 mutation status. In a retrospective analysis of outcomes after treatment with R-CD in 50 patients with untreated WM, the ORR was 96% and the median PFS was 34 months. The response rate and duration of response were independent of MYD88 mutation status.		

CHOP-R: cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab CR: Complete response; DOR: Duration of response; IPSS: International prognostic scoring system; IRC: Independent Review Committee; IWWM: International Workshop of Waldenström's Macroglobulinemia; NE: not evaluable; NHL: non-Hodgkin lymphoma; ORR: Overall response rate; OS: Overall survival; PR: Partial response; R: Rituximab; VGPR: Very Good Partial Response; WM: Waldenström's Macroglobulinemia; WMCTG: Waldenström Macroglobulinemia Clinical Trials Group

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The Applicant's Position:

There are limited treatment options for patient with WM; ibrutinib monotherapy received full approval in 2015 for the treatment of WM patients [Study 1118 (NCT01614821): open-label, multi-center, single-arm trial in previously treated patients (n=63). Major response rate (CR +VGPR+PR) was 61.9%; VGPR was 11.1% and PR 50.8%]. Subsequently in 2018, ibrutinib in combination with rituximab was approved. These treatments are the only FDA-approved drugs for the treatment of patients with WM.

According to the National Comprehensive Cancer Network (NCCN) Guidelines, treatment should be initiated for patients with diagnosis of WM only if they are symptomatic (NCCN Guidelines 2020). Treatment depends on symptom severity, complications requiring immediate therapy, or presentation with bulky disease (Anderson et al 2012; Kastritis et al 2018). The most common indications for treatment start include anemia, hyperviscosity as well as neuropathy, bulky organomegaly, and cytopenias (Kastritis et al 2018).

Frontline treatments include dexamethasone, rituximab, and cyclophosphamide (DRC); bortezomib and rituximab (VR); bortezomib, dexamethasone and rituximab (BDR); bendamustine and rituximab (BR); rituximab alone; fludarabine; and ibrutinib. In the salvage setting, an alternative frontline regimen such as ibrutinib, everolimus, or stem cell transplantation may be considered (Treon et al 2015c; Leblond et al 2016).

In the United States, prior to the addition of BTK inhibitors, therapeutic approaches for WM had been based solely on alkylating agents, anti-CD20 therapies, purine analogues, and proteasome inhibitors, used either as single agents or in combination. While treatment with chemoimmunotherapy has demonstrated efficacy in WM, it comes at a cost, with hematologic toxicity and risk of treatment-related malignancy. Rituximab-based combinations (with alkylating agents, purine analogues, proteasome inhibitors, and immunomodulatory drugs) have produced an encouraging pooled overall response rate (ORR) of 84% and a major response rate (MRR) of 71% in metanalyses, but rates of commonly observed ≥ Grade 3 hematologic adverse effects were common (Zheng et al 2019). In addition, infusion-related reactions are observed in ≥ 25% of patients who receive rituximab, particularly during the first infusion, and can be associated with transient dyspnea and hypertension, angioedema, bronchospasm, cough, pyrexia, chills, rash, and vomiting (RITUXAN Product Monograph 2019). Treatment-related adverse events following rituximab combinations have also included myelodysplasia, secondary malignancies, prolonged myelosuppression, immunosuppression, neuropathy, and rituximab-associated IgM flare producing hyperviscosity and exacerbating IgM-driven morbidities (Treon and Castillo 2017).

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Despite progress in treating WM patients, few patients achieve complete remission, and relapse has not been preventable despite improved therapeutic tools, such as the BTK inhibitor ibrutinib. WM remains a rare, serious, and life-threatening disease and is incurable with currently available therapy.

Study BGB-3111-302 (ASPEN) demonstrated at least comparable clinical efficacy of zanubrutinib to ibrutinib in terms of the primary endpoint (CR+VGPR) with support of secondary outcome measures in adult patients with WM. Furthermore, the zanubrutinib CR+VGPR and MRR rate observed in the ASPEN trial (32%, 78%, respectively) were numerically higher than the ibrutinib response presented in the IMBRUVICA USPI (11%, 62%, respectively[1]). These responses occurred in the setting of an imbalance of the stratification factor CXCR4, where a higher proportion (34% versus 22%) of patients with CXCR4 mutations were randomized to the zanubrutinib arm than the ibrutinib arm when CXCR4 was analyzed using the more sensitive methodology (next generation sequencing) than what was used to stratify the patients on the study (Sanger sequencing).

In the WM population pool of 244 patients from ASPEN, BGB-3111-AU-003 and BGB-3111-210, the CR+VGPR and MRR response were 36% and 75%, respectively, offering a robust response with a median follow-up time of 23 months, while median duration of major response was not yet reached. In addition, the safety and tolerability of zanubrutinib compared to ibrutinib in the ASPEN study offer clear advantages. Zanubrutinib provides a new tolerable and effective treatment option to WM patients.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of the current therapies for WM. Specific treatment regimens are determined by age, symptoms, and other comorbidities. There are currently two FDA approved therapies for WM, ibrutinib monotherapy and ibrutinib+rituximab combination therapy. Ibrutinib monotherapy was approved in 2015 based on a single arm trial demonstrating a major response rate (CR+VGPR+PR) of 62%. Ibrutinib+rituximab combination therapy was approved in 2018 based on the results of a randomized, double-blind placebo controlled, phase 3 study (INNOVATE) of ibrutinib or placebo in combination with rituximab. In this study, 150 patients were randomized 1:1 to receive either ibrutinib 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. A PFS advantage was demonstrated with a HR of 0.2 (95% CI: 0.11, 0.38) favoring the ibrutinib+rituximab arm. Efficacy was further supported by the response rate (CR+VGPR+PR) of 72% in the

[1] IMBRUVICA USPI

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Reference ID: 4850271

ibrutinib+rituximab arm compared to 32% in the placebo+rituximab arm.

Additional accepted therapies for WM include alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies, corticosteroids, and proteasome inhibitors. Combination regimens, such as dexamethasone-rituximab-cyclophosphamide (DCR), Bendamustine-rituximab (BR) and bortezomib-dexamethasone-rituximab are also used. A summary of FDA approved and accepted therapies is provided in FDA Table 1..

The FDA does not agree with the Applicant's inclusion of the results of Study BGB-3111-302 in this section.

The FDA also does not agree with the Applicant's statement in BeiGene Table 1, "Based on the totality of the evidence, addition of rituximab to ibrutinib appears to add toxicity without clinically meaningful efficacy benefit". There are no formal head-to-head comparisons of ibrutinib monotherapy and ibrutinib+rituximab. Therefore, any conclusions regarding the comparative effectiveness and safety of the two regimens would be considered subjective and definitive conclusions cannot be made. This statement is subjective, and does not represent the opinion of the FDA.

The FDA does not agree with the Applicant's statement, "the safety and tolerability of zanubrutinib compared to ibrutinib in ASPEN study offer clear advantages". This language is promotional. Refer to Sections 8.2 for discussion of the FDA's safety and tolerability findings in Study BGB-3111-302 (ASPEN).

For discussion regarding Study BGB-3111-302, responses observed with zanubrutinib, the safety of zanubrutinib in WM, and the FDA's assessment of overall benefit/risk, refer to the corresponding sections in this review.

FDA Table 1: FDA Approved Therapies for WM

Product(s)	Relevant	Year of	Dosing/	Efficacy Information	Important Safety and

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Name	Indication	Approval	Administration		Tolerability Issues
Ibrutinib Monotherapy	For the treatment of adult patients with WM	2015	420 mg PO daily until disease progression or unacceptable toxicity	• ORR (CR+VGPR+PR) per IRC assessment: 62% • Median DOR: NR after a median follow up of 11.8 months	Warnings and precautions include: • Hemorrhage • Infections • Cytopenias • Cardiac arrhythmias • Second primary malignancies • Tumor lysis syndrome • Embryofetal toxicity
Ibrutinib + Rituximab	For the treatment of adult patients with WM	2018	Ibrutinib: 420 mg PO daily until disease progression or unacceptable toxicity	• PFS HR 0.2 (95% CI: 0.11, 0.38) for I+R vs placebo+R • ORR (CR+VGPR+PR) per IRC assessment: 72% (vs. 32% in placebo arm) • Median DOR: NR in I+R arm	Warnings and precautions include: • Hemorrhage • Infections • Cytopenias • Cardiac arrhythmias • Second primary malignancies • Tumor lysis syndrome • Embryofetal toxicity

Source: FDA Clinical Reviewer's Analysis

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

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Zanubrutinib was first approved by the US FDA on 14 November 2019 under the accelerated approval (Subpart H) for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (NDA 213217).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the U.S. Regulatory and Marketing History of Zanubrutinib.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of key interaction with the FDA pertaining to zanubrutinib development in the WM population is presented in the table below.

BeiGene Table 2 Major regulatory milestones for zanubrutinib for the treatment of patients with WM

Date	Milestone and details
12 Jun 2015	IND 125326 for the treatment of B-Cell malignancies in effect
12 May 2016	Type B – End-of-Phase 1
29 June 2016	Orphan Designation granted for zanubrutinib in WM patients
05 Apr 2017	Type C- Guidance: Discuss early zanubrutinib drug development plans
27 Jun 2017	Type C – Guidance - Discuss study design for Study BGB-3111-302
17 Nov 2017	Type C – Guidance: Discuss Clinical pharmacology package
07 Dec 2017	Type C – Guidance: Discuss Module 3/CMC package
01 Mar 2018	Type B – End-of-Phase 2 Meeting (BGB-3111-AU-003)
19 July 2018	Fast Track designation granted for zanubrutinib in WM
30 Oct 2018	Type C- Guidance on NDA format and Content
13 Dec 2018	Type A - Discuss FDA written response dated October 30, 2018
08 Jul 2019	Type B – End-of-Phase 2 Meeting, WM (BGB-3111-302)
14 Nov 2019	NDA 213217 approved (MCL)
09 Sept 2020	Type C – Guidance WM sNDA filing

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the key interactions between the FDA and the Applicant pertaining to the development of zanubrutinib for patients with WM.

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Reference ID: 4850271

The FDA notes that at the End-of-Phase 1 meeting on May 12, 2016, the FDA stated that major response rate (defined as PR+VGPR+CR) would be an acceptable endpoint in WM. This was reiterated at the March 1, 2018 meeting. At that time, the Agency stated that if the Applicant intends to rely on CR +VGPR as the primary endpoint, they will need to provide adequate justification that this is reasonably likely to predict clinical benefit.

The FDA also notes that at the July 8, 2019 meeting, the FDA did not agree with the Applicant's proposal (b) (4) The FDA states that it would be acceptable to include sensitivity analyses or secondary analyses which evaluated response based on IgM alone.

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

4.1. Office of Scientific Investigations (OSI)

Clinical sites were not inspected for this sNDA. The Applicant was recently inspected in October 2019 during review of the initial application for the mantle cell lymphoma indication. At that time, no study integrity issues were identified. Additionally, based on the review of the data included in this submission, the reviewer did not have concerns with the data quality and integrity of the Study. Therefore, clinical site inspections were not required for approval of this sNDA submission.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Even though patients were assigned to Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WT}$) based on MYD88 mutational status, the FDA did not require a companion diagnostic with this application. The MYD88 mutation is very common, occurring in >90% of patients with WM and responses have been demonstrated in both the $MYD88^{MUT}$ and $MYD88^{WT}$ populations. In addition, the FDA notes previous regulatory precedent with ibrutinib.

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Reference ID: 4850271

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Not Appliable. No new pharmacology/toxicology information was submitted with this application.

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 WM 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; please refer to the original NDA submission for pharmacology data and analyses.

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable. No new information is provided in this application.

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

The FDA's Assessment:
Not applicable.

Safety Pharmacology
Data:
No new information is provided in the current supplemental submission.
The Applicant's Position:

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Not applicable

The FDA's Assessment:
Not applicable.

5.4. ADME/PK

Data:
Two new DMPK reports are submitted in this application:

- Report C19047 / BGB-3111: Evaluation of Cytochrome P450 2C Induction Potential in Human Hepatocytes. This study demonstrated that under the experimental conditions, BGB-3111 at concentrations of up to 30 µM showed induction potential for CYP 2C8, 2C9 and 2C19.
- Report BGB-3111-DMPK-PK-DDI-001 / Absorption and transport characteristics of BGB-3111 using MDCK-MDR1 and Wild-type MDCK cell lines. The results indicated that BGB-3111 over a concentration of 1 µM to 10 µM was likely to be a substrate of human P-gp efflux transporter.

The Applicant's Position:
The results from these two new reports are consistent with findings presented in the initial NDA.

The FDA's Assessment:
Not applicable. This information was not reviewed as part of this application.

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:
Not applicable.

5.5.2. Genetic Toxicology

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

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Reference ID: 4850271

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable.

5.5.3. Carcinogenicity

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

The FDA's Assessment:
Not applicable.

5.5.4. Reproductive and Developmental Toxicology

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

5.5.5. Other Toxicology Studies

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

The FDA's Assessment:
Not applicable.

X X

Primary Reviewer Supervisor

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Reference ID: 4850271

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Zanubrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor. Zanubrutinib received accelerated approval (based on overall response rate) in November 2019 for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The current supplement proposes addition of an indication for treatment of adult patients with Waldenström's macroglobulinemia (WM). The proposed dosage regimen for patients with WM is 160 mg by mouth (PO) twice daily (BID) or 320 mg PO once daily (QD).

The primary evidence of efficacy in patients with WM is based on the results of a Phase 3 study (BGB-3111-302) comparing zanubrutinib 160 mg PO BID to ibrutinib 420 mg PO QD. Supportive evidence for efficacy comes from two single-arm, open-label studies of zanubrutinib in patients with WM (BGB-3111-AU-003 and BGB-3111-210). The safety assessment includes the three studies in patients with WM and three additional studies in patients with other hematologic malignancies (including MCL).

New or updated Clinical Pharmacology information reviewed in the current supplement includes *in vitro* studies evaluating zanubrutinib as an inducer of CYP2C8, 2C9, and 2C19 and as a substrate of P-gp; updated non-compartmental pharmacokinetic (PK) analysis from study BGB-3111-AU-003; updated population PK (PopPK) report; and exposure-response (E-R) analyses for efficacy (in patients with WM) and safety (in patients with WM or other hematologic malignancies).

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in NDA 213217 S-004. This supplemental NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	In Study BGB-3111-302, 102 patients with $MYD88^{MUT}$ WM were treated with zanubrutinib 160 mg PO BID. The major response rate (PR or better) was 77.5%. In Study BGB-3111-AU-003, the major response rate for patients with WM was 80.9% for zanubrutinib 160 mg PO BID and 81.8% for zanubrutinib 320 mg PO QD.
General dosing instructions	The recommended dosage of zanubrutinib for patients with WM is 160 mg PO BID or 320 mg PO QD with or without food. This dosage is identical to the previously approved recommended dosage for patients with MCL who have received at least one prior therapy.

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Review Issue	Recommendations and Comments
Dosing in patient subgroups	*Renal Impairment:* No dosage modification is recommended for patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min). The effects of dialysis on zanubrutinib are not known.
Extrinsic Factors	*Drug-Drug Interactions:* Zanubrutinib induces CYP2C8 *in vitro*.
Labeling	Revisions to the label were based on updated PK data, including an update to the recommendations for patients with severe renal impairment. Overall, the proposed labeling recommendations are acceptable upon the applicant's agreement to the FDA revisions to the label.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
The sNDA included updated clinical pharmacology results since the last new drug application (NDA) approval, including:

- An updated non-compartmental PK analysis (N=169, Report BGB-3111-CP-006) based on additional data from study BGB-3111-AU-003 since the initial PK reporting (N=132, Report BGB-3111-AU-003 CSR).
- An updated population PK analysis (N=632, Report BGB-3111-CP-008) based on additional data from studies BGB-3111-AU-003 and BGB-3111-302 since the initial population PK reporting (N=600, ReportBGB-3111-CP-002).
- Exposure-Response(E-R) analysis to understand the relationship between exposure and efficacy and safety endpoints and to support the dose recommendation of zanubrutinib in patients with WM (Report BGB-3111-CP-007).

In order to better capture observed Cmax variability in subjects, an implementation of time-dependent residual error model was subsequently incorporated into the 2-compartment pop PK model. In summary, the population analyses show that baseline ALT and health status were identified as statistically significant covariates on the PK of zanubrutinib. However, sensitivity analysis indicated that the impact of baseline ALT on the PK of zanubrutinib is unlikely to be clinically meaningful. Other covariates including body weight, baseline age, albumin, AST, bilirubin, CrCL (renal impairment), sex, tumor type, and use of acid-reducing agents did not show a statistically significant impact on the PK of zanubrutinib.

To support dose recommendations, exposure-safety and exposure-efficacy relationships were evaluated in patients with B-cell malignancies receiving zanubrutinib monotherapy in clinical studies. Overall, E-R analyses indicated that there were no evident E-R relationships between PK exposure (AUC 0-24, Cmax, or Cmin) and efficacy endpoints (response data) in patients with

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Reference ID: 4850271

WM (Report BGB-3111-CP-007). The exposure-response analysis also included additional patients with B-cell malignancies for the exposure-safety analysis (N=542 vs N=372). The updated results were similar to those previously reported (Report BGB-3111-CP-007), indicating no apparent relationship between zanubrutinib exposure and safety endpoints across the dose range from 40 mg to 320 mg.

The Applicant's Position:
The PK profile remains consistent with the data reported in the initial NDA.

The FDA's Assessment:
The pharmacology and clinical pharmacokinetics of zanubrutinib were generally consistent with data reported in the original NDA (Refer to the original Multidisciplinary Review). The following information was updated based on new data submitted to S-004:

Zanubrutinib Exposure: 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 Cmax is 295 (55%) ng/mL following 160 mg twice daily and 537 (55%) ng/mL following 320 mg once daily.

Distribution: The geometric mean (%CV) apparent volume of distribution (Vz/F) of zanubrutinib is 537 (73%) L based on non-compartmental analysis (NCA) in patients treated with zanubrutinib.

Elimination: The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib is 128 (58%) L/h based on NCA in patients treated with zanubrutinib.

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.

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.

In Study BGB-3111-AU-003, at dosing regimens of 40, 80, 160, and 320 mg once a day and 160mg twice a day, the maximum tolerated dose was not reached, and no dose-limiting toxicities were observed during the dose-escalation part of the study. Moreover, nearly full

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Reference ID: 4850271

occupancy of BTK in PBMCs was achieved in patients at all administered doses from 40mg to 320mg. The BTK occupancy in lymph node tissue was also assessed. At the 160mg twice-daily and 320mg once-daily doses, the median BTK occupancy of lymph node tissues at steady-state trough was 100% and 94%, respectively. To maximize the inhibition in target tissues, the 160 mg twice daily dose has been used in Study BGB-3111-302 as well as other ongoing Phase 2/3 clinical studies.

BeiGene Table 3 Assessment of Response by Dose (WM Efficacy Evaluable Set)

	Total Waldenström's Macroglobulinemia		
Response Category	**< 320 mg QD (N = 4) n (%)**	**160 mg BID (N = 47) n (%)**	**320 mg QD (N = 22) n (%)**
Best Overall Response, n (%)			
CR	0 (0.0)	0 (0.0)	1 (4.5)
VGPR	3 (75.0)	23 (48.9)	7 (31.8)
PR	1 (25.0)	15 (31.9)	10 (45.5)
MR	0 (0.0)	8 (17.0)	2 (9.1)
SD	0 (0.0)	1 (2.1)	2 (9.1)
PD	0 (0.0)	0 (0.0)	0 (0.0)
VGPR or CR Rate, n (%)	3 (75.0)	23 (48.9)	8 (36.4)
95% CI [a]	(19.4, 99.4)	(34.1, 63.9)	(17.2, 59.3)
Major Response Rate (PR or Better), n (%)	4 (100.0)	38 (80.9)	18 (81.8)
95% CI [a]	(39.8, 100.0)	(66.7, 90.9)	(59.7, 94.8)
Overall Response Rate (MR or Better), n (%)	4 (100.0)	46 (97.9)	20 (90.9)
95% CI [a]	(39.8, 100.0)	(88.7, 99.9)	(70.8, 98.9)
Median Study Follow-up (Range) month [a]	63.13 (42.81, 64.16)	31.51 (4.44, 55.00)	43.37 (8.05, 46.72)

Source: BGB-3111-AU-003, Table 14.2.1.1.1.5.
Abbreviations: BID, twice daily; CI, confidence interval; CR, complete response; MR, minor response; PD, progressive disease; PR, partial response, QD, once daily; SD, stable disease; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.
Percentages are based on N, the number of patients in the WM Efficacy Evaluable Set (ie, received ≥ 1 dose of zanubrutinib, had baseline IgM or M-protein ≥ 5 g/L, and no prior exposure to a BTK inhibitor).
[a] Calculated using the Clopper-Pearson method.
Data cutoff: 31MAR2020

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Reference ID: 4850271

There is now extensive experience at the 160 mg twice-daily and 320 mg once-daily zanubrutinib doses, with both schedules showing a high level of activity without compromise in the tolerability profile as compared with lower doses of zanubrutinib.

The Applicant's Position:
The zanubrutinib dose of 160 mg twice daily or 320 mg once daily was identified as the recommended dose based on the totality of safety, efficacy, PK, and pharmacodynamics (BTK occupancy data) results from Study BGB-3111-AU-003, Study BGB 3111-1002, and Study BGB-3111-302.

The FDA's Assessment:
FDA agrees with the Applicant's position. The recommended dosage of zanubrutinib for patients with WM is 160 PO BID or 320 mg PO QD with or without food. This dosage is identical to the previously approved recommended dosage for patients with MCL who have received at least one prior therapy.

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:
Renal Impairment: No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥ 15 mL/min, estimated by Cockcroft-Gault). The effect of dialysis on zanubrutinib pharmacokinetics is unknown.

Refer to the original Multidisciplinary Review for recommendations for patients with hepatic impairment or drug-drug interactions.

6.2.2.3. Outstanding Issues

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

The FDA's Assessment:
Two clinical pharmacology post-marketing studies (PMR 3735-3 and PMC 3735-4) were issued at the time of the original approval of NDA 213217. Both remain outstanding.

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Reference ID: 4850271

6.3. Comprehensive Clinical Pharmacology Review

General Pharmacology and Pharmacokinetic Characteristics

Data:
No new information is provided in the current submission.
The Applicant's Position:
The clinical pharmacology and PK data submitted in the original NDA supports a 160 mg twice daily or 320 mg once daily zanubrutinib dose for the treatment of adult patients with WM. Results from additional bioanalytical and PopPK data remain consistent with the data provided in the original NDA.

The FDA's Assessment:
The general pharmacology and pharmacokinetic characteristics of zanubrutinib were generally consistent with data reported in the original NDA (Refer to the original Multidisciplinary Review). The Applicant submitted updated non-compartmental PK and population PK analyses and new *in vitro* studies evaluating zanubrutinib as an inducer of CYP2C8, 2C9, and 2C19 and as a substrate of P-gp. A summary of new or updated information based on these studies is provided in the table below.

<table>
<tr><th colspan="3">Dose and Exposure</th></tr>
<tr><td>Therapeutic dose and exposure</td><td colspan="2">The proposed dosing regimen is 160 mg PO BID or 320 mg PO QD with or without food. Steady-state C_{max} and daily AUC in patients following administration of the proposed dosing regimen is summarized below.
<table>
<tr><th>Geometric Mean (%CV)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-24} (h·ng/mL)</th></tr>
<tr><td>160 mg PO BID</td><td>295 (55%) (n=76)</td><td>2,099 (42%) (n=55)</td></tr>
<tr><td>320 mg PO QD</td><td>537 (55%) (n=73)</td><td>1,917 (59%) (n=27)</td></tr>
</table></td></tr>
<tr><th colspan="3">Pharmacokinetic (PK) Features</th></tr>
<tr><td>Distribution</td><td>Vz/F</td><td>Geometric Mean (%CV): 537 (73%) L</td></tr>
<tr><td>Elimination</td><td>CL/F</td><td>Geometric Mean (%CV): 128 (58%) L/h</td></tr>
<tr><td>Transporters</td><td colspan="2">Zanubrutinib is likely to be a substrate of P-gp.</td></tr>
<tr><td>Intrinsic Factors</td><td colspan="2">No clinically significant differences in the PK 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 PK is unknown. There were too few</td></tr>
</table>

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	Black patients (n=3) with PK data to assess whether there are differences in zanubrutinib PK in Black patients.	
Extrinsic Factors	Drug interactions – zanubrutinib as perpetrator	*In vitro*, zanubrutinib induces CYP2C8, 2C9, and 2C19. Refer to the original Multidisciplinary Review for evaluation of zanubrutinib as an inducer of CYP2C9 and CYP2C19 *in vivo*.
Population PK Analyses	A two-compartment model with sequential zero-order then first-order absorption and first-order elimination from the central compartment was used to describe the PK of zanubrutinib. The model included data from 632 patients enrolled in 9 studies. Baseline ALT (on CL/F) and health status (patient vs healthy volunteer; on CL/F) were identified as significant covariates. Other covariates, including age, body weight, AST, bilirubin, creatinine clearance, sex, tumor type, and use of gastric acid-reducing agents did not show statistically significant impact on the PK of zanubrutinib. The results of the current Population PK analysis were generally consistent with the previously submitted PopPK analysis (refer to original Multidisciplinary Review).	
Pharmacodynamic (PD) Features		
Exposure-Response Analyses	There was no significant relationship between zanubrutinib exposure and response rates (VGPR or better; PR or better; MR or better) in patients with WM. There were no significant relationships between zanubrutinib exposure and adverse events including cytopenias, infections, atrial fibrillation and flutter, and bleeding in a pooled patient population.	

Clinical Pharmacology Questions

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

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

The FDA's Assessment:
The primary evidence of effectiveness in patients with WM comes from Study BGB-3111-302. In

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this Phase 3, randomized study, 201 patients with MYD88^{MUT} WM were treated with zanubrutinib 160 mg PO BID (n=102) or ibrutinib 420 mg PO QD (n=99). The major response rate (PR or better) was 77.5% for patients treated with zanubrutinib compared to 77.8% for patients treated with ibrutinib.

In addition, a non-randomized cohort of 28 patients with MYD88^{WT} WM were enrolled in Study BGB-3111-302 and treated with zanubrutinib 160 mg PO BID. Among 26 evaluable patients, the major response rate (PR or better) was 50%. Refer to **Section 8.1.1** for a detailed review of efficacy results.

Additional evidence of effectiveness and support for the alternative starting dose option of 320 mg PO QD was provided by Study BGB-3111-AU-003. This Study is a Phase 1/2 study of zanubrutinib in 385 patients with B-cell lymphoid malignancies including 78 patients with WM. Of the 73 efficacy-evaluable patients with WM, 47 received zanubrutinib 160 mg PO BID, 22 received zanubrutinib 320 mg PO QD, and 4 received doses <320 mg per day. The major response rate (PR or better) was similar for patients with WM who received zanubrutinib 160 mg PO BID or 320 mg PO QD (81% vs 82%; refer to **BeiGene Table 3**). In addition, except for minor differences, the safety profile was not substantially different between the two dosage regimens among all patients with B-cell malignancies (**FDA Table 2**).

FDA Table 2: Summary of Treatment-Emergent Adverse Events by Zanubrutinib Dose in Study BGB-3111-AU-003

	Zanubrutinib 160 mg PO BID (n=278)	Zanubrutinib 320 mg PO QD (n=95)
Patients with at least one TEAE	98.6%	98.9%
Grade 3 or Higher	68.3%	56.8%
Serious	54.7%	43.2%
Leading to Death	6.8%	3.2%
Leading to Discontinuation	12.9%	8.4%
Leading to Dose Reduction	10.1%	4.2%
Patients with at least one treatment-related TEAE	73.0%	74.7%
Grade 3 or Higher	28.1%	27.4%
Serious	15.1%	16.8%
Leading to Death	0.7%	1.1%
Leading to Discontinuation	4.3%	2.1%
Leading to Dose Reduction	8.3%	2.1%

Source: BGB-3111-AU-003 CSR, Table 14.3.1.2.1.2

The proposed dosing regimens are further supported by pharmacodynamic data previously reviewed from Study BGB-3111-AU-003 and new exposure-response analyses. Briefly, high BTK occupancy in peripheral blood mononuclear cells (PBMCs) and lymph nodes was observed from patients with B-cell malignancies treated with zanubrutinib 160 mg PO BID or 320 mg PO QD.

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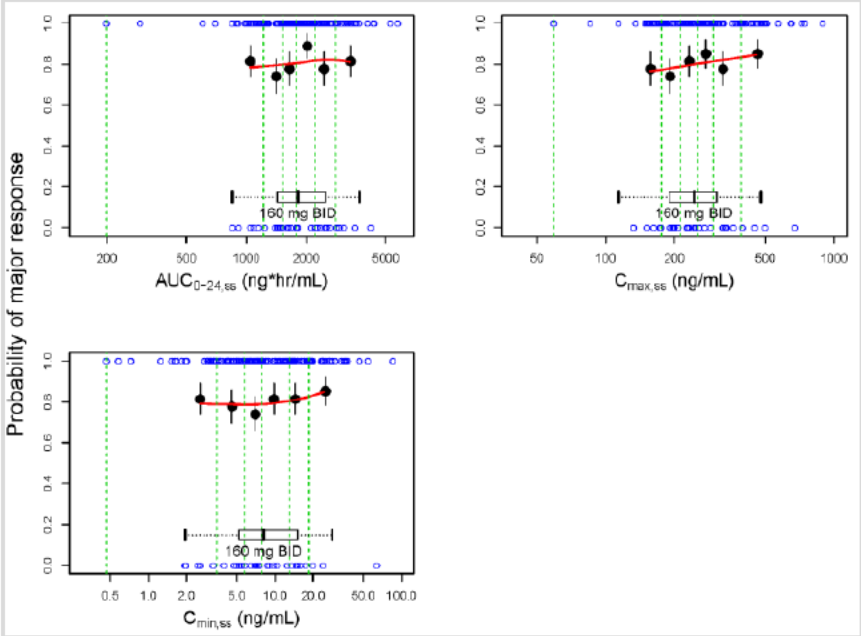
Reference ID: 4850271

The results indicate similar near-complete target inhibition at a total daily zanubrutinib dose of 320 mg throughout the dosing interval regardless of dose regimen (160 mg BID or 320 mg QD). Refer to the original Multidisciplinary Review for additional information.

Exposure-Response (E-R) Analyses: E-R analyses were conducted for both efficacy (in patients with WM) and safety (in patients with hematologic malignancies). For both analyses, the zanubrutinib PopPK model was used to generate individual PK parameters ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{min,ss}$) for patients with PK data. The exposure distribution for patients with and without the endpoint of interest were compared and probability of response was plotted versus exposure.

E-R for Efficacy in Patients with WM: Data from 162 patients with WM with both efficacy and PK data were included in the efficacy E-R analysis. Patients with WM were treated in Studies BGB-3111-AU-003 (n=62) and BGB-3111-302 (n=100) and received zanubrutinib total daily doses ranging from 40 to 320 mg. Most patients received zanubrutinib 160 mg PO BID (n=143) or 320 mg PO QD (n=15). For the full analysis, three efficacy response levels were evaluated based on Investigator assessment: VGPR or better, PR or better, and MR or better. An additional analysis based on IRC assessment in Study BGB-3111-302 only was also conducted. For all efficacy endpoints evaluated there was no significant E-R relationship with any of the tested PK parameters (**FDA Figure 1**). Refer to **Appendix 19.4.1.2** for detailed review of the efficacy E-R analysis.

FDA Figure 1: Major Response Rate per Investigator Assessment in Studies -AU-003 and -302



Source: BGB-3111-CP-007, Figure 4

FDA conducted an exploratory E-R analysis using FDA-adjudicated efficacy data from 128

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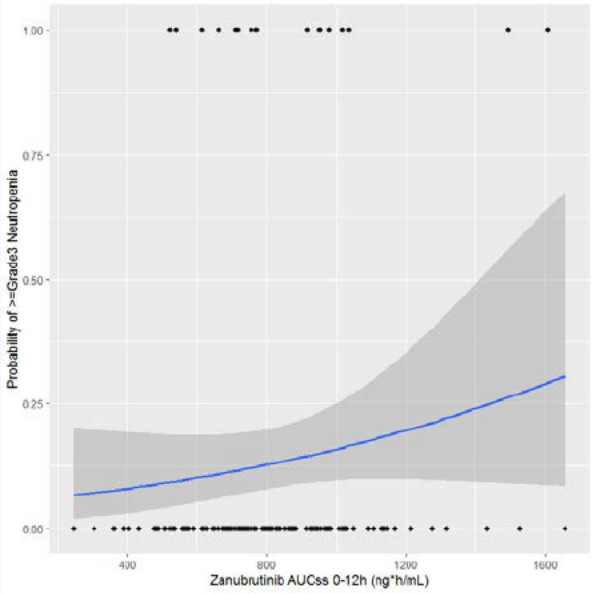
Reference ID: 4850271

patients with WM treated with zanubrutinib 160 mg BID in Study BGB-3111-302. Results were generally consistent with the Applicant's analysis, showing no significant E-R relationship between zanubrutinib exposure and response in patients with WM. Refer to **Appendix 19.4.1.4** for additional information.

E-R for Safety in Patients with Hematologic Malignancies: Data from 542 patients with hematologic malignancies (including WM) with both safety and PK data were included in the safety E-R analysis. Patients were treated in Studies BGB-3111-AU-003 (n=337), BGB-3111-302 (n=128), BGB-3111-205 (n=13), BGB-3111-206 (n=20), and BGB-3111-1002 (n=44) and received zanubrutinib total daily doses ranging from 40 to 320 mg. Most patients received zanubrutinib 160 mg PO BID (n=442) or 320 mg PO QD (n=93). Safety endpoints included Grade ≥3 neutropenia, Grade ≥3 thrombocytopenia, Grade ≥3 infections/infestations, Grade ≥3 anemia, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and any bleeding events. No significant E-R relationships were identified for any tested safety events. There was a positive but non-significant trend for increased incidence of Grade ≥3 neutropenia with increasing exposure. Refer to **Appendix 19.4.1.2** for detailed review of the safety E-R analysis.

FDA conducted an exploratory E-R analysis using safety data for neutropenia from 128 patients with WM treated with zanubrutinib 160 mg BID in Study BGB-3111-302. A positive but non-significant trend was observed for ≥Grade 3 neutropenia (**FDA Figure 2**), similar to the Applicant's analysis. Refer to **Appendix 19.4.1.4** for additional information.

FDA Figure 2: E-R for ≥Grade 3 Neutropenia in Study BGB-3111-302



Source: Reviewer's Analysis, Appendix 19.4.1.4

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Reference ID: 4850271

In summary, the use of either 160 mg PO BID or 320 mg PO QD as a starting dose in patients with WM is supported by the totality of evidence including the similar response rates and safety profiles between regimens, near-complete target inhibition for both dose regimens, and lack of significant E-R relationships for efficacy and safety.

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

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

The FDA's Assessment:
Yes. The proposed zanubrutinib dose of 160 mg BID resulted in a response rate comparable to the ibrutinib arm in patients with WM (refer to **Section 8.1**). In addition, a dosing regimen of 320 mg QD is an appropriate alternative starting dose for the general patient population of patients with WM based on the PK, PD, safety, and efficacy data as described above.

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:
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. The population PK analysis included too few Black patients (n=3) to assess whether there are differences in zanubrutinib pharmacokinetics in Black patients.

Renal Impairment: Creatinine clearance was not a significant covariate on either clearance or volume of zanubrutinib in the population PK analysis (see **Appendix 19.4.1.1**). As shown in FDA Figure 3, steady-state total zanubrutinib exposure (AUC and Cmin) were similar in patients with normal renal function (CLcr >90 mL/min; n=204) and mild (CLcr 60-89 mL/min; n=231), moderate (CLcr 30-59 mL/min; n=96), or severe (CLcr 15-29 mL/min; n=10) renal impairment. There was limited data available from patients with end-stage renal disease (CLcr <15 mL/min; n=1).

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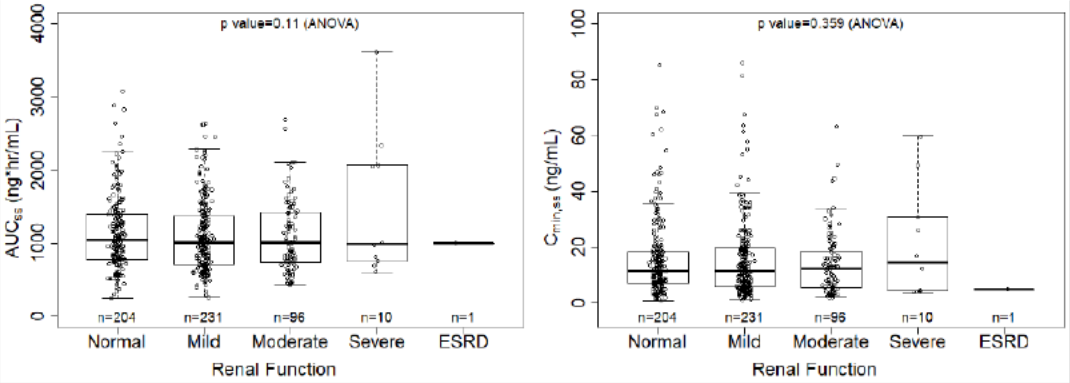
FDA Figure 3: Steady-State Exposure of Zanubrutinib by Renal Function



Source: BGB-3111-CP-008 Population PK Report, Figure 19

FDA conducted an exploratory PopPK analysis evaluating an alternative model structure. In FDA's model, creatinine clearance was not a statistically significant covariate on zanubrutinib apparent clearance. The geometric mean of CL in patients with normal, mild, moderate, and severe renal impairment were 162, 184, 187, and 186, respectively (Refer to **Appendix 19.4.1.3** for additional information). Based on the updated population PK analyses, no dosage modification is recommended for patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min).

MYD88 and CXCR4 Status: In the ASPEN study, MYD88 L265P and CXCR4 [WHIM] mutations were centrally tested in CD19+ unselected bone marrow aspirates of 228 patients (N=225 fresh) prior to cohort assignment. One patient did not provide samples to the central laboratory. MYD88 L265P was detected using a laboratory developed test (LDT; PCR-based followed by bidirectional Sanger sequencing (b) (4) designed to detect MYD88 mutations in amino acids Q262-I266 [Reference Sequence ID: NM_002468.4] with an approximately 0.5% limit of detection. Mutations between T318 to S341 in CXCR4 were detected by Sanger sequencing (10-15% sensitivity for detecting nonsense, frameshift, and other CXCR4 mutations [Reference Sequence ID: NM_003467.2]) and results were used for stratification (WHIM versus Wild-Type (WT)/missing). Refer to **Sections 8.1.1** for additional details.

Of 229 patients enrolled, about 87% (N=200) had a MYD88 L265P mutation and thus were assigned to Cohort 1; one additional patient was assigned to Cohort 1 based on local test results. The remaining 12% with no MYD88 L265P detected (N=26) or with unknown status (N=2) were assigned to Cohort 2. Approximately 9.5% of patients in Cohort 1 (N=19) were determined to have CXCR4 mutations [WHIM status], which is a lower than expected frequency based on the literature (30-40% depending on method and population, Treon 2015, Garcia-Sanz 2016, Kaiser 2021). Twelve unique CXCR4 mutations were detected (frameshift n= 9, nonsense n=2; deletion at S338 n=1), with S338Ter occurring in 42% (8/19) of the cases. One additional patient was found to have a CXCR4 mutation (frameshift) in Cohort 2.

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In a subsequent post-hoc analysis, CXCR4 and MYD88 mutations were retrospectively tested in residual samples of 190 patients in Cohort 1 (95%) and of 20 patients in Cohort 2 (71%) using a central next generation sequencing (NGS) assay with a reported 0.25% limit of detection for CXCR4 (b) (4)). This testing identified a CXCR4 WHIM mutation in 28% (53/190) of available samples in Cohort 1 (25 unique 43% S338Ter) vs. 9.5% (19/200) by the Sanger assay used for stratification. Of note, CXCR4 nonsense mutations, which have been associated with poorer clinical outcome compared to frameshift mutations (Wang 2021), appeared to be more frequent in the ibrutinib arm, although numbers are small. Also, when assessed by geographic region, the frequency of CXCR4 WHIM mutations ranged from approximately 13% in the Australia/New Zealand region, ibrutinib arm to 67% (6/9 patients) in the US region, zanubrutinib arm. In Cohort 2, the one patient was also confirmed to have CXCR4 WHIM mutation by NGS. Distribution of CXCR4 genotype by test and across arms and treatment status are presented in **FDA Table 3** and FDA Table 4 In response to an FDA information request of April 13, 2021, the Applicant noted that for the 36 cases detected as CXCR4 WHIM only by NGS in Cohort 1, the median variant allele frequency (VAF) was 1.9% (range: 0.36% to 14.49%), and of these, 34 (94%) had VAF below 10%, which is the lower bound of the Sanger assay sensitivity. In contrast, the median VAF was 20.93% (range: 7.93% to 46.96%) for the 18 cases (17 in Cohort 1) detected as CXCR4 WHIM by both Sanger and NGS. Regarding MYD88 status in Cohort 1 using NGS, non-L265P mutations, some of which are predicted to lead to a non-functional protein, were identified in 7 patients in addition to MYD88 L265P [zanubrutinib arm: (1) M232T; (2) D165del; (3) L72M; (4) V217F; (5) P182L; (6) T107SfsTer24; ibrutinib arm: (7) W91Ter and G93Ter], and 10 patients with MYD88 L265P positive WM at study entry did not have MYD88 mutations detected by NGS. In Cohort 2, 2 patients with MYD88 L265P negative WM at study entry were determined to have subclonal MYD88 L265P mutations based on NGS (VAF 0.21% (under the MYD88 LDT validated sensitivity) and 1.09%).

FDA Table 3: CXCR4 status by Sanger Sequencing and by NGS in the ASPEN Study (N=229)

		CXCR4 by NGS, N			
		WT	**WHIM**	Unknown *	**Total**
CXCR4 by Sanger, N	Cohort 1				
	WT	136	36	9	181
	WHIM	1	17	1	19
	Unknown *	0	0	1	1
	Total	137	53	11	201
	Cohort 2				
	WT	18	0	5	23
	WHIM	0	1	0	1
	Unknown *	1	0	3	4
	Total	19	1	8	28
Total		156	54	19	229

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*Source: Reviewer's exploratory analysis (admutat dataset). WT=wild type, refers to mutation not detected; *Unknown: Missing or insufficient sample for testing or failed QC.*

FDA Table 4: Distribution of CXCR4 WHIM mutation by Sanger and NGS across Arms and Treatment Status in the ASPEN Study, Cohort 1 (N=201)

	Zanubrutinib (N=102)		Ibrutinib (N=99)		
	Treatment Naïve	Relapsed/ Refractory	Treatment Naïve	Relapsed/Refractory	§Total Detected
CXCR4 WHIM by Sanger (stratification), N [*only by Sanger]	1 [0]	10 [0]	0 [0]	8 [2]	19 [2]
CXCR4 WHIM by NGS (post hoc), N [*only by NGS]	8 [7]	25 [15]	1 [1]	19 [13]	53 [36]

*Source: Reviewer's exploratory analysis (adsl dataset). *Only: refers to samples positive for CXCR4 WHIM mutations by one of the methods (Sanger or NGS) and negative or with unknown status by the other method. §Unknown or negative status not represented. Patients with NGS samples (zanubrutinib N=98, ibrutinib N=92); Patients with Sanger samples (zanubrutinib N=102, ibrutinib N=98 [excludes patient enrolled with local test])*

The CXCR4 WHIM status has been associated with a more aggressive disease compared to CXCR4 WT. The increased sensitivity of NGS compared to Sanger may have contributed to the higher frequency of CXCR4 mutations identified post-hoc compared to at randomization, although with a lower median VAF (**FDA Table 4**). This higher frequency created a potential imbalance in the distribution of patients with CXCR4 mutations between arms, which may have affected the magnitude of treatment effect. Additionally, differences in the frequency of CXCR4 WHIM mutation types (nonsense vs frameshift) per arm, and regional differences, including differences in the proportion of CXCR4 mutations and of treatment naïve vs relapsed or refractory within each region were noted. Refer to **Sections 8.1.1** for additional discussion on the potential impact of these factors in the stratification and treatment outcome.

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

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

The FDA's Assessment:
The Applicant submitted two new *in vitro* studies evaluating the potential for zanubrutinib to induce CYP2C8, 2C9, and 2C19 and zanubrutinib as a potential substrate of P-gp.

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Induction of CYP2Cs: The results of Study C19047 showed that zanubrutinib at up to 30 µM had potential to induce mRNA expression and enzyme activity of CYP2C8, 2C9, and 2C19 in human hepatocytes.

CYP2C8: In the original NDA submission, the Applicant included a Physiologically-Based Pharmacokinetic (PBPK) model evaluating the effects of multiple doses of zanubrutinib on rosiglitazone (CYP2C8 substrate); however, the model only evaluated effects of zanubrutinib as an inhibitor of CYP2C8 and an inducer of CYP3A4. Potential induction of CYP2C8 caused by zanubrutinib was not evaluated.

Based on the new *in vitro* study results, zanubrutinib caused concentration-dependent increases in CYP2C8 mRNA expression and enzyme activity (FDA Table 5) After administration of zanubrutinib 320 mg PO QD the expected maximum hepatic concentration would be approximately 2 µM, assuming a maximum hepatic concentration of 30-fold the mean unbound steady-state C_{max}. At 3 µM zanubrutinib (~50% higher than the expected maximum hepatic concentration), the fold change in CYP2C8 mRNA expression and enzyme activity was >2-fold in all 3 donors. Relative to positive control (rifampin 25 µM), the maximum induction caused by zanubrutinib 3 µM was 33 – 70% for mRNA expression and 14 – 53% for enzyme activity. *In vivo*, rifampin is a moderate inducer of CYP2C8. Based on the limited data available from the *in vitro* study and lack of clinical data, there is insufficient data to quantify the magnitude of induction of CYP2C8 by zanubrutinib *in vivo*. However, the likelihood of moderate or strong CYP2C8 induction *in vivo* caused by zanubrutinib is expected to be low given the observed weak induction of CYP3A and CYP2C19 *in vivo*, lack of significant induction of CYP2C9 *in vivo* (refer to original Multidisciplinary Review), and lower induction potential at clinically relevant concentrations *in vitro* compared to rifampin (a moderate CYP2C8 inducer). The Applicant's proposed labeling was updated to reflect that zanubrutinib induces CYP2C8 *in vitro*.

FDA Table 5: Induction of CYP2C8 mRNA Expression and Enzyme Activity

Fold Change	Donor	Zanubrutinib Concentration			Negative Control	Positive Control
		0.3 µM	3 µM	30 µM		
mRNA Expression	1	1.33	6.47	8.41	0.84	8.84
	2	1.24	5.15	17.28	1.16	9.66
	3	0.98	3.43	3.81	1.25	8.41
Enzyme Activity	1	1.39	3.78	3.94	1.17	6.22
	2	1.09	2.39	6.48	0.96	11.22
	3	1.51	3.57	3.64	1.36	14.55

Notes: negative control = flumazenil 25 µM; positive control = rifampin 25 µM
Source: Study C19047, Tables S-1 and S-2

CYP2C9 and CYP2C19: At the original NDA approval for zanubrutinib, the labeling included results of an *in vivo* DDI study that included evaluation of the effects of multiple doses of zanubrutinib on substrates of CYP2C9 (warfarin) and CYP2C19 (omeprazole). Given the prior *in vivo* results, no update to the label is necessary based on the new *in vitro* results for CYP2C9

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Reference ID: 4850271

and 2C19. Refer to the original Multidisciplinary Review.

Substrate of P-gp: In Study BGB-3111-DMPK-PK-DDI-0001, zanubrutinib exhibited high permeability (>10x10^{-6} cm/s) in wild-type MDCK cells. The efflux ratios for zanubrutinib in MDCK-MDR1 and wild-type MDCK cells with and without verapamil are summarized in **FDA Table 6.**

FDA Table 6: Zanubrutinib Efflux Ratios in MDCK-MDR1 and Wild-Type MDCK Cells

Cells	Zanubrutinib Concentration	Efflux Ratio	
		Zanubrutinib Alone	Zanubrutinib + Verapamil
MDCK-MDR1	1 µM	3.46	1.59
	10 µM	2.19	1.14
Wild-Type MDCK	1 µM	1.86	0.79
	10 µM	1.30	1.09

Source: Study BGB-3111-DMPK-PK-DDI-0001, Table 2

In the original NDA submission, the Applicant included results of a prior *in vitro* study of zanubrutinib as a potential substrate of P-gp in a Caco-2 monolayer model. Results of that study showed that zanubrutinib may be a substrate of P-gp with potential for efflux at low concentrations; however, significant clinical impact of P-gp inhibition was considered unlikely given the high permeability of zanubrutinib. The labeling included language stating that zanubrutinib is likely to be a substrate of P-gp. Results of the new *in vitro* study are consistent with those previously reported and therefore no update to the label is necessary. Refer to the original Multidisciplinary Review.

X X

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Reference ID: 4850271

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

BeiGene Table 4 List of Clinical Trials Relevant to this sNDA.

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
BGB-3111-302 ASPEN NCT03053440	Phase 3, randomized, open-label, comparison of BGB-3111 and ibrutinib (cohort 1), with a nonrandomized cohort (cohort 2)	Cohort 1: Zanubrutinib 160mg BID (n=101; 82 RR) Ibrutinib 420 mg QD (n=98; 80 RR) Cohort 2: Zanubrutinib 160mg BID (n=28; 23RR) oral	Primary: VGPR or CR per overall combined assessment by IRC Secondary: VGPR plus CR rate (by Investigator) MRR, PFS, DOR assessed by IRC and INV; Resolution of treatment precipitating symptoms Anti-lymphoma effect Exploratory: Disease response in Cohort 2; OS, TTR, IgM response, QOL	Until PD or unacceptable toxicity	229	WM RR or TN unsuitable for chemo-immunotherapy MYD88 mutation (Cohort 1) or MYD88 wild type or unknown (Cohort 2)	US, Australia; Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain,

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							Sweden, and UK
Additional Studies to Support Efficacy							
BGB-3111-AU-003 NCT02343120	Phase 1/2 Single arm, open-label, multiple dose, dose escalation and expansion study of BGB-3111 in subjects with B-cell lymphoid malignancies	WM patients: Part 1: Zanubrutinib 40 to 320 mg QD, 160 mg BID Part 2: Zanubrutinib 320 mg QD or 160 mg BID oral	Primary: VGPR or CR rate Secondary: MRR, ORR (MR or better), Duration of VGPR or CR, MRR, ORR, Time to VGPR or CR, PFS, OS	Until PD or unacceptable toxicity	Part 1: 17 Part 2: 385	Subgroup with WM: N = 78 RR WM: N = 54 TN: WM: N= 24 Total: CLL/SLL, MCL, FL, MZL, DLBCL, WM, HCL, MALT, Richter's Transf.	US, Australia, New Zealand, South Korea, Italy, UK
BGB-3111-210 NCT03332173	Phase 2 Single arm, open-label multicenter study in RR WM	Zanubrutinib 160mg BID oral	Primary: MRR by IRC Secondary: response rate, PFS, DOR, time to response assessed by IRC and Investigator per overall combined assessment and by	Until PD or unacceptable toxicity	44	R/R WM	China

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			IRC per overall IgM criteria, Resolution of treatment precipitating symptoms, Anti-lymphoma effect				
Additional Studies to Support Safety							
BGB-3111-206 NCT03206970	Phase 2 Single arm, open-label multicenter study in RR MCL	160mg BID oral	Response, safety	Until PD or unacceptable toxicity	86	R/R MCL	China
BGB-3111-1002 NCT03189524	Phase 1, safety and tolerability, PK/PD study in B-cell malignancies	160 mg BID and 320 mg QD oral	Response, safety, PK	Until PD or unacceptable toxicity	44	R/R CLL/SLL, MCL, FL, MZL, WM	China
BGB-3111-205 NCT03206918	Phase 2 Single arm, open-label multicenter study in RR CLL	160mg BID oral	Response, safety	Until PD or unacceptable toxicity	91	R/R CLL	China

Source:BGB-3111-302 CSR, BGB-3111-210 CSR, and BGB-3111-AU-003 CSR, m2.7.4 Table 1
Abbreviations: BID, twice daily; CR, complete response; CSR, clinical study report; DOR, duration of response; IgM, immunoglobin M; IRC, Independent Review Committee; MR, minor response; MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QOL, quality of life; R/R, relapsed/refractory; TN, treatment-naïve; TTR, time to response; UK, United Kingdom; US, United States; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

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The Applicant's Position:

The primary study to support the evaluation of efficacy is BGB-3111-302 ASPEN. Study BGB-3111-302, supported by Studies BGB-3111-AU-003 and BGB-3111-210, demonstrated at least comparable clinical efficacy of zanubrutinib to ibrutinib in terms of the primary endpoint with support of secondary outcomes in adult patients with Waldenström's macroglobulinemia. Three additional trials are included in the overall safety pool for a total of 779 patients with a median duration of exposure of 26 months (min/max: 0.1/65.3 months) while almost 75% of patients were treated for longer than 12 months.

Zanubrutinib treatment was generally well tolerated in all patient groups and the safety profile was consistent across patient groups. The spectrum of adverse events observed across all patient groups is consistent with the known toxicity profile for the BTK inhibitor class as well as those intrinsic to B-cell malignancy patient populations; these could be readily monitored with conventional safety assessments, were manageable, and for the most part, were reversible. For toxicities such as diarrhea and cardiovascular adverse events, including atrial fibrillation/flutter and hypertension, the incidence among zanubrutinib-treated patients appears appreciably lower than for the first generation and less selective BTK inhibitor, ibrutinib. The comprehensive analysis of adverse events did not reveal any new or unanticipated safety signals. The improved safety profile predicted from its pharmacokinetic and pharmacodynamic profiles, as well as from its superior selectivity, is corroborated by results from Study BGB-3111-302 as well as all available safety data. The favorable safety findings with zanubrutinib were accompanied by improvements in daily life, with greater improvements seen overall for zanubrutinib over ibrutinib even when disease is controlled to a similar extent. Taken together, these results demonstrate that zanubrutinib offers the potential for improved safety and tolerability and an improved benefit versus risk profile over existing treatment options for patients with WM.

The FDA's Assessment:

The FDA agrees that the pivotal study to support the efficacy of zanubrutinib in patients with WM is Study BGB-3111-302 (ASPEN). Studies BGB-3111-AU-003 and BGB-3111-210 were supportive. The FDA review was based primarily on the data from Study BGB-3111-302.

Study BGB-3111-302 is the pivotal study supporting efficacy of zanubrutinib in adult patients with Waldenström's macroglobulinemia who required therapy according to consensus panel criteria from the 6th IWWM (IWWM-6). The primary endpoint is CR+VGPR rate. Due to a lack of efficacy of ibrutinib in patients with MYD88^{WT}, an exploratory cohort (Cohort 2) of MYD88^{WT} patients (approximately 10% of the overall WM population) were not randomized and were treated with zanubrutinib. The clinical study report presents analysis of available efficacy data through the protocol-specified data cutoff of August 31, 2019. Additional efficacy and safety data with cutoff of March 31, 2020 were also submitted.

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Reference ID: 4850271

The FDA does not agree with the Applicant's inclusion of safety results from study BGB-3111-302 in this section. Additionally, the FDA does not agree with the Applicant's statement, "Zanubrutinib treatment was generally well tolerated in all patient groups". This statement is promotional, broad, and subjective. See the Safety sections of this review for additional discussion of the safety findings from study BGB-3111-302.

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8 Statistical and Clinical Evaluation

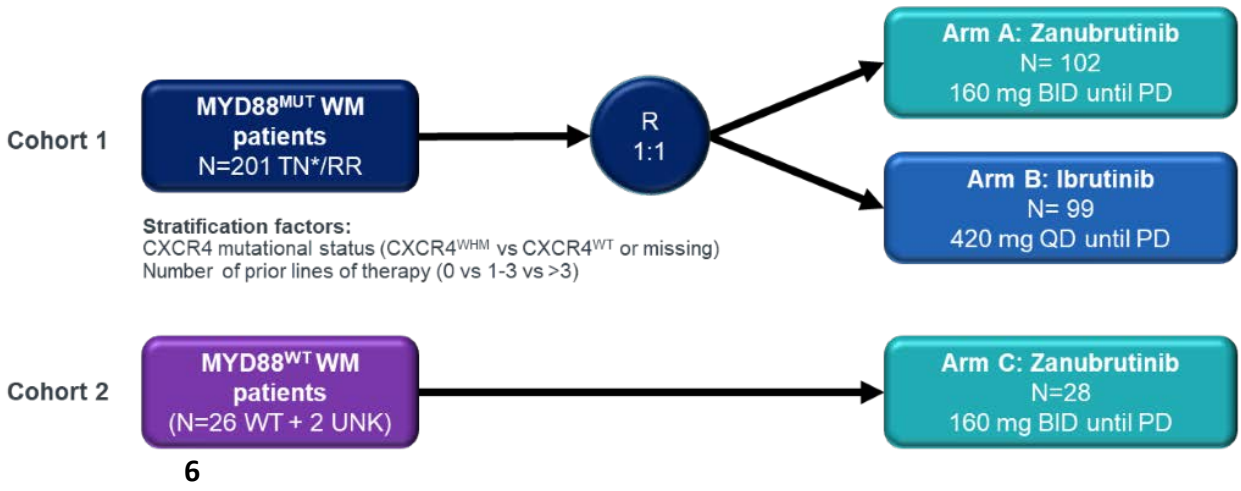
8.1. Review of Relevant Individual Trials Used to Support Efficacy

BGB-3111-302 / ASPEN

Trial Design

BGB-3111-302 is an ongoing, Phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of zanubrutinib and ibrutinib in patients with WM who required therapy according to the consensus panel criteria from the IWWM-7 (Dimopoulos et al 2014). Patients may have been TN, have relapsed, or been refractory to prior therapy. Patients with no prior therapy (ie, TN) comprised no more than 20% of Cohort 1. The study schema is presented in Figure 1.

BeiGene Figure 1 Schema for Study BGB-3111-302



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Abbreviations: BID, twice a day; CXCR4, CXC-chemokine receptor 4; *MYD88*^{MUT}, mutated MYD88 gene; *MYD88*^{WT}, wild-type MYD88 gene; PD, progressive disease; QD, once a day; R, randomization; RR, relapsed or refractory; TN, treatment naive; UNK, unknown; WHIM, Warts, Hypogammaglobulinemia, Immunodeficiency,
and Myelokathexis syndrome; WM, Waldenström's Macroglobulinemia; WT, wild-type
*TN: treatment-naive and unsuitable for chemoimmunotherapy (up to 20% of overall population)

Trial location: US, Australia, EU countries

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Reference ID: 4850271

Choice of control groups

Ibrutinib was chosen as the comparator since it was approved in many countries for the treatment of WM in adults who have received prior treatment for their disease or in previously untreated patients for whom treatment with chemoimmunotherapy is not suitable and approved by the US FDA for the treatment of WM in adults.

Selection of study population

Key Inclusion Criteria

- Men and women ≥ 18 years of age with a clinical and definitive histological diagnosis of relapsed/refractory Waldenström's macroglobulinemia or who were treatment-naïve and considered by their treating physician to be unsuitable for standard chemo-immunotherapy regimens were eligible for the study
- Patients had to meet at least 1 criterion for treatment according to consensus panel criteria from the IWWM-7 (Dimopoulos et al 2014) and have measurable disease, as defined by a serum IgM level > 0.5 g/dL.
- For patients who received no prior therapy for Waldenström's macroglobulinemia, "unsuitable for treatment with a standard chemo-immunotherapy regimen" was a physician-determined status based on comorbidities and risk factors.
- Patients who relapsed after stem cell transplant were eligible if they were at least 3 months (autologous) or 6 months (allogeneic) post-transplant.
- Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate hematologic, kidney, heart, and liver function, and adequate coagulation parameters.

Key Exclusion Criteria

Patients who had the following were not eligible for the study:

- Central nervous system involvement by Waldenström's macroglobulinemia
- Prior exposure to a BTK inhibitor
- Evidence of disease transformation
- Corticosteroid therapy with antineoplastic intent within the past 7 days
- Chemotherapy, targeted therapy, radiation therapy or antibody-based therapies within the past 4 weeks

1. Zanubrutinib Dose Modifications for Hematologic Toxicity

For the first occurrence of hematologic toxicity, zanubrutinib treatment may have restarted at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. If the same event recurred, patients restarted at 1 dose level lower upon recovery of the toxicity to ≤ Grade 1 or

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Reference ID: 4850271

baseline. A maximum of 2 dose reductions was allowed.

2. Zanubrutinib Dose Modifications for Nonhematologic Toxicity

For nonhematological toxicities ≥ Grade 3, other than hypertension adequately controlled with oral medication or asymptomatic laboratory events suspected to be study drug related, zanubrutinib was held until recovery to ≤ Grade 1 or baseline, then restarted at the original dose level. For patients experiencing atrial fibrillation that was symptomatic and/or incompletely controlled, zanubrutinib may have been restarted at either the original dose or dose level -1, per investigator discretion, after the atrial fibrillation was adequately controlled.

Zanubrutinib was held for any ≥ Grade 3 bleeding. The drug was permanently discontinued for any related ≥ Grade 3 hemorrhage, with the exception of those patients where the underlying condition could be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of a rebleed was deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug was held and the risk of rebleeding was assessed. If the risk of rebleeding was deemed unacceptable, which was expected in the majority of cases, the study drug was permanently discontinued. Study drug was not resumed unless event resolution was demonstrated by computed tomography (CT) scans or MRI, the risk of rebleeding was deemed low, and the patient did not have a need for concurrent anticoagulation or antiplatelet medications (except low dose aspirin or low molecular weight heparin used to prevent venous thromboembolism). Study drug resumption only occurred after a discussion and approval by the study medical monitor.

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. An independent review Committee (IRC) was established to provide the independent assessment of clinical data and imaging, (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 9.4.7.3 and 9.4.7.4 of the CSR.

Treatment Compliance
Patient diaries were used to record administration of study drug. At all visits to the study center, patient diaries were reviewed, and patients were questioned about compliance with study instructions.

Subject Completion, Discontinuation, or Withdrawal

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Reference ID: 4850271

Zanubrutinib or ibrutinib were 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:
FDA agrees with the above description. Cohort 2 was a nonrandomized cohort of MYD88^{WT} patients (approximately 10% of the overall WM population) treated with zanubrutinib. The Agency considers the analysis results from Cohort 2 as exploratory.

Study Endpoints

The Applicant's Description:
The primary and select secondary and exploratory efficacy endpoints are summarized in the table below. The primary analysis included analysis of efficacy and safety data through a data cutoff of 31 August 2019 (pre-specified). Based on FDA feedback at the Type C meeting held 09 Sept 2020, an additional efficacy and safety analysis with a data cutoff of 31 March 2020 was conducted to support the WM submission and labeling claims.

The 31 March 2020 response were only assessed by investigators. Overall, the concordance rates between Independent Review Committee and investigator were high: determination of VGPR was 100% for zanubrutinib and 98% for ibrutinib and approximately 94% for best overall response categories for both arms assessed with the 31 August 2019 datasets (discussed in Section 8.1.2 Study Results / Efficacy Results – Primary Endpoint of this assessment aid) Finally, throughout this assessment aid, the data cut of 31 March 2020 is discussed (unless otherwise noted).

BeiGene Table 5 Primary, Secondary and Exploratory Efficacy Objectives and Endpoints (BGB-3111-302)

	Objectives	**Endpoints (pre-specified*, unless otherwise stated**, 31 August 2019 data cutoff)**	**Endpoint (longer follow-up, 31 March 2020 datacutoff**
Primary	To compare the efficacy of zanubrutinib versus ibrutinib in patients with *MYD88^{MUT}* WM	Rate of CR or VGPR, as assessed by IRC with adaptation of the response criteria updated at the Sixth IWWM (Owen et al 2013; NCCN 2015)	
Secondary	To further compare the	MRR (CR, VGPR, or PR) as assessed by IRC	

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Reference ID: 4850271

	Objectives	**Endpoints (pre-specified*, unless otherwise stated**, 31 August 2019 data cutoff)**	**Endpoint (longer follow-up, 31 March 2020 datacutoff**
	efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib versus ibrutinib in patients with *MYD88^{MUT}* WM	Rate of CR or VGPR as assessed by the Investigator	Rate of CR or VGPR and MRR as assessed by the Investigator
		DOR as assessed by IRC	
		DOR as assessed by the Investigator	DOR as assessed by the Investigator
		PFS as assessed by the IRC	
		PFS as assessed by the Investigator	PFS as assessed by the Investigator
		Resolution of treatment-precipitating symptoms, that triggered initiation of study treatment (per the IWWM treatment guidelines)	Resolution of treatment-precipitating symptoms, that triggered initiation of study treatment (per the IWWM treatment guidelines)
		Anti-lymphoma effect, defined as any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or splenomegaly by CT scan.	
		Time to Response	Time to major response, and time to VGPR or CR
Exploratory	To evaluate the anticancer activity and safety of zanubrutinib in patients with *MYD88^{WT}* WM (Cohort 2)	CR/VGPR rate, MRR, ORR, PFS, duration of response, and overall survival, as assessed by the IRC and by the Investigator in patients with *MYD88^{WT}* WM (Cohort 2)	CR/VGPR rate, MRR, ORR, PFS, duration of response, and overall survival, as assessed by Investigator in patients with *MYD88^{WT}* WM (Cohort 2)
	To further compare the efficacy, clinical benefit, and anti-lymphoma	OS (Cohort 1)	OS (Cohort 1)
		MRR, TTR for MRR, according to CXCR4 sequence (*CXCR4^{WHIM}* versus *CXCR4^{WT}* using central laboratory sanger sequencing)	MRR, TTR for MRR, according to CXCR4 sequence (*CXCR4^{WHIM}* versus *CXCR4^{WT}* using central laboratory sanger sequencing) in

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Reference ID: 4850271

	Objectives	**Endpoints (pre-specified*, unless otherwise stated**, 31 August 2019 data cutoff)**	**Endpoint (longer follow-up, 31 March 2020 datacutoff**
	effects of zanubrutinib versus ibrutinib in subjects with *MYD88^{MUT}* WM (cohort 1)	in patients with *MYD88^{MUT}* WM (Cohort 1)	patients with *MYD88^{MUT}* WM (Cohort 1)
		Time to next treatment (Cohort 1)	Time to next treatment (Cohort 1)
			MRR, TTR, PFS, OS according to CXCR4 sequence (*CXCR4^{WHIM}* versus *CXCR4^{WT}* using next generation sequencing) in patients with *MYD88*^{MUT} WM (Cohort 1)
			Additional MYD88 Mutations Determined by Next Generation Sequencing and their response (cohort 1 and cohort 2)
	To evaluate quality of life by EORTC QLQ-C30 and EQ-5D in MYD88^{MUT} patients	Change in QOL as assessed by EORTC QLQ-C30 and EQ-5D in all patients *and by VGPR/CR status**	Change in QOL as assessed by EORTC QLQ-C30 and EQ-5D in all patients, by VGPR/CR status and by major response status
		Medical resource utilization as assessed by the number of hospitalizations, length of hospital stay, and supportive care	Medical resource utilization as assessed by the number of hospitalizations, length of hospital stay, and supportive care
		Change from baseline and maximum reduction per patient were summarized for IgM level and hemoglobin using descriptive statistics.	Change from baseline and maximum reduction per patient were summarized for IgM level and hemoglobin using descriptive statistics.
		*The IgM reduction over time analyzed by an MMRM and an AUC analysis**	The IgM reduction over time analyzed by an MMRM and an AUC analysis

Source: BGB-3111-302 Clinical Study Report and Statistical Analysis Plan
Abbreviations: CR, complete response; CXCR4, chemokine receptor 4; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core-30; EQ-5D, EuroQol 5 dimensions questionnaire; IRC, Independent Review Committee; IWWM, International Workshop for Waldenström's macroglobulinemia; MRR, major

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Reference ID: 4850271

	Objectives	Endpoints (pre-specified, *unless otherwise stated**, 31 August 2019 data cutoff)	Endpoint (longer follow-up, 31 March 2020 datacutoff

response rate; *MYD88^{MUT}*, activating mutations in the MYD88 gene; *MYD88^{WT}*, wild type MYD88 gene; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; QOL, quality of life; PR, partial response; TTR, time to response; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

The FDA's Assessment:

The primary endpoint of the ASPEN study was to demonstrate superiority of zanubrutinib relative to ibrutinib based on CR/VGPR rates assessed by IRC with adaptation of the response criteria updated at the Sixth IWWM compared to ibrutinib in the relapsed/refractory patient population in Cohort 1.

During the sponsor meeting on May 12, 2016, the FDA stated, "For WM, the Agency considers major response rates (PR+VGPR+CR) an acceptable primary efficacy endpoint ", and expressed concerns with the Applicant's proposal to use CR+VGPR as a primary endpoint. However, the Sponsor designed the pivotal study with CR +VGPR rates as the primary endpoint to demonstrate superiority over Ibrutinib. In the protocol Amendment 1 (November 1, 2016), the Applicant changed the primary endpoint from major response rate (PR+VGPR+CR) by the Independent Review Committee to CR+VGPR rate by the Independent Review Committee, based on a clarification of the primary study hypothesis that stemmed from examination of First in Human study data. (b) (4)

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The FDA does not agree with the modified IWWM-6 criteria for the assessment of response. The IWWM-6 consensus response criteria includes complete resolution of extramedullary disease as part of the definition of VGPR, whereas the modified IWWM-6 criteria allows for any reduction in extramedullary disease if present at baseline, but does not require resolution. The FDA sent several Information Requests to the Applicant throughout the review process to obtain additional information regarding the modified response criteria, including a request for data and justification to support that the responses assessed using the modified criteria are indicative or predictive of long-term clinical benefit, such as an improvement in overall survival. The Applicant was unable to provide this data and the FDA continues to have concerns regarding the use of the modified consensus criteria. The FDA recommended including only responses as assessed by the standard response criteria in the USPI. Ultimately, the decision was made to present both the consensus and modified responses in the USPI along with information describing the differences. Approval was based on MRR using the standard IWWM-6 consensus criteria

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The submitted clinical study report presents analyses of available efficacy, PK, and safety data through the protocol-specified data cutoff of August 31, 2019, as well as additional efficacy and safety data with a data cutoff March 31, 2020. The long term follow up data was a post hoc analysis and there was no multiplicity adjustment for the additional efficacy analysis based on data cutoff of March 31, 2020. Therefore, the additional analysis is considered as a post-hoc analysis.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The statistical analysis plan for the primary analysis of the study was based on the protocol Amendment 4 (dated September 2018). The SAP was signed off in October 2019 before the unblinded data download or analysis occurred in November/December 2019. The primary analysis included analysis of efficacy, PK, and safety data through a data cutoff of 31 August 2019 (pre-specified). Based on FDA feedback in the Type C meeting held 09 Sept 2020 an additional efficacy and safety analysis with a data cutoff of 31 March 2020 was conducted to support the WM submission.

The primary analysis of superiority in the primary endpoint was performed in the Relapsed/Refractory Analysis Set first when 15 months after 90% enrollment in the Relapsed/Refractory Analysis Set was completed as planned in the Statistical Analysis Plan (SAP). At the time, 90% of Cohort 1 patients were expected to have at least 19 months of study follow-up. If the superiority of the CR or VGPR rate was demonstrated in the Relapsed/Refractory Analysis Set, then the superiority of the CR or VGPR rate was further tested in the ITT Analysis Set.

The analysis sets used in Study BGB-3111-302 Cohort 1 included the following:

- The Intent-to-Treat (ITT) Analysis Set included all randomised patients assigned to a treatment arm in Cohort 1. This analysis set was used for all efficacy analyses.

- The Relapsed/Refractory Analysis Set (a subset of the ITT Analysis Set) included all randomised patients with at least 1 prior line of therapy as determined by the Interactive Response Technology system. This was the primary analysis set used for efficacy analyses.

- The Safety Analysis Set included all patients who received any dose of zanubrutinib or ibrutinib. This was the analysis set used for all safety analyses for Cohort 1 and Cohort 2.

- The Efficacy Analysis Set in Cohort 2 included all patients who received any dose of zanubrutinib and were centrally confirmed to have *MYD88^{WT}*.

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Reference ID: 4850271

- The PK Analysis Set included all patients who had at least 1 post-dose zanubrutinib concentration.

The primary endpoint of VGPR/CR rate by Independent Review Committee was tested for superiority in the Relapsed/Refractory Analysis Set first and in the ITT Analysis Set using the hierarchical test to adjust for multiplicity. The 2-sided p-value from the Cochran Mantel-Haenszel test was compared to 0.05 for primary inference. The 95% confidence interval for the Mantel-Haenszel common risk difference (Mantel and Haenszel 1959) was constructed to quantify treatment effect.

Non-inferiority of the zanubrutinib arm to the ibrutinib arm in major response rate (PR or better) by Independent Review Committee, the key secondary endpoint and defined as the proportion of patients achieving CR, VGPR, and PR, was tested under the margin of 8% only if the primary endpoint was significant in the analysis set in which the CR or VGPR rate was superior. If the lower bound of the confidence interval was greater than the non-inferiority margin of -8%, then it could be concluded that the major response rate in zanubrutinib was non-inferior to the major response rate in ibrutinib.

The distribution of PFS, including the PFS rate at selected timepoints such as 12, 18, and 24 months, was estimated using Kaplan-Meier methodology. The 95% confidence intervals for the progression-free survival rate at the selected timepoints were estimated using the Greenwood formula (Greenwood 1926). The duration of follow-up for progression-free survival was estimated using the reverse Kaplan-Meier method.

Changes to the Planned Analyses

Changes to the planned analyses since finalization of the SAP are listed below:

- Time to next treatment (TTNT) was summarized only by descriptive statistics, instead of using Kaplan-Meier method.
- The IgM reduction over time was also analyzed by a mixed model for repeated measures (MMRM) and an AUC analysis.
- Analysis of best overall response, time to response, duration of response, PFS, and overall survival was repeated using NGS to determine CXCR4 status in *MYD88^{MUT}* patients in addition to the Sanger method result used in the original analyses.
- Stratified Cox regression was also performed for PFS.
- Determination of MYD88 mutational status using NGS (examination of Cohort 1 and Cohort 2 baseline bone marrow samples for additional mutations in the MYD88 gene).
- QOL change from baseline by VGPR/CR status and major response rate status.

The FDA's Assessment:
FDA agrees with the Applicant's general description of the Statistical Analysis Plan and amendments. The primary endpoint has been written in multiple ways by the Applicant; CR/VGPR; CR+VGPR and CR or VGPR. The FDA has consistently reported this as CR+VGPR. The

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Reference ID: 4850271

pre-specified primary efficacy analysis was that the superiority of the primary endpoint of CR +VGPR was tested using the Cochran-Mantel-Haenszel (CMH) test stratified by the CXCR4 status (WHIM vs WT/missing), the prior line of therapy (1-3 vs. >3 for analysis in the Relapsed/Refractory Analysis Set; 0 vs 1-3 vs>3 for analyses in the ITT Analysis Set and age group (<=65 vs >65) at a 1-sided significance level of 0.025. However, including age in the model could potentially overfit the model because age is not a stratification variable. The FDA performed a sensitivity analysis excluding age in the CMH model, and the results are presented in the Section 8.

During the sponsor meeting on June 27, 2017, the FDA stated that patients with relapsed/refractory WM and treatment-naïve WM should be considered as two distinct patient populations. The FDA strongly recommended that the trial be limited to patients with relapsed or refractory WM after at least one prior therapy. The sponsor opted to power the study for the relapsed/refractory population for the primary efficacy analysis.

The sample size calculation was based on the comparison of the primary endpoint, which is CR+VGPR rate in relapsed/refractory subjects in Cohort 1. Assuming the primary response rate in the zanubrutinib arm was 0.35 and in the control arm was 0.15, seventy-five subject per arm (150 total) could provide a power of 0.814 in testing the response rate difference in the relapsed/refractory population in Cohort 1 using a normal approximation to binomial test with a two-sided significance of 0.05. Assuming MRR=0.90 in the study arm and MRR=0.80 in the control arm, the power of demonstrating NI of zanubrutinib in the relapsed/refractory population is 85.5% when a NI margin of 0.08 is used. In addition to 150 relapsed/refractory subjects, approximately 20% (38) treatment-naïve subjects with $MYD88^{MUT}$ would be enrolled in Cohort 1.

Assuming $MYD88^{MUT}$ mutation was present in 90% of the enrolled subjects, a total of approximately 210 subjects would be enrolled in Cohort 1 and Cohort 2 combined according to the Statistical Analysis Plan (SAP).

Protocol Amendments

The Applicant's Description:

The protocol was amended 5 times before the data cutoff date. No patients enrolled under the original protocol (dated 29 July 2016). Key changes are described below.

Amendment 1 (01 November 2016)

No patients enrolled before Amendment 1 of the study protocol, and a total of 67 patients enrolled in the study under Amendment 1. Changed the study design from all-comer WM randomized to receive zanubrutinib or ibrutinib stratified by MYD88 mutational status and

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Reference ID: 4850271

others to the present 2-cohort study that identified treatment cohorts based on MYD88 mutational status: Cohort 1 (*MYD88^{MUT}*) and newly added Cohort 2 (*MYD88^{WT}*)

- Changed the primary objective from major response rate by the Independent Review Committee to VGPR/CR rate by the Independent Review Committee, based on a clarification of the primary study hypothesis that stemmed from examination of data (FIH data)
- Identified patients with *MYD88^{MUT}* WM as the primary population for randomization and study analyses (Cohort 1)
- Updated background with new zanubrutinib results and data on role of MYD88 mutation in responsiveness of WM to BTK inhibitors
- Added the inclusion criterion to clarify that TN patients were considered inappropriate candidates for intensive therapy

Amendment 2 (08 May 2017)

A total of 155 patients enrolled under Amendment 2 of the study protocol.

- Added study rationale, benefit/risk assessment, and dose justification
- Updated the timing of response assessments to every 4 weeks (each cycle)
- Added EQ-5D to quality-of-life assessments
- Updated the eligibility criteria to clarify that patients may have had relapsed/refractory or TN WM considered by their treating physician to be inappropriate for standard chemoimmunotherapy regimens

Amendment 3 (02 February 2018)

A total of 7 patients enrolled under Amendment 3 of the study protocol. Updated the total number of patients to approximately 210. Cohort 1 included approximately 150 relapsed/refractory and 38 TN *MYD88^{MUT}* patients. Cohort 2 included approximately 22 *MYD88^{WT}* patients.

- Revised the statistical analysis methods to power analysis of relapsed/refractory *MYD88^{MUT}* patients
- Changed the timing of the interim analysis to 6 months after the first 50 relapsed/refractory patients were randomized to Cohort 1
- Updated the sample size considerations to have the power to test the primary endpoint in the Cohort 1 Relapsed/Refractory Analysis Set
- Changed the timing of the primary analysis from 9 months to 12 months
- Added an assessment of impact of plasmapheresis on zanubrutinib PK as a new exploratory objective and endpoint

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Reference ID: 4850271

- Revised the zanubrutinib and ibrutinib guidelines for dose modification, reduction, and discontinuation
- Added that patients who continued to benefit from zanubrutinib after disease progression may have remained on study upon discussion with the medical monitor or designee

Amendment 4 (21 September 2018)

No patients enrolled under Amendment 4 of the study protocol.

- Removed the QT/QT interval corrected for heart rate (QTc) prolonging drug guidance
- Removed the adverse events of special interest list, including protocol definitions and associated expedited reporting requirements
- Updated Phase 1 first-in-human study data
- Added guidance about the potential for opportunistic infections in patients with hematologic malignancies, particularly for those having received prior lymphodepleting chemotherapy or prolonged corticosteroid exposure
- Clarified that the serum IgM value at Cycle 1 Day 1 served as the baseline for all assessments except for patients who had undergone plasmapheresis

Amendment 5 (26 August 2019)

No patients enrolled under Amendment 5 of the study protocol. Specified actions to be done for patients with an intracranial hemorrhage

- Added section on dose modifications for zanubrutinib when coadministered with strong/moderate CYP3A inhibitors/inducers
- Clarified medications to be used with caution
- Clarified use of efficacy criteria with and without consideration of extramedullary disease

Supportive Studies:

BGB-3111-AU-003 is an ongoing phase 1/2, open-label, multiple-dose, dose-escalation and expansion study to investigate the safety and pharmacokinetics of the zanubrutinib in patients with B-cell malignancies. It consists of a dose-escalation phase and a dose-expansion phase in disease specific cohorts, including specific cohorts patients with WM.

BGB-3111-210 is an ongoing single-arm, multicenter Phase 2 study in Chinese patients with relapsed or refractory WM, who exhibit one or more of the criteria for requiring treatment based on consensus guidelines from the Seventh IWWM (Dimopoulos et al 2014). A total of 44 patients were enrolled.

Study BGB-3111-AU-003 and BGB-3111-210 are being presented to support the efficacy of zanubrutinib in WM, as determined by the frequency and durability of major responses (MRR),

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Reference ID: 4850271

independent of line-of-therapy or MYD88 mutational status.

Results from the supportive studies are included in Section 8.1.5 Integrated Assessment of Effectiveness

The FDA's Assessment:
FDA agrees with the Applicant's description of the protocol amendments for Study BGB-3111-302.

Study Results

Compliance with Good Clinical Practices

Data:
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 12 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 FDA agrees with the Applicant's assessment of their compliance with Good Clinical Practices.

Financial Disclosure

Data:
BeiGene certified that it has not entered into any financial arrangement with any investigators and/or sub-investigators of study BGB-3111-302.
Financial interest was disclosed by 6 investigators/sub-investigators in studies BGB-3111-205 and/or -206, and/or -210, and/or -1002.
The Applicant's Position:
It is unlikely that the significant payment of other sorts disclosed biased studies BGB-3111-205 and/or -206, and/or -210, and/or -1002.
Studies BGB-3111-210 is supportive of efficacy and safety.
Studies BGB-3111-205, BGB-3111-206, and BGB-3111-1002 are supporting the overall safety

profile (n=779) of zanubrutinib in this application.

The FDA's Assessment:
The FDA agrees that the financial disclosure information for the Study BGB-3111-302 was submitted with this application. The financial disclosure information is acceptable.

Patient Disposition

Data:
Cohort 1: A total of 201 patients were randomised (99 in the ibrutinib arm and 102 in the zanubrutinib arm) Two patients were randomised but not treated, 1 in the zanubrutinib treatment arm due to an adverse event (unrelated to screening procedures) and 1 in the ibrutinib treatment arm due to progressive disease (central nervous system).
In **Cohort 2**, a total of 28 patients were enrolled and received zanubrutinib. Two patients were not evaluable as their mutation status was unknown.

BeiGene Table 6 Patient Disposition (Cohort 1) (ITT Analysis Set) and Cohort 2 (Safety Analysis Set)(Data Cutoff 31 March 2020)

Category			
	Ibrutinib n (%)	**Zanubrutinib n (%)**	**Cohort 2**
Number of patients randomized	99 (100.0)	102 (100.0)	28 (100.0)
Patients randomized, but not treated	1 (1.0)	1 (1.0)	—
Adverse event	0 (0.0)	1 (1.0)	—
Progressive disease	1 (1.0)	0 (0.0)	—
Number of patients treated	98 (99.0)	101 (99.0)	28 (100.0)
Patients remaining on treatment	69 (69.7)	79 (77.5)	15 (53.6)
Patients discontinued from treatment	29 (29.3)	22 (21.6)	13 (46.4)
Adverse event	15 (15.2)	4 (3.9)	3 (10.7)
Progressive disease	6 (6.1)	9 (8.8)	7 (25.0)
Investigator's discretion	5 (5.1)	2 (2.0)	2 (7.1)
Withdrawal by patient	0 (0.0)	5 (4.9)	1 (3.6)

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Reference ID: 4850271

Category			
	Ibrutinib n (%)	Zanubrutinib n (%)	Cohort 2
Other	3 (3.0)	2 (2.0)	—
Median study follow-up (months)	26.32	25.76	23.84
Min, max	0.5, 38.1	0.4, 38.2	2.3, 34.8

BGB-3111-302 CSR Source: Table 14.1.1.1.1a, Listing 16.2.1.1a
Abbreviations: ITT, Intent-to-Treat; MYD88, myeloid differentiation factor 88.
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on the number of patients randomized.
Study follow-up time is defined as the time from the randomization (enrollment) date to the death date or end of study date (whichever occurred first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
Data cutoff 31 March 2020

The Applicant's Position:
With a median follow up of approximately 26 months a greater percentage of patients remain on treatment on the zanubrutinib arm versus the ibrutinib arm. This was mainly due to a lower number of treatment discontinuations due to adverse events on the zanubrutinib arm (3.9%) versus the ibrutinib arm (15.3%).

In Cohort 1, the ITT analysis set was used to assess efficacy, as per the statistical analysis plan. For Cohort 1, the Safety Analysis Set consisted of 98 patients who received any dose of ibrutinib and 101 patients who received any dose of zanubrutinib.

For Cohort 2, the Safety Analysis Set consisted of 28 patients who received any dose of study drug. The Efficacy Analysis Set consisted of the 26 patients who received any dose of zanubrutinib and were centrally confirmed to have $MYD88^{WT}$.

The FDA's Assessment:
The FDA's analysis was based on the pre-specified data cutoff of August 31, 2019. (b) (4) (b) (4) (b) (4) Therefore, the results from the March 31, 2020 data cutoff are considered exploratory.

The FDA agrees that a total of 201 patients were randomized (zanubrutinib: 102; ibrutinib: 99). At the time of the data cutoff, the majority of patients remain on treatment (zanubrutinib:

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79.4%; ibrutinib 77.8%). A similar number of subjects in both treatment arms discontinued treatment (zanubrutinib: 19.6%; ibrutinib 21.2%). Overall, the most common reasons for treatment discontinuation were progressive disease and adverse events. In Cohort 1, 9% of subjects in the ibrutinib arm discontinued treatment due to an adverse event, compared to 4% in the zanubrutinib arm. A summary of the patient disposition based on underlying disease status in Cohorts 1 and 2 with a data cutoff of August 31, 2019 is provided in FDA Table 7 and FDA Table 8 below.

FDA Table 7: Study BGB-3111-302 (Cohort 1): Patient Disposition (Data Cutoff: August 31, 2019)

	Treatment Naive		Relapsed/ Refractory		Overall	
	Ibrutinib n(%)	Zanubrutinib n(%)	Ibrutinib n(%)	Zanubrutinib n(%)	Ibrutinib n(%)	Zanubrutinib n(%)
Randomized	18 (100.0)	19 (100.0)	81 (100.0)	83 (100.0)	99 (100.0)	102 (100.0)
Received Treatment	18 (100.0)	19 (100.0)	80 (98.8)	82 (98.8)	98 (99.0)	101 (99.0)
Remain on Treatment	14 (77.8)	14 (73.7)	63 (77.8)	67 (80.7)	77 (77.8)	20 (19.6)
Discontinued Treatment	4 (22.2)	5 (26.3)	17 (21.0)	15 (18.1)	21 (21.2)	20 (19.6)
Reason for Treatment Discontinuation						
Progressive Disease	0 (0.0)	3 (15.8)	5 (6.2)	4 (4.8)	5 (5.1)	7 (6.9)
Adverse Event	3 (16.7)	0 (0.0)	6 (7.4)	4 (4.8)	9 (9.1)	4 (3.9)
Investigator's Discretion	0 (0.0)	0 (0.0)	4 (4.9)	2 (2.4)	4 (4.0)	2 (2.0)
Withdrawal by Patient	0 (0.0)	2 (10.5)	0 (0.0)	3 (3.6)	0 (0.0)	5 (4.9)
Other	1 (5.6)	0 (0.0)	2 (2.5)	2 (2.4)	3 (3.0)	2 (2.0)

Source: FDA Clinical Reviewer's Analysis

FDA Table 8: Study BGB-3111-302 (Cohort 2): Patient Disposition (Data Cutoff: August 31, 2019)

	Treatment Naïve n(%)	Relapsed/ Refractory n(%)	Overall n(%)
Enrolled	5 (100.0)	23 (100.0)	28 (100.0)
Received Treatment	5 (100.0)	23 (100.0)	28 (100.0)
Remain on Treatment	3 (60.0)	14 (60.9)	17 (60.7)
Discontinued Treatment	2 (40.0)	9 (39.1)	11 (39.3)
Reason for Treatment Discontinuation			
Progressive Disease	1 (20.0)	5 (21.7)	6 (21.4)
Adverse Event	0 (0.0)	2(8.7)	2 (7.1)
Investigator's Discretion	1 (20.0)	1 (4.3)	2 (7.1)
Withdrawal by Patient	0 (0.0)	1 (4.3)	1 (3.6)

Source: FDA Clinical Reviewer's Analysis

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Reference ID: 4850271

Protocol Violations/Deviations

Data:
Study conduct was monitored during this study by the clinical research organization (b) (4) and the sponsor's (BeiGene) medical monitor and clinical scientist team. The clinical research organization and BeiGene identified potential protocol deviations in 2 ways: observable protocol deviations were identified by monitors and other project team members, usually during site visits coincident with the source document verification process; and programmatic protocol deviations, identified via automated edit checks by the data management team, of the data in the clinical database. The clinical research organization assessed protocol deviations as either potential deviations or potential important deviations. These were reviewed by the medical monitor and clinical science team before a final determination was made. Important protocol deviations were defined as those that are likely to have 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.

The following 7 patients (all Cohort 1) had important protocol deviations.

- Patient (b) (6) (ibrutinib) had positive hepatitis B virus (HBV) core antibody at screening but did not have monthly HBV DNA testing at Cycles 2, 3, and 6 through 10.
- Patient (b) (6) (zanubrutinib) had positive HBV core antibody (HBV surface antigen negative) but did not have monthly HBV DNA testing at Cycles 2 through 7.
- Patient (b) (6) (zanubrutinib) had positive HBV core antibody (HBV surface antigen negative) but did not have monthly HBV DNA testing at Cycles 2 through 5, 9, and 13 through 16.
- Patient (b) (6) (zanubrutinib) had positive HBV core antibody (HBV surface antigen negative) but did not have monthly HBV DNA testing at Cycles 2 through 14.
- Patient (b) (6) (zanubrutinib) had a CT scan performed for the purposes of the study protocol before being consented.
- Patient (b) (6) (zanubrutinib) had positive HBV core antibody at screening but did not have monthly HBV DNA testing at Cycles 1 through 7.
- Patient (b) (6) (ibrutinib) was taking 9 mg prednisolone at screening due to mixed connective tissue disease with the aim to down titrate to 7.5 mg by Cycle 1 Day 1. However, the patient received prednisolone at varying doses between 8 and 10 mg once a day for 239 days while on study treatment.

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 FDA agrees with the Applicant's description of the major protocol deviations. The FDA agrees with the Applicant's assessment that the protocol deviations were unlikely to impact the

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Reference ID: 4850271

overall interpretation of efficacy or safety from the study.

Table of Demographic Characteristics

Data:

Demographics for patients in Cohorts 1 and 2 are shown below in BeiGene Table 7.

BeiGene Table 7 Demographics and Baseline Characteristics: Cohort 1 (ITT Analysis Set) and Cohort 2 (Safety Analysis Set) BGB-3111-302

Characteristic	Cohort 1		Cohort 2
	Overall		Overall
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 28)
Age (Years)			
Mean (SD)	69.9 (8.59)	69.2 (10.26)	70.1 (13.57)
Median	70.0	70.0	72.0
Min, Max	38, 90	45, 87	39, 87
Age Group, n (%)			
≤ 65 years	29 (29.3)	41 (40.2)	9 (32.1)
> 65 years	70 (70.7)	61 (59.8)	19 (67.9)
≤ 75 years	77 (77.8)	68 (66.7)	16 (57.1)
> 75 years	22 (22.2)	34 (33.3)	12 (42.9)
Gender, n (%)			
Male	65 (65.7)	69 (67.6)	14 (50.0)
Female	34 (34.3)	33 (32.4)	14 (50.0)
Race, n (%)			
Asian	0 (0.0)	4 (3.9)	—
White	95 (96.0)	88 (86.3)	27 (96.4)
Not Reported/ Unknown	4 (4.0)	10 (9.8)	1 (3.6)
Ethnicity, n (%)			
Not Hispanic or Latino	91 (91.9)	82 (80.4)	24 (85.7)
Hispanic or Latino	5 (5.1)	4 (3.9)	3 (10.7)

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Reference ID: 4850271

Characteristic	Cohort 1		Cohort 2
	Overall		Overall
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 28)
Not Reported/ Unknown	3 (3.0)	16 (15.7)	1 (3.6)
ECOG Performance Status, n (%)			
0	42 (42.4)	46 (45.1)	9 (32.1)
1	50 (50.5)	50 (49.0)	15 (53.6)
2	7 (7.1)	6 (5.9)	4 (14.3)
HBcAb, n (%)			
Positive	4 (4.0)	7 (6.9)	2 (7.1)
Negative	94 (94.9)	95 (93.1)	26 (92.9)
Missing	1 (1.0)	0 (0.0)	—-
HCV Antibody, n (%)			
Positive	1 (1.0)	0 (0.0)	0 (0.0)
Negative	97 (98.0)	102 (100.0)	28 (100.0)
Missing	1 (1.0)	0 (0.0)	—-
12-lead ECG at Screening			
QTcF (msec), n (%)			
> 450	7 (7.1)	15 (14.7)	1 (3.6)
> 480	0 (0.0)	0 (0.0)	0 (0.0)
> 500	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 14.1.2.2.1a
Source: Table 14.1.2.2.2a
Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HCV, hepatitis C virus; MYD88, myeloid differentiation factor 88; QTcF, QT corrected with Fridericia's formula; SD, standard deviation
Cohort 2 includes patients with wild type and unknown MYD88.
Baseline value is the last nonmissing result before the first dose of study treatment.
Data cutoff 31 March 2020

The Applicant's Position:

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Reference ID: 4850271

Overall, demographics and baseline characteristics were generally comparable between the ibrutinib and zanubrutinib treatment arms except for age. The zanubrutinib treatment arm had a higher proportion of patients > 75 years of age (33.3% versus 22.2%) or ≤ 65 years of age (40.2% versus 29.3%) compared with the ibrutinib treatment arm; this was especially pronounced in the relapsed/refractory population. Cohort 2 consisted mostly of elderly patients with almost 43% >75 years of age.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the baseline demographic characteristics of patients enrolled in Study BGB-3111-302. The FDA also agrees with the Applicant's statement that the baseline characteristics were generally comparable between the two treatment arms, except for age as noted. Although not noted in the tables above, the ASPEN study Cohort 1 enrolled 62 (30.8%) patients from Australia, 120 (59.7%) patients from Europe and 19 patients (9.4%) from the United States. A total of 9 US sites screened at least one patient and 7 sites enrolled 19 patients to Cohort 1 and 2 patients to Cohort 2 on the ASPEN study. The Applicant provided justification for the applicability of the results to the study to the US patient population. They noted that the standard of care practice is the same across the regions for the treatment of WM and data obtained from the 182 patients in Europe or Australia, representing 90.5% of Cohort 1, should be generalizable to patients in the United States. Ninety percent of the patients in the zanubrutinib arm cohort 1 had received Chemoimmunotherapy regimens. The FDA notes that most subjects in BGB-311-302 were white and there were no Black or African American subjects enrolled in this study. Across the development program for zanubrutinib in WM (n=253), there was only one Black or African American patient with WM who received zanubrutinib. A PMC was issued with this application to further characterize the safety and efficacy of zanubrutinib in racial and ethnic minorities with WM.

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

Data:

Disease history:
BeiGene Table 8 Disease History and Baseline Characteristics (ITT/Safety Analysis Set)

	BGB-3111-302		
	Cohort 1 Ibrutinib (N = 99) n (%)	Cohort 1 Zanubrutinib (N = 102) n (%)	Cohort 2 Zanubrutinib (N = 28) n (%)
Time from Initial Diagnosis to First Dose [d] (Years)			

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Reference ID: 4850271

	BGB-3111-302		
	Cohort 1 Ibrutinib (N = 99) n (%)	**Cohort 1 Zanubrutinib (N = 102) n (%)**	**Cohort 2 Zanubrutinib (N = 28) n (%)**
N	99	102	28
Mean (SD)	6.12 (5.053)	6.48 (6.189)	5.34 (4.895)
Median	4.94	4.25	3.65
Q1, Q3	2.06, 8.69	1.76, 9.45	1.62, 8.06
Min, Max	0.1, 24.9	0.1, 23.2	0.1, 20.3
WM prognostic score [e], n (%)			
Low	13 (13.1)	17 (16.7)	5 (17.9)
Intermediate	42 (42.4)	38 (37.3)	11 (39.3)
High	44 (44.4)	47 (46.1)	12 (42.9)
Peripheral blood cytopenia			
Aneaemia (Haemoglobin <= 110 g/L)	53 (53.5)	67 (65.7)	15 (53.6)
Thrombocytopaenia (Platelet count <= 100 x 10^9/L)	12 (12.1)	12 (11.8)	3 (10.7)
Neutropenia (ANC <= 1.5 x 10^9/L)	7 (7.1)	11 (10.8)	1 (3.6)
Baseline IgM (g/L)			
N	98	102	27
Mean (SD)	36.31 (20.904)	33.19 (18.273)	32.32 (17.922)
Median	34.15	31.75	28.50
Q1, Q3	20.40, 48.60	18.30, 47.40	17.40, 42.50
Min, Max	2.4, 108.0	5.8, 86.9	5.6, 73.4
≥ 40 g/L	38 (38.4)	36 (35.3)	8 (28.6)
< 40 g/L	60 (60.6)	66 (64.7)	19 (67.9)
Missing	1 (1.0)	0 (0.0)	1 (3.6)

Data Source: Table 2.7.3.2.2.1
Date of Cut-off: 31Mar2020
Abbreviations: ITT, Intent-to-treat; Min, minimum; Max, maximum; SD, standard deviation; WM, Waldenström's macroglobulinemia.

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Reference ID: 4850271

Prior Anticancer Therapies:
The most common prior anticancer therapies were rituximab (149 [90.9%] patients), alkylating agents (140 [85.4%] patients), and corticosteroids (111 [67.7%] patients), and they were generally comparable between the ibrutinib and zanubrutinib arms.

The Applicant's Position:
In Cohort 1, disease history was generally comparable between the ibrutinib and zanubrutinib arms. The major difference between the treatment arms was a higher percentage of patients with anemia on the zanubrutinib arm versus the ibrutinib arm. Median hemoglobin level was higher on the ibrutinib arm compared with the zanubrutinib arm (109.00 g/L versus 102.50 g/L), and a higher proportion of zanubrutinib-treated patients had baseline hemoglobin ≤ 110 g/L compared with ibrutinib (65.7% versus 53.5%).
Disease history is consistent with the target population and prior anti-cancer therapies are representative of the US standard of care in this population.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the baseline disease history for patients enrolled in Study BGB-3111-302. The FDA notes that in Cohort 1, there were 37 patients who were treatment naïve (zanubrutinib: n=19; ibrutinib: n=18), with the remainder of subjects having received prior therapy for WM. In Cohort 2, there were 5 subjects who were treatment naïve. A PMC will be issued with this application to obtain additional safety and efficacy data with zanubrutinib in the newly diagnosed patient 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 (Data Cutoff 31 March 2020): With additional follow-up there were no significant changes in concomitant medication usage across the study arms.

In Cohort 1, almost all patients received ≥ 1 concomitant medication. The most common concomitant medications in both arms were antibacterials for systemic use (78 [79.6%] patients on the ibrutinib arm and 74 [73.3%] patients on the zanubrutinib arm) and analgesics (50 [51.0%] patients on the ibrutinib arm and 50 [49.5%] patients on the zanubrutinib arm). This was followed by drugs for acid-related gastrointestinal disorders on the ibrutinib arm (42 [42.9%] patients) and antithrombotic agents on the zanubrutinib arm (39 [38.6%] patients). For the ATC class of drugs for acid-related disorders, the percentage of patients who received PPIs was slightly higher for patients on the ibrutinib arm (36.7%) compared with those on the zanubrutinib arm (30.7%).

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Reference ID: 4850271

Antidiarrheals, intestinal anti-inflammatory/anti-infective agents were more common on the ibrutinib arm (20 [20.4%] patients) compared with the zanubrutinib arm (3 [3.0%] patients), consistent with the increased frequency of diarrhea in the former. Anti-anemic preparations were more common on the zanubrutinib arm (36 [35.6%] patients) compared with the ibrutinib arm (16 [16.3%] patients), consistent with lower hemoglobin levels at baseline in the zanubrutinib-treated patients. Of note, 30.6% of patients randomized to receive ibrutinib were taking vitamins versus 21.8% for zanubrutinib.

In Cohort 2, all patients received ≥ 1 concomitant medication. The most common concomitant medications were antibacterials for systemic use (22 [78.6%] patients), followed by analgesics (13 [46.4%] patients), and antivirals for systemic use and drugs for acid related disorders (each 14 [50.0%] patients). For the ATC class of drugs for acid related disorders, all 5 TN patients (100%) received PPIs before study participation compared with 8 of 23 patients with R/R disease (34.8%).

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 FDA agrees with the Applicant's description of the concomitant medications used in Study BGB-3111-302. The FDA agrees that the use of concomitant medications was unlikely to have impacted the study results.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
The pre-specified primary endpoint was VGPR/CR rate by IRC with a data cutoff of 31 August 2019. Following the FDA recommendation (FDA meeting of 09 Sept 2020), BeiGene has included updated analyses with a data cutoff of 31 March 2020 to demonstrate sustained and prolonged safety and efficacy of zanubrutinib in patients with WM. For the purpose of this Assessment Aid, the primary and secondary endpoints discussed are presented with the updated datacuts. Results from both data cutoffs are in the Clinical Study Report.

The response assessed with the 31 March 2020 datacut is by Investigator. The concordance between IRC and INV assessment, evaluated with the 31 August 2019 data cutoff, demonstrated a high level of concordance. In Cohort 1, the concordance rates for VGPR/CR per overall combined assessment between Independent Review Committee and investigator assessments for the zanubrutinib and ibrutinib arms were 100% and 98.0%, respectively. The concordance rates for best overall response for the zanubrutinib and ibrutinib arms were 94.1% (96/102 patients) and 94.9% (94/99 patients), respectively.

In Cohort 2, the concordance rate for best overall response per overall combined assessment

between Independent Review Committee and investigator assessments was 88.5% (23/26 patients). Since the statistical primary endpoint was not met, all p values below are descriptive.

Response : VGPR/CR Rate by Investigator with a data cutoff of 31 March 2020

When overall combined response was assessed by investigator with further follow-up (data cutoff 31 March 2020), the zanubrutinib arm had an additional 4 VGPR for a total VGPR/CR rate of 32.4% compared with an additional 2 VGPR in ibrutinib arm, for a total of 19.2% on the comparator arm.

As described in section 2.1 Analysis of Condition, depth of response correlates with longer PFS and supports the use of VGPR and CR rate as a meaningful clinical endpoint in assessing treatment success in WM.

The analyses were repeated using the CXCR4 status per NGS results as the stratification factor. Upon adjustment, the estimated VGPR rate difference was 15.5% (p=0.0146) between patients treated with zanubrutinib and those treated with ibrutinib.

In Cohort 2, the proportion of patients who achieved VGPR or CR per overall combined assessment was 30.8%.

BeiGene Table 9 Analysis of Disease Response per Overall Combined Assessment by Investigator: Cohort 1 (ITT Analysis Set) and Cohort 2 (Efficacy Analysis Set) BGB-3111-302

Response Category	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Best overall response, n (%)			
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Very good partial response (VGPR)	19 (19.2)	33 (32.4)	8 (30.8)
Partial response (PR)	58 (58.6)	47 (46.1)	6 (23.1)
Minor response (MR)	16 (16.2)	17 (16.7)	7 (26.9)
Stable disease (SD)	3 (3.0)	3 (2.9)	4 (15.4)
Progressive disease (PD)	2 (2.0)	1 (1.0)	1 (3.8)
Not Evaluable (NE)[a]	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment [b]	1 (1.0)	1 (1.0)	0 (0.0)
VGPR or CR Rate, n (%)	19 (19.2)	33 (32.4)	8 (30.8)
95% CI[c]	(12.0, 28.3)	(23.4, 42.3)	(14.3, 51.8)

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Reference ID: 4850271

Response Category	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Risk difference [d]		14.4	—
95% CI		(2.4, 26.5)	—
p-value [e]		0.0206	—
Major response rate (PR or better), n (%)	77 (77.8)	80 (78.4)	14 (53.8)
95% CI [c]	(68.3, 85.5)	(69.2, 86.0)	(33.4, 73.4)
Risk difference [d]		0.0	—
95% CI		-11.6, 11.5)	—
Overall response rate (MR or better), n (%)	93 (93.9)	97 (95.1)	21 (80.8)
95% CI [c]	(87.3, 97.7)	(88.9, 98.4)	(60.6, 93.4)

Source: BGB-3111-302, Table 14.2.1.3.1a and Table 14.2.1.3.2a
Abbreviations: CMH, Cochran-Mantel-Haenszel; CI, confidence interval; CXCR4, chemokine receptor 4; IgM, immunoglobulin M; IRT, Interactive Response Technology; ITT, Intent-to-Treat; UNK = unknown; WT, wild type.
Cohort 1 includes patients with activating mutations in MYD88.
Cohort 2 includes patients with wild type and unknown MYD88.
Percentages are based on N.
[a] Includes NE and IgM flare.
[b] Includes patients who discontinued study prior to the first response assessment.
[c] 95% CI is calculated using the Clopper-Pearson method.
[d] Mantel-Haenszel common risk difference with the 95% confidence interval calculated using a normal approximation and Sato's standard error (Sato 1989) stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65). Ibrutinib is the reference group.
[e] Based on CMH test stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65).
Data cutoff: 31MAR2020.

The Applicant's Position:

FDA regulations regarding the regular approval of drugs require sponsors to establish "substantial evidence of safety and effectiveness" supported by clinical trials that demonstrate this evidence through a "direct measure of clinical benefit". Regular approval is not based on a

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Reference ID: 4850271

comparative effectiveness standard. Regular approval of a cancer therapy via a single-arm trial established precedents that were subsequently applied to other drugs of the same class in the same disease setting (BeiGene Table 10); this includes establishing the endpoints used in those trials as direct measures of clinical benefit sufficient for regular approval. MRR continues to be an endpoint that is a direct measure of clinical benefit in WM that provides substantial evidence of effectiveness to support a regular approval for BTK inhibitors in this disease. Considering the totality of the evidence, the benefit/risk of zanubrutinib for the treatment of patients with WM is positive; the unmet medical need for additional options for treatment individualization based on, for example, cardiovascular comorbidities, and the level of evidence for safety and effectiveness is consistent with regulations.

BeiGene Table 10 Examples of follow-on agents granted regular approval based on single-arm studies following regular approval of the innovator therapy based on a single-arm study.

Disease Area	Drug Class	Endpoint	Rare Disease?	Drugs
Advanced Prostate Cancer	GNrH analogues	Testosterone	No	Lupron, Eligard, multiple others
ROS-1 Associated NSCLC	ROS1 inhibitors	ORR	Yes	Entrectinib, crizotinib
Basal Cell Carcinoma	Hedgehog Pathway Inhibitor*	ORR	No	Vismodigeb, sonidegib*the trial supporting the approval of sonidegib was a randomized comparison of low dose vs high dose. There was no control
DLBCL	CAR-T	ORR/DoR	Yes	Yescarta, Kymriah
WM	BTKi	MRR/DoR	Yes	Imbruvica

The FDA's Assessment:

The Agency agrees that there is no comparative efficacy standard for regular approval and notes prior precedent for approvals based on single arm trials. However, FDA notes that the Study was designed with a primary endpoint to demonstrate superior CR+VGPR of zanubrutinib to ibrutinib and study failed to meet the primary endpoint. FDAs assessment of efficacy was based on descriptive MRR in the ITT population from Cohort 1 without a formal comparison.

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Reference ID: 4850271

In this multi-disciplinary review and evaluation supplemental report, the Applicant only reports the analysis results based on the data cutoff of March 31, 2020. The following analysis results were based on the pre-specified data cutoff of August 31, 2019, as this was the protocol predefined data cutoff. The FDA considered the other analyses based on the March 31, 2020 data cutoff as sensitivity analyses.

The Agency did not agree with the use of the adaptation of the response criteria updated at the IWWM-6 for description of efficacy endpoints. The following table shows the analyses for the primary endpoint of CR+VGPR and the endpoint of major response (defined as PR+VGPR+CR) using the standard consensus criteria based on IRC assessment for the August 31, 2019 cutoff

Table 9 Efficacy Analysis -Standard Consensus Criteria IWWM-6 (data cut-off August 31, 2019)

	Treatment Naive		Relapsed/Refractory		ITT	
	Ibrutinib N=18	Zanubrutinib N=19	Ibrutinib N=81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
Primary Efficacy Endpoint						
VGPR or CR Rate, n(%) 95% CI	2 (11.1) (1.4, 24.7)	3 (15.8) (3.4, 39.6)	5 (6.2) (2.0, 13.8)	13 (15.7) (8.6, 25.3)	7 (7.1) (2.9, 14.0)	16 (15.7) (9.2, 24.2)
Risk Difference, %, 95% CI	NA		9.7 (-0.1, 19.4) P=0.0511		8.8 (-0.2, 17.8) P=0.0562	
Secondary Efficacy Endpoints						
Major Response Rate, n(%) 95% CI	12 (66.7) (41.0, 86.7)	14 (73.7) (48.8, 90.9)	65 (80.2) (69.9, 88.3)	65 (78.3) (67.9, 86.6)	77 (77.8) (68.3, 85.5)	79 (77.5) (68.1, 85.1)
Risk Difference, %, 95% CI	NA		-3.5 (-16.0, 9.0)		-0.5 (-12.2,11.1)	

Source: FDA Statistical Reviewer's Analysis

FDA notes that there is a difference in the CR +VGPR rates using the standard and modified consensus response criteria definitions. The rates of CR +VGPR are lower in both arms using the

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Reference ID: 4850271

standard response criteria than the rates assessed using the modified response criteria. This was driven primarily by patients assessed as achieving VGPR despite not achieving complete resolution of extramedullary disease. The major response rates between the zanubrutinib and ibrutinib arms based IRC assessed response did not differ.

Using modified response criteria, based on a data cutoff of August 31, 2019, in the ITT patient population, the proportion of patients who achieved VGPR +CR by Independent Review Committee (IRC) were 19.2% and 28.4%, for the ibrutinib and zanubrutinib arms in Cohort 1, respectively. The VGPR +CR rate difference between the 2 arms adjusted for the stratification factors and age group was estimated to be 10.2% for the ITT set by IRC, with p-value of 0.09. For the relapsed/refractory population, the proportion of patients who achieved VGPR +CR by IRC were 19.8% and 28.9%, respectively. The VGPR +CR rate difference between the 2 arms, adjusted for the stratification factors and age group, was estimated to be 10.7%, with p-value of 0.116 (Table 10). As a result, all subsequent hypothesis tests and associated p-values are descriptive only. The results of efficacy endpoints are provided in the FDA Table 10.

FDA Table 10: Efficacy Analysis Results by IRC with a data cutoff of August 31, 2019

	Treatment Naive		Relapsed/Refractory		ITT	
	Ibrutinib N=18	Zanubrutinib N=19	Ibrutinib N=81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
Primary Efficacy Endpoint						
VGPR or CR Rate, n (%) 95% CI	3 (16.7) (3.6, 41.4)	5 (26.3) (9.1, 51.2)	16 (19.8) (11.7, 30.1)	24 (28.9) (19.5, 39.9)	19 (19.2) (12.0, 28.3)	29 (28.4) (19.9,38.2)
Risk Difference, % , 95% CI			10.7 (-2.5, 23.9) P=0.116		10.2 (-1.5, 22.0) P=0.09	
Secondary Efficacy Endpoints						
Major Response Rate, n(%) 95% CI	12 (66.7) (41.0, 86.7)	14 (73.7) (48.8, 90.9)	65 (80.2) (69.9, 88.3)	65 (78.3) (67.9, 86.6)	77 (77.8) (68.3, 85.5)	79 (77.5) (68.1, 85.1)
Risk Difference, % , 95% CI			-3.5 (-16.0, 9.0)		-0.5 (-12.2,11.1)	

Source: FDA Statistical Reviewer's Analysis

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FDA Table 11: Efficacy Analysis Results using Standard Consensus Criteria by IRC with a data cutoff of August 31, 2019

Since the age is not a stratification variable, the reviewer also performed a sensitivity analysis using CMH model excluding age from the primary efficacy model, based on both IRC assessment and investigator model. The results are presented in FDA Table **11** below.

FDA Table 12: FDA's Sensitivity Analysis for the Primary Efficacy Endpoint

VGPR or CR Rate Risk Difference, 95% CI	Relapsed/Refractory		ITT	
	Ibrutinib N=81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
Data Cutoff 31 August 2019				
FDA's Model by IRC excluding age from the CMH model	9.6 (--3.4,22.7) P=0.152		9.5 (-2.1, 21.3) P=0.1106	
by Investigator	12.9 (-0.0, 25.9) p=0.0529		12.1 (0.5, 23.7) p=0.0437	
FDA's model by investigator excluding age from the CMH model	12.0 (-0.0, 24.8) p=0.0682		11.6 (0.00, 23.1) p=0.051	

Source: FDA Statistical Reviewer's Analysis

Data Quality and Integrity

Data:
Not applicable
The Applicant's Position:
No issues were identified with the data quality or integrity from ASPEN which could affect the efficacy results.

The FDA's Assessment:
Data, statistical programs, and study reports for the primary analyses of this application were submitted electronically on March 24, 2021. The overall quality of the submission was acceptable, and the reviewer was able to perform all analyses using the submitted data. Derivation from key variables were verified, as well as demographic variables. No

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Reference ID: 4850271

inconsistencies were found in the reported efficacy results or patient baseline characteristics.

Efficacy Results – Secondary and other relevant endpoints

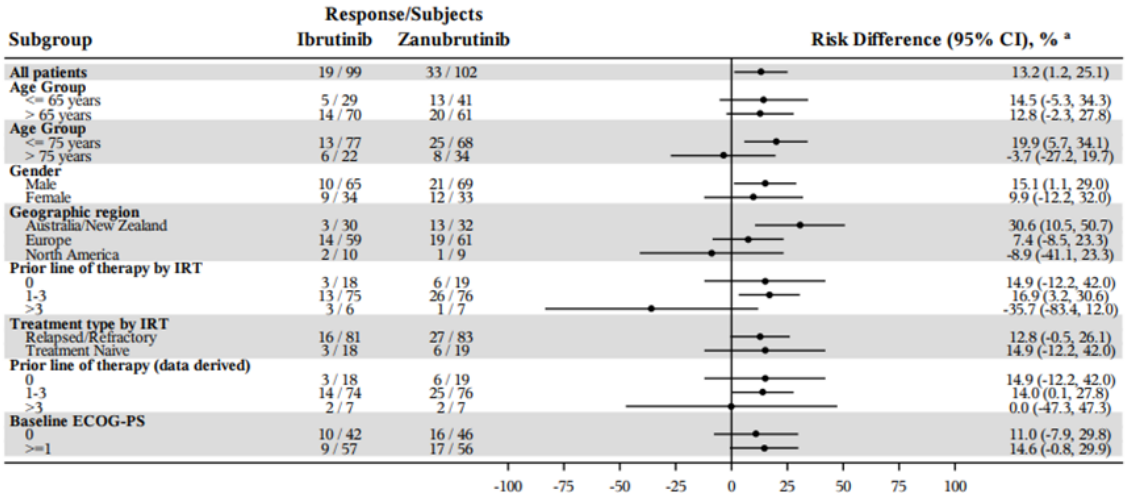
Data:

Subgroup Assessments of VGPR/CR Rate

The proportions of patients in **Cohort 1** who achieved a VGPR or CR per overall combined assessment were generally consistent for subgroups of interest with a few exceptions mostly in the subgroups of small sample size. Zanubrutinib treatment was favored in patients ≤ 75 years and in prognostically more difficult to treat populations such as those with higher IgM (≥ 40 g/L), cytopenias (eg, hemoglobin concentration ≤ 110 g/L, and patients with baseline platelet count ≤ 100 x 10^9/L), extramedullary disease, and medium/high International Prognostic Scoring System scores. In terms of geographic location, patients from Australia or New Zealand fared better and patients from North America fared worse with zanubrutinib, albeit with low numbers of patients enrolled in North America (BeiGene Figure 2).

In **Cohort 2**, there were no clinically meaningful differences in response between subgroups. The small sample size in Cohort 2 makes interpretation of the subgroup analysis more difficult.

BeiGene Figure 2 Forest Plot of CR or VGPR Rate by Subgroups (Overall Combined Assessment by Investigator) (ITT Analysis Set) BGB-3111-302



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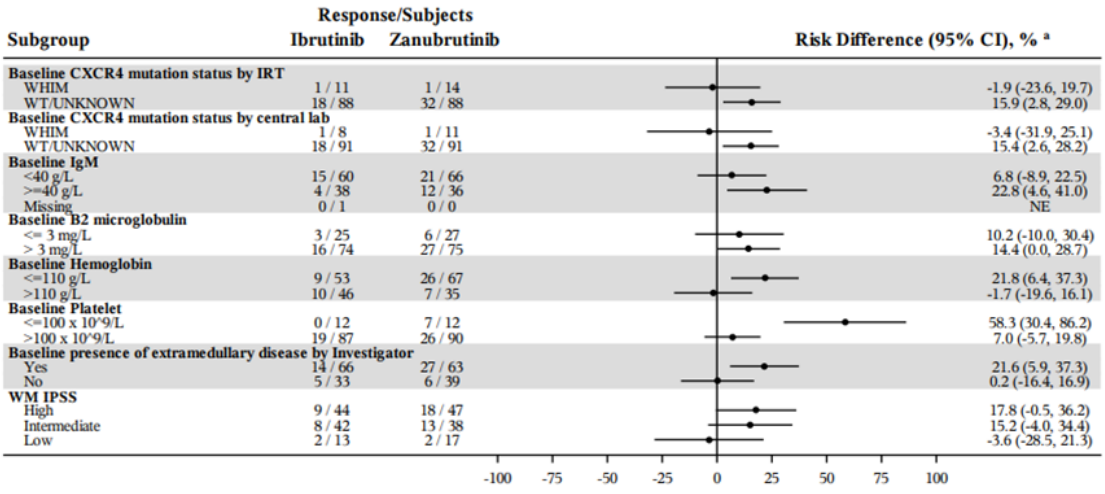

Source: BGB-3111-302, Figure 14.2.1.1.8a
Abbreviations: CR, complete response; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; IRC, Independent Review Committee; IRT, Interactive Response Technology; ITT, Intent-to-Treat; NE, not evaluable; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild type.
Cohort 1 includes patients with activating mutations in MYD88.
[a] Unstratified rate difference and 95% CI.
Data cutoff: 31MAR2020

Major Response Rate by Investigator

In **Cohort 1**, the proportions of patients overall in the ibrutinib and zanubrutinib treatment arms, who achieved a major response were similar at 77.8% and 78.4%, respectively. (BeiGene Table 9).

In **Cohort 2**, the proportion of patients overall who achieved a major response per overall combined assessments was 53.8% (BeiGene Table 9).

Duration of Response by Investigator

Per the overall combined assessment by investigator, the median follow-up time for duration of VGPR or CR in the ibrutinib and zanubrutinib arms was 11.0 months (range 0.0 to 26.6 months) and 17.5 months (range 0.0 to 28.6 months), respectively, as estimated by the reverse Kaplan-Meier method. Three events occurred in patients with VGPR or CR in the ibrutinib arm while only 1 event occurred in patients with VGPR or CR in the zanubrutinib arm. The median durations of VGPR or CR and major response per overall combined assessment had not been reached for the overall or relapsed/refractory populations in either treatment arm who achieved a response to study treatment (BeiGene Table 11)

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Reference ID: 4850271

The median follow-up time for duration of major response in the ibrutinib and zanubrutinib treatment arms in Cohort 1 was 20.5 months (range 1.2 to 34.0 months) and 22.1 months (range 0.0 to 32.3 months), respectively. Ten events occurred in patients who achieved a major response in the ibrutinib arm while 8 events occurred in patients with a major response in the zanubrutinib arm. The event-free rates at 12, 24, and 30 months for patients overall in the ibrutinib and zanubrutinib treatment arms who achieved a major response per overall combined assessment were 93.2, 86.8%, and 64.5% for ibrutinib, and 94.7%. 90.3%, and 90.3% for zanubrutinib, respectively, numerically trending higher for zanubrutinib. The estimated major response event-free rates at 12, 24, and 30 months were 93.2%, 86.8%, and 64.5 in the ibrutinib arm and 94.7%, 90.3%, and 90.3% in the zanubrutinib arm, respectively.

The median follow-up time for duration of overall response in the ibrutinib and zanubrutinib treatment arms was 23.7 months (range 1.2 to 34.9 months), and 23.9 months (range 0.0 to 32.6 months), respectively. As of the data cutoff date, the median duration of overall response per the overall combined assessment has not been reached (not estimable [NE] for both). Eighteen events occurred in patients in the ibrutinib arm and 12 events occurred in patients in the zanubrutinib arm. The estimated event-free rates for patients with overall response at 12, 24, and 30 months were 87.8%, 82.2%, and 61.0% in the ibrutinib arm and 94.7%, 87.1%, and 87.1% in the zanubrutinib arm, respectively.

In **Cohort 2**, the median follow-up time for duration of CR or VGPR was 14.4 months (range 2.7 to 24.8 months). Median duration of VGPR or CR of 22.2 months was reached due to one patient followed for the longest time since first reaching VGPR (at 22.0 months after reaching VGPR) who had a PFS event at that time thus dropping the event-free rate to 0%. The estimate is not adequate with both lower bound and upper bound of the 95% confidence interval of NE. The 95% confidence interval of median major response was wide at (3.5, 25.7). Two events occurred in 8 patients who achieved a CR or VGPR. The event-free rates for patients who achieved a CR or VGPR per overall combined assessment at 12, 24, and 30 months were 100.0%, 40.0%, and NE.

The median follow-up time for duration of major response (or better) was 22.0 months (range 1.4 to 25.7 months). Median duration of VGPR or CR of 22.0 months was reached due to one of the two patients followed for the longest time since first reaching VGPR (at 22.0 months and 24.8 months after reaching VGPR) who had a progression-free survival event at 22.0 months thus dropping the event-free rate to 50%. The estimate is not adequate with upper bound of the 95% confidence interval of NE. The 95% confidence interval of median major response was wide at (3.5, 25.7).

Seven events occurred in patients who achieved a major response. The event-free rates for patients who achieved a major response per overall combined assessment at 12, 18, and 30 months were 64.3%, 57.1%, and 0.0%.

The median follow-up time for duration of overall response was 22.3 months (range 0.0 to 26.7 months). The median duration of major response was 25.7 months (range 9.3, NE months). Eight events occurred in patients who achieved an overall response. The event-free rates for

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Reference ID: 4850271

patients who achieved a major response per overall combined assessment at 12, 18, and 30 months were 69.6%, 39.3%, and NE.

BeiGene Table 11 Duration of Response per Overall Combined Assessment by Investigator (ITT Analysis Set) BGB 3111-302

Response Category	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Duration of CR or VGPR			
Number of responders	19	33	8
Events, n (%)	3 (15.8)	1 (3.0)	2 (25.0)
Progressive disease	2 (10.5)	1 (3.0)	2 (25.0)
Death	1 (5.3)	0 (0.0)	--
Follow-up time in months [a]			
Median (95% CI)	11.0 (8.3, 20.2)	17.5 (13.5, 22.2)	14.4 (2.7, 24.8)
(Min, Max)	(0.0, 26.6)	(0.0, 28.6)	(2.7, 24.8)
Duration of CR or VGPR (months) [b]			
Median (95%CI)	NE (11.3, NE)	NE (NE, NE)	22.0 (13.8, NE)
Range	(0.0+, 26.6+)	(0.0+, 28.6+)	(2.7+, 24.8+)
Event free rate at % (95% CI) [c]			
6 months	94.1 (65.0, 99.1)	100.0 (NE, NE)	100.0 (NE, NE)
12 months	74.9 (38.8, 91.5)	100.0 (NE, NE)	100.0 (NE, NE)
24 months	74.9 (38.8, 91.5)	95.5 (71.9, 99.3)	40.0 (1.1, 82.9)
30 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Duration of Major Response (PR or better)			
Number of responders	77	80	14
Events, n (%)	10 (13.0)	8 (10.0)	7 (50.0)

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Reference ID: 4850271

Response Category	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	**Zanubrutinib (N = 102)**	**Zanubrutinib (N = 26)**
Progressive disease	7 (9.1)	7 (8.8)	6 (42.9)
Death	3 (3.9)	1 (1.3)	1 (7.1)
Follow-up time in months [a]			
Median (95% CI)	20.5 (19.4, 23.0)	22.1 (19.4, 22.5)	22.0 (16.6, 24.8)
(Min, Max)	(1.2, 34.0)	(0.0, 32.3)	(1.4, 25.7)
Duration of major response (months) [b]			
Median	NE (28.9, NE)	NE (30.2, NE)	25.7 (3.5, 25.7)
Range	(1.2+, 34.0+)	(0.0+, 32.3+)	(1.4, 25.7)
Event free rate at % (95% CI) [c]			
6 months	97.3 (89.8, 99.3)	97.4 (90.1, 99.4)	78.6 (47.2, 92.5)
12 months	93.2 (84.3, 97.1)	94.7 (86.4, 98.0)	64.3 (34.3, 83.3)
24 months	86.8 (74.7, 93.4)	90.3 (80.8, 95.3)	57.1 (28.4, 78.0)
30 months	64.5 (27.6, 86.1)	90.3 (80.8, 95.3)	0.0 (NE, NE)
Duration of Overall response (months)			
Number of responders	93	97	21
Events, n (%)	18 (19.4)	12 (12.4)	8 (38.1)
Progressive disease	14 (15.1)	10 (10.3)	7 (33.3)
Death	4 (4.3)	2 (2.1)	1 (4.8)
Follow-up time in months [a]			
Median (95% CI)	23.7 (21.3, 24.2)	23.9 (21.2, 24.0)	22.3 (20.2, 24.0)
(Min, Max)	(1.2, 34.9)	(0.0, 32.6)	(0.0, 26.7)

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Response Category	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Duration of overall response (months) [b]			
Median (95% CI)	NE (29.7, NE)	NE (32.1, NE)	25.7 (9.3, NE)
Range	(1.2+, 34.9+)	(0.0+, 32.6+)	(0.0+, 26.7+)
Event free rate at % (95% CI) [c]			
6 months	92.3 (84.6, 96.3)	94.7 (87.8, 97.8)	85.0 (60.4, 94.9)
12 months	87.8 (79.0, 93.0)	94.7 (87.8, 97.8)	69.6 (44.5, 85.1)
24 months	82.2 (71.9, 88.9)	87.1 (77.8, 92.7)	64.3 (39.3, 81.2)
30 months	61.0 (28.4, 82.4)	87.1 (77.8, 92.7)	NE (NE, NE)

Source: BGB-3111-302, Table 14.2.1.12.1a and Table 14.2.1.12.2a
Abbreviation(s): CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; Q1, first quartile; Q3, third quartile; CI, confidence interval; NE, not estimable; + = censored.
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on number of responders.
[a] Estimated by reverse Kaplan-Meier method.
[b] Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Data cutoff: 31MAR2020.

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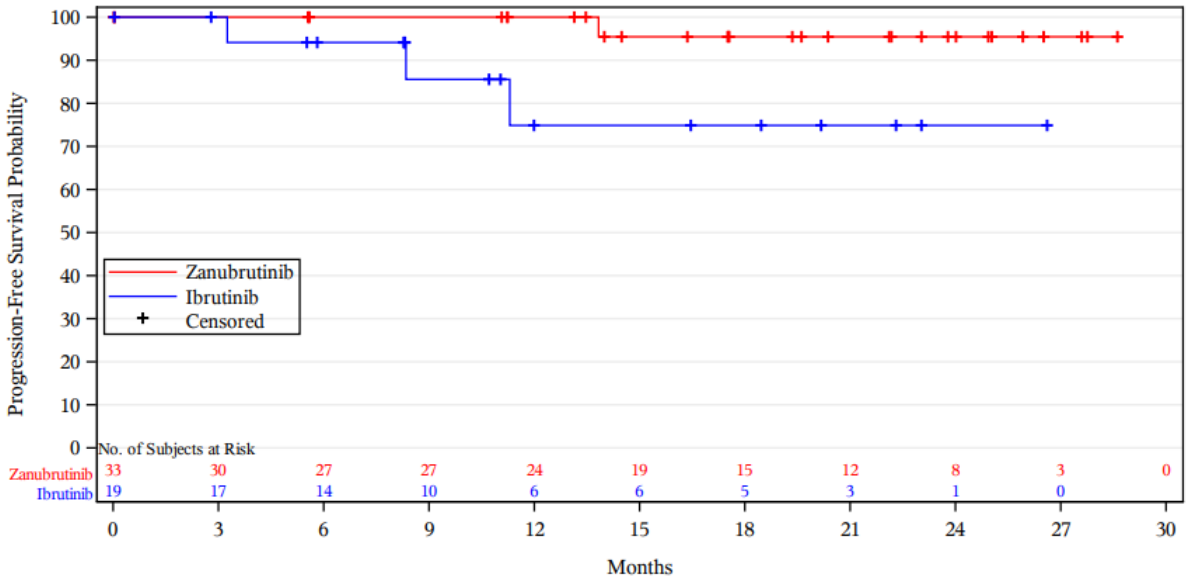
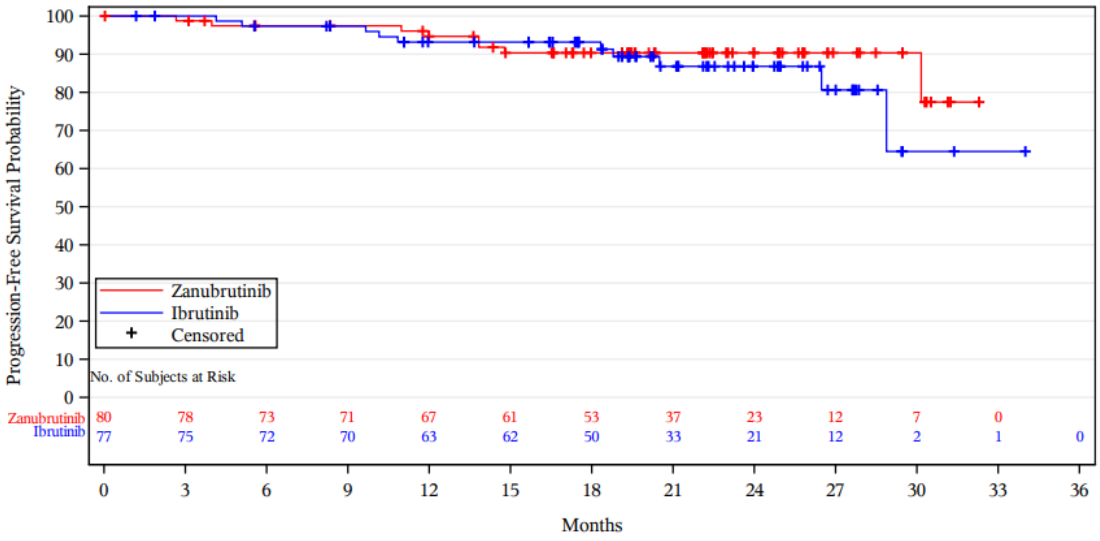
BeiGene Figure 3 Kaplan-Meier Plot of Duration of VGPR or CR per Overall Combined Assessment by Investigator (Cohort 1) (ITT Analysis Set) BGB-3111-302



Source: Figure 14.2.1.4.99.67.4a
Abbreviations: CR, complete response; ITT, Intent-to-Treat
Cohort 1 includes patients with activating mutations in MYD88.
Data cutoff; 31 March 2020.

BeiGene Figure 4 Duration of Major Response per Overall Combined Assessment by Investigator (Cohort 1) (ITT Analysis Set) BGB-3111-302



Source: Figure 14.2.1.4.10a, BGB-3111-302
Abbreviations: CR, complete response; ITT, Intent-to-Treat

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Reference ID: 4850271

Cohort 1 includes patients with activating mutations in MYD88.
Data cutoff: 31MAR2020.

Progression-free Survival by Investigator

In **Cohort 1**, the median progression-free survival had not been reached in the overall patient population and was NE in the ibrutinib arm and 33.2 months in the zanubrutinib arm for the relapsed/refractory patients (BeiGene Table 12). The event-free rates for patients overall in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 89.4% versus 93.9%, respectively, at 12 months; were 86.2% versus 89.6%, respectively, at 18 months; and 81.0% and 87.1%, respectively, at 24 months.

The event-free rates for relapsed/refractory patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 88.5% versus 96.3%, respectively, at 12 months; 84.6% versus 92.2%, respectively, at 18 months; and 78.3% versus 89.1%, respectively, at 24 months.

In the overall population in **Cohort 2**, the event-free rates per overall combined assessment at 12, 24 and 30 months were 69.2%, 61.5%, and NE.

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BeiGene Table 12 Progression-free Survival per Overall Combined Assessment by Investigator (ITT Analysis Set) BGB-3111-302

Progression-free Survival	Cohort 1		Cohort 2
	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Progression-free Survival			
Events, n (%)	20 (20.2)	14 (13.7)	11 (42.3)
Progressive disease	16 (16.2)	12 (11.8)	10 (38.5)
Death	4 (4.0)	2 (2.0)	1 (3.8)
Follow-up time (months) [a]			
Median (95% CI)	24.9 (23.9, 27.4)	24.9 (22.3, 25.3)	24.9 (22.2, 25.1)
(Min, Max)	(0.0, 36.0)	(0.0, 36.0)	(1.6, 28.0)
Progression-free survival (months) [b]			
Median (95% CI)	NE (30.7, NE)	NE (33.2, NE)	27.5 (11.1, NE)
Range	(0.0+, 36.0+)	(0.0+, 36.0+)	(1.6, 28.0+)
Event free rate at % (95% CI) [c]			
6 months	93.7 (86.6, 97.1)	95.0 (88.3, 97.9)	88.5 (68.4, 96.1)
12 months	89.4 (81.3, 94.2)	93.9 (87.0, 97.2)	69.2 (47.8, 83.3)
18 months	86.2 (77.4, 91.7)	89.6 (81.5, 94.3)	61.5 (40.3, 77.1)
24 months	81.0 (71.1, 87.8)	87.1 (78.4, 92.5)	61.5 (40.3, 77.1)
30 months	75.3 (62.5, 84.3)	85.0 (75.1, 91.2)	NE (NE, NE)

Source: BGB-3111-302, Table 14.2.1.8.1a and Table 14.2.1.8. 2.a
Abbreviation(s): CI, confidence interval; Q1, first quartile; Q3, third quartile; NE, not estimable, + = censored.
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on N.
[a] Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

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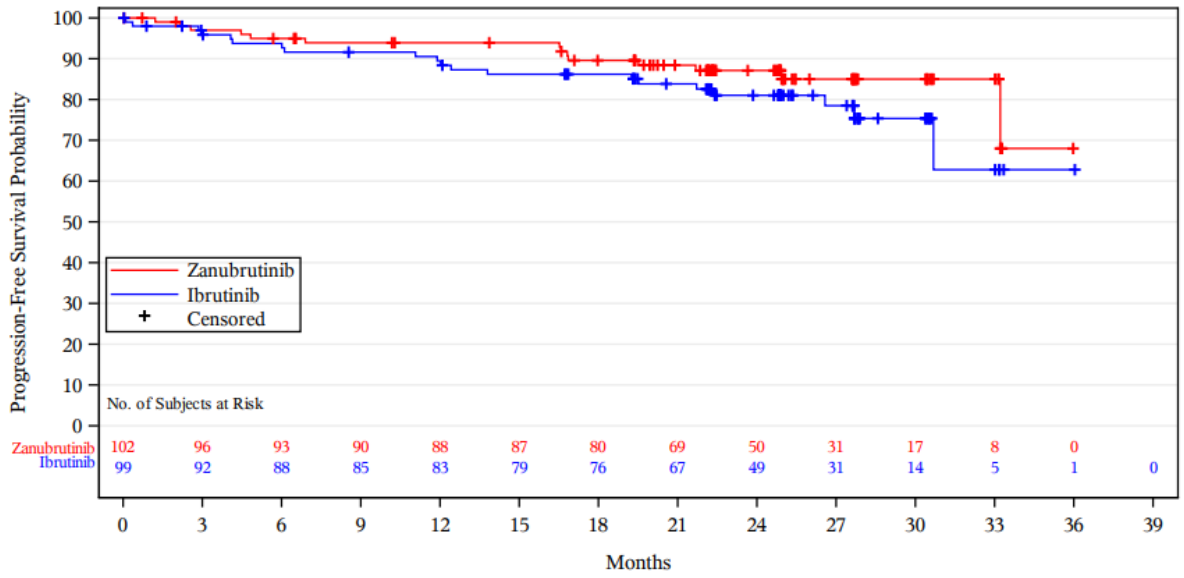
Reference ID: 4850271

[c] Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Data cutoff: 31MAR2020

BeiGene Figure 5 Kaplan Meier Curve of Progression-free Survival per Overall Combined Assessment by Investigator- Cohort 1 (ITT Analysis Set) BGB-3111-302



Source: BGB-3111-302, Figure 14.2.1.3.9a
Cohort 1 includes patients with activating mutations in MYD88
Data cut-off: 31MAR2020.

Time to Response by Investigator

In the overall population in **Cohort 1**, the median time to VGPR or CR per overall combined assessment was shorter in the zanubrutinib arm, specifically 10.15 months and 5.55 months in the ibrutinib and zanubrutinib treatment arms, respectively (BGB-3111-302, Table 14.2.1.16.1a). Conversely, time to major response and overall response was similar between treatment arms, 2.84 months and 2.83 months, respectively.

Exploratory Efficacy Endpoints

A. CXCR4 Mutations in Patients With *MYD88^{MUT}* Waldenström's Macroglobulinemia

In Study, BGB-3111-302, testing for the stratification factor CXCR4 was performed on non B-cell enriched Sanger sequencing with a sensitivity of 10 to 15%. Eight patients in the ibrutinib treatment arm (all relapsed/refractory) and 11 patients in the zanubrutinib treatment arm (1 treatment- naïve and 10 relapsed/refractory) had *CXCR4^{WHIM}* by central laboratory using Sanger sequencing on bone marrow. Data on these patents are detailed in the BGB-3111-302

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Reference ID: 4850271

CSR. This percentage of *CXCR4*^{WHIM} (9.5% across both treatment arms) was inconsistent with published literature (25% to 40%) (Treon et al 2015a; Garcia-Sanz et al 2016; Treon et al 2018, Xu et al 2016; Hunter et al 2014). To address this issue, a more sensitive (sensitivity of 0.25% for CXCR4) next generation sequencing (NGS) assay was performed using residual bone marrow samples procured at baseline (b) (4) In total, 190 of 201 (95%) residual Cohort 1 samples were available for testing, and additional patients in Cohort 1 with CXCR4 mutations were identified. Of the patient samples tested across the treatment arms in Cohort 1, 53 of 190 (27.4%) samples had the CXCR4 mutation with 34% *CXCR4*^{WHIM} on the zanubrutinib treatment arm and 22% *CXCR4*^{WHIM} on the ibrutinib treatment arm as shown in Table 14.

Similar to what has been reported in the literature (Treon 2020a), patients who had *MYD88*^{MUT} *CXCR4*^{WHIM} WM treated with either BTK inhibitor demonstrated lower response rates of VGPR compared to patients with *MYD88*^{MUT}*CXCR4*^{WT} Waldenström's macroglobulinemia, although numerically higher VGPR rates were seen in patients treated with zanubrutinib (21.1%) than ibrutinib (5%). Given that more patients (>10%) with *CXCR4*^{WHIM} were randomized to receive zanubrutinib, and the primary endpoint of study was VGPR + CR rate, the unbalanced stratification in the study favored the ibrutinib arm. When adjusting *CXCR4*^{WHIM} status as determined by NGS in the CMH analyses, the estimated risk differences were numerically higher in both the relapsed/refractory patients and overall. Similarly, *CXCR4*^{WHIM} Waldenström's macroglobulinemia patients treated with zanubrutinib had higher MRR (72.7%) than those treated with ibrutinib (60%).

BeiGene Table 13 CXCR4 Mutational Status and Response Based on NGS Analyses (BGB-3111-302)

CXCR4 Genotypes [a] Response rates [b]	**Overall**	
	Ibrutinib N=99	**Zanubrutinib N=102**
With NGS Results	92	98
CXCR4^{WHIM} [a]	20 (21.7)	33 (33.8)
CR or VGPR, n (%) [b]	1 (5.0%)	7 (21.2%)
MRR(PR or better), n (%) [b]	12 (60.0%)	24 (72.7%)
ORR (MR or better), n (%) [b]	19 (95.0%)	30 (90.9%
CXCR4^{WT} [a]	72 (78.3%)	65 (66.3%)
CR or VGPR, n (%) [b]	17 (23.6%)	25 (38.5%)

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Reference ID: 4850271

MRR (PR or better), n (%) [b]	60 (83.3%)	53 (81.5%)
ORR (MR or better), n (%) [b]	68 (94.4%)	63 (96.9%)

Source: BGB-3111-302, Table 14.2.1.2.5a
[a] Percentage is based on the number of patients with NGS results.
[b] Percentage is based on the number of patients with corresponding CXCR4 genotypes.

Time to Major Response and VGPR by CXCR4 Mutational Status by Next Generation Sequencing

When time to response was examined for ibrutinib versus zanubrutinib according to CXCR4 mutational status determined by NGS, median times to VGPR or CR in *CXCR4^{WHIM}* by investigator were 16.59 months and 11.10 months. As expected, the median times to VGPR or CR in ibrutinib and zanubrutinib-treated patients with *CXCR4^{WT}* Waldenström's macroglobulinemia by NGS by investigator were considerably shorter at 8.41 months and 4.80 months, respectively.

The median times to major response in patients with *CXCR4^{WHIM}* by NGS in the ibrutinib and zanubrutinib treatment arms were 6.57 months and 3.02 months, respectively. As before, with time to VGPR or CR, the median time to major response in patients with *CXCR4^{WT}* by NGS was shorter. Specifically, median time to MRR was 2.81 months in the ibrutinib treatment arm and 2.79 months in the zanubrutinib arm (BGB-3111-302, Table 14.2.1.22.3a).

Additional MYD88 Mutations in Cohorts 1 and 2 Determined by Next Generation Sequencing

On a molecular basis, Waldenström's macroglobulinemia is characterized by a specific point mutation in the MYD88 gene *(MYD88^{L265P})*, present in over 90% of patients with Waldenström's macroglobulinemia, which results in constitutive NFκB activation (Treon 2012). Non-L265P mutation variants (V217F, S219C, M232T, S243N) have also been identified, although expression estimates for these variants are 1% to 2% in Waldenström's macroglobulinemia (Treon 2015, Varettoni 2017). In the ASPEN study, MYD88 mutational status was analyzed by the central laboratory without CD19+ cell selection using a proprietary assay that employs locked oligonucleotides to block amplification of *MYD88^{WT}* DNA during PCR followed by bidirectional Sanger sequencing of the amplicon (Section 9.5.1.3 of the BGB-3111-302 Clinical Study Report).The MYD88 assay was developed to amplify exon 5 of MYD88 (G259-N291) and 110 nucleotides located in the 5 intronic region in order to cover the splice site and part of intron 4. This approach captures all mutations from MYD88 encompassing amino acids Q262-I266 and includes the predominant mutation in Waldenström's macroglobulinemia (L265P) with an approximately 0.5% limit of detection. Of note, this assay would not pick up any of the 4 aforementioned variants. With this methodology 201 patients were found to have MYD88^{L265P} and were enrolled in Cohort 1 to be randomized 1:1 to receive either zanubrutinib or ibrutinib.

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Reference ID: 4850271

An additional 26 patients were found not to have the mutation and were assigned to Cohort 2 along with 2 patients who failed to have a result.

Using residual samples from Cohort 1 (n=190/201) and from Cohort 2 (n=20/26) an NGS test that can identify mutations across the entirety of the gene was performed and identified additional mutations in 7/190 samples. In addition to the previously identified M232T and V217F variants, 4 additional mutations were identified. Of note, all 7 patients with additional MYD88 mutations had high risk IPSS scores. Clinically, 5/7 patients had hyperviscosity (typically found in approximately 15% of WM patients) (Dreyling 2014) and 2/7 patients had amyloidosis either at baseline or associated with disease progression, a rare finding thought to occur in approximately 3% of patients (Gertz 1993). All patients achieved a best response of PR or higher except for patient 3374004 who received only 10 days of ibrutinib therapy prior to progressive disease/amyloidosis/light chain deposition by ECHO and cytological examination.

Cohort 2: While present along with the L265P in 7/190 of the samples from Cohort 1, none of the variant alleles were found in Cohort 2 and 18/20 were confirmed as $MYD88^{WT}$. Of the 2 patients in which non-L265P mutations were detected, one was detected at a VAF of 0.21%, which is below the validated sensitivity of the assay. The other was detected at a VAF of 1.09%. None of the non-L265P MYD88 mutations were identified in tested samples negative for $MYD88^{L265P}$.

Overall Survival

A total of 18 deaths (9 in the ibrutinib arm and 9 in the zanubrutinib arm) were observed in the ITT Analysis Set in **Cohort 1**. In the relapsed/refractory set, 15 deaths (9 in the ibrutinib arm and 6 in the zanubrutinib arm) were observed. (BGB-3111-302, Table 14.2.1.18.1a)

The event-free rates at 12, 24, and 30 months for patients overall were 93.9%, 92.8%, and 89.9% in the ibrutinib arm and 97.0%, 90.3%, and 90.3% in the zanubrutinib arm, respectively.

A total of 3 deaths were observed in **Cohort 2**. The event free rates at 12, 24, and 30 months for the overall population were 96.2%, 88.1%, and 88.1% (BGB-3111-302, Table 14.2.1.18.2a).

BeiGene Figure 6 Kaplan-Meier Plot of Overall Survival (Cohort 1) (ITT Analysis Set) Study BGB-3111-302

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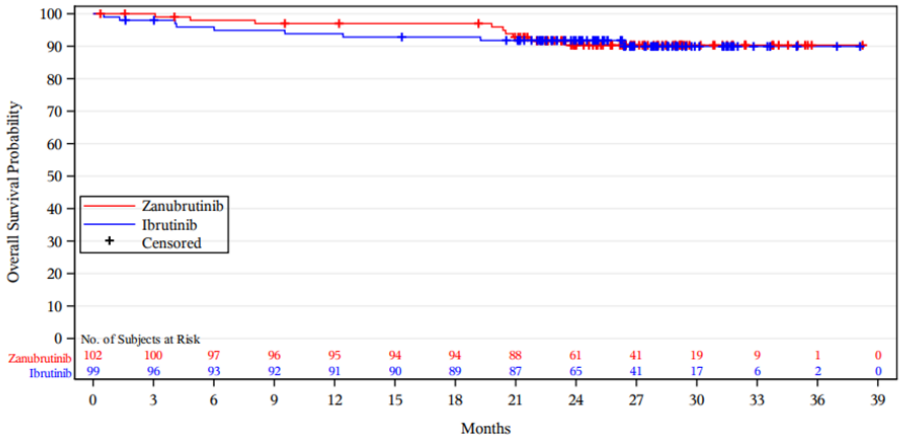
Reference ID: 4850271

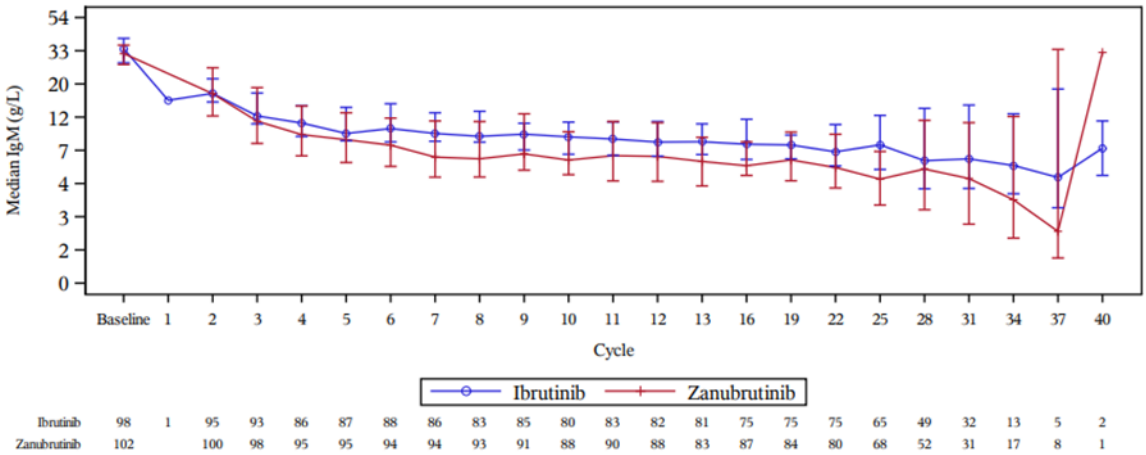


Source: BGB-3111-302, Figure 14.2.1.5.2a
Abbreviations: ITT, Intent-to-Treat.
Cohort 1 includes patients with activating mutations in MYD88.
Data cutoff 31MAR2020

Serum IgM Improvement Over Time

Relief from the clinical symptoms of WM including peripheral neuropathy, cryoglobulinemia, cold-agglutinemia, amyloidosis and hyperviscosity comes from reducing the burden of pathologic serum IgM (Trotman et al 2020; Kapoor et al 2017). In Cohort 1, serum IgM levels decreased (ie, improved) over time for patients overall in both treatment arms, with median decreases consistently larger in the zanubrutinib arm than the ibrutinib arm in the ITT Analysis Set (BeiGene Figure 7).

BeiGene Figure 7 Changes in Serum IgM Levels Over Time (Cohort 1) (ITT Analysis Set) BGB-3111-302



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Source: BGB-3111-302, Figure 14.2.1.8.4a
Abbreviations: IgM, immunoglobulin M; ITT, Intent-to-Treat.
Cohort 1 includes patients with activating mutations in MYD88.
In the case of multiple IgM readings in the same cycle, the average of the readings is used.
The bars represent the confidence limits of the medians.
Data in log scale Data cutoff: 31MAR2020

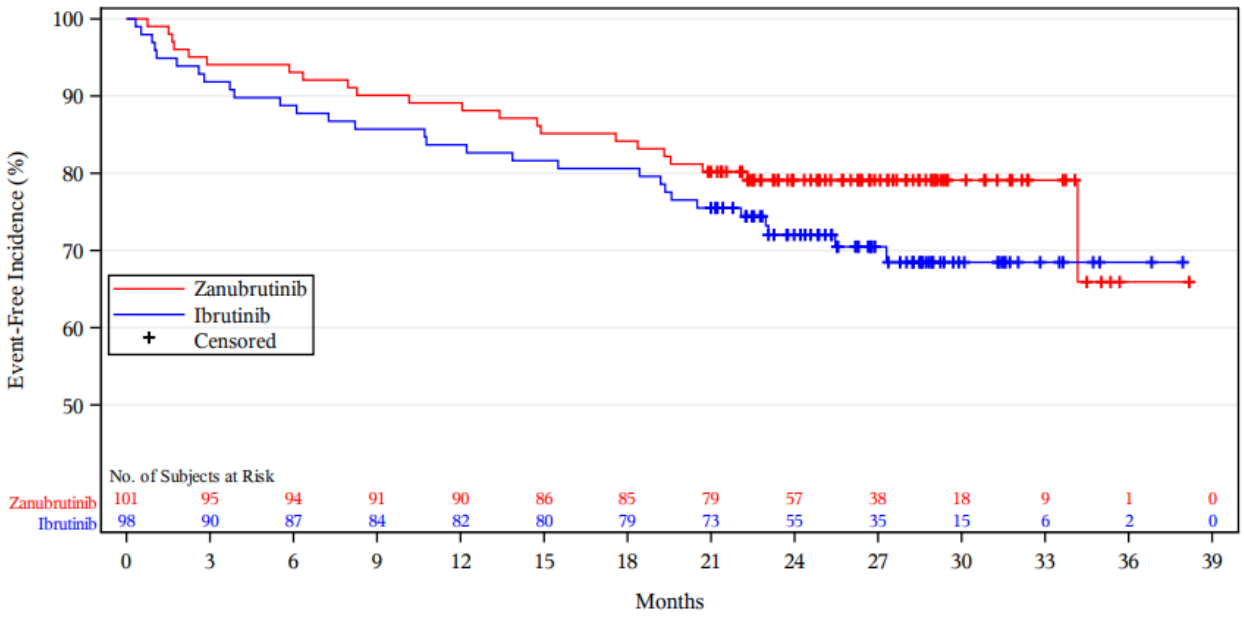
Time to Treatment Discontinuation

A Kaplan-Meier analysis of cumulative time to event suggested a trend toward a shorter time to discontinuation for ibrutinib than zanubrutinib in **Cohort 1** (BeiGene Figure 8).

The event-free rates at 12, 24, and 30 months for patients in the ibrutinib and zanubrutinib treatment arms overall were 83.7% versus 89.1%, 72.0% versus 79.1%, and 68.5% versus 79.1%, respectively, (BGB-3111-302, Table 14.3.1.1.2.1a). This observation was more evident in the event of discontinuation due to adverse events. Events of discontinuation due to other reasons were censored.

The number of discontinuation events was small; however, the early separation maintained through median follow-up time was 25.76 months for ibrutinib-treated patients and 25.07 months for zanubrutinib-treated patients.

BeiGene Figure 8 Time to Treatment Discontinuation Overall (Cohort 1) BGB3111302 Safety Analysis Set



Source: BGB-3111-302, Figure 14.1.1.5.1a
Cohort 1 includes patients with activating mutations in MYD88. Data cutoff: 31MAR2020

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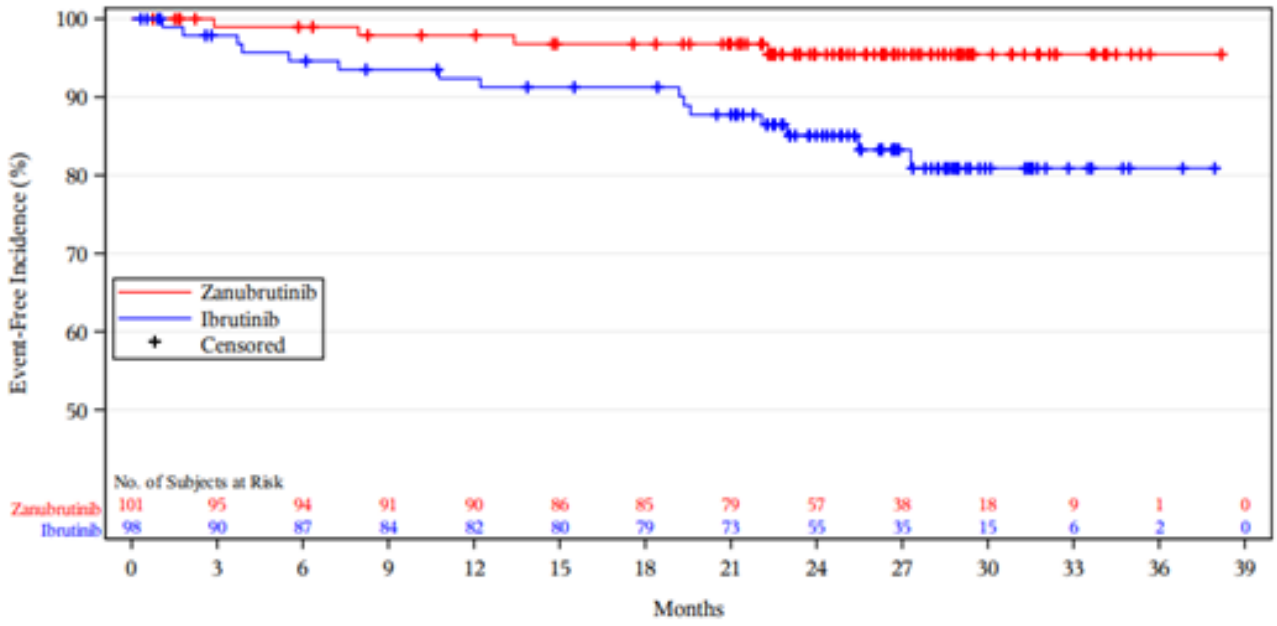
BeiGene Figure 9 Time to Treatment Discontinuation Due to Adverse Events (Cohort 1)
BGB-3111-302 Safety Analysis Set



Source: BGB-3111-302, Figure 14.1.1.5.3a
Cohort 1 includes patients with activating mutations in MYD88. Data cutoff: 31MAR2020

The Applicant's Position:
Efficacy data provided have demonstrated that zanubrutinib has a clear efficacy benefit in the treatment of patients with Waldenström's macroglobulinemia, independent of line of therapy and independent of MYD88 and CXCR4 mutational status. Zanubrutinib treatment resulted in rapid, deep, and sustained reduction in IgM, high overall and major responses, and high rates of VGPR, with trends towards improved response quality and PFS over ibrutinib. These differentiating factors were present at the primary analysis in Study BGB-3111-302 (data cutoff 31 August 2019; median follow up 19.4 months) and continued to strengthen over time (data cutoff 31 March 2020; median follow up 26 months). The efficacy data analysis suggests that zanubrutinib is at least comparable to, if not more effective, than ibrutinib in patients with WM. Furthermore, Zanubrutinib demonstrated a longer time to treatment failure of any cause, particularly for discontinuation of treatment due to an adverse event.

The FDA's Assessment:
FDA does not agree with the Applicant's statement, "Efficacy data provided have demonstrated that zanubrutinib has a clear efficacy benefit in the treatment of patients with Waldenström's macroglobulinemia, independent of line of therapy and independent of MYD88 and CXCR4 mutational status. Zanubrutinib treatment resulted in rapid, deep, and sustained reduction in

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Reference ID: 4850271

IgM, high overall and major responses, and high rates of VGPR, with trends towards improved response quality and PFS over ibrutinib". The FDA also does not agree with the Applicant's statement, "The efficacy data analysis suggests that zanubrutinib is at least comparable to, if not more effective, than ibrutinib in patients with WM".

The study did not meet the primary endpoint of superiority of VGPR/CR rate in relapsed/refractory Waldenström's Macroglobulinemia in zanubrutinib patients compared with ibrutinib, as assessed by Independent Review Committee (2-sided p=0.116). All subsequent hypothesis tests and associated p-values are descriptive only. FDA also notes that the trial did not demonstrate non-inferiority of zanubrutinib compared to ibrutinib for the secondary endpoint of major response rate. So, the Applicant statement above is false and misleading.

The FDA agrees with the Applicant's statement regarding subgroup analysis that the proportion of patients in Cohort 1 who achieved a VGPR or CR per overall combined assessment was generally consistent for the subgroups of interest with a few exceptions, mostly in the subgroups that had a small sample size. The small size of subgroups precludes any meaningful conclusions regarding efficacy in these subgroups. Additionally, the study did not meet the primary endpoint, and any subgroup comparisons are not valid.

In Study BGB-3111-302, there were only 19 subjects (10 subjects in Ibrutinib arm and 9 subjects in Zanubrutinib arm) enrolled in the United States. The FDA noted that in the 9 patients enrolled in the U.S. who received zanubrutinib, the response rate (CR+VGPR) was 0%. An Information Request was sent to the Application to provide the major response rate (PR+VGPR+CR) for these patients and to provide an explanation for the lower response rate seen in U.S. patients. In the Applicant's response, they noted the major response rate in the U.S. population of patients who received zanubrutinib was 67% (n=6/9), which is also slightly lower than the major response rate for patients in Europe (n=46/61, 75%) and Australia (n=27/32, 84%). While the baseline demographics for patients treated with zanubrutinib were mostly balanced across regions, the Applicant noted that patients treated with zanubrutinib in the United States had a higher rate of CXCR4 WHIM mutation as determined by NGS (n=6/9, 67%) than either Europe (n=19/61; 31%) or Australia (n=7/32; 22%). Because CXCR4 WHIM has been associated with a poor prognosis, this could potentially explain the lower response rates in the U.S. patient population. Additionally, the Applicant noted that patients in the U.S. treated with zanubrutinib had a lower median baseline hemoglobin and slightly higher IPSS than patients treated with zanubrutinib from Europe or Australia. While these factors may all have contributed to the differences in response rate in the U.S. population, overall, the number of patients enrolled in the U.S. was small and any conclusions should be interpreted with caution. In each of the post-marketing commitments issued with this application, the Applicant will be required to enroll a sufficient number of patients in the U.S. to allow for the interpretation of the results in the U.S. patient population.

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Reference ID: 4850271

Based on data cutoff of August 31, 2019 in Cohort 1, the proportion of patients who achieved a major response (defined as PR or better) per overall combined assessment in the ibrutinib and zanubrutinib arms were 77.8% and 77.5%, respectively. The difference in major response rates between the two arms was estimated to be -0.5% with a 95% CI of (-12.2, 11.1). In patients with relapsed/refractory disease, the major response rates on the ibrutinib and zanubrutinib arms were 80.2% and 78.3%, respectively, with an estimated major response rate difference of -3.5% and a 95% CI of (-16.0, 9.0). The noninferiority of major response rate was not met in either population.

The FDA also performed subgroup analysis based on major response rate (PR or better) per IRC assessment at the data cutoff of August 31, 2019. The proportion of patients in Cohort 1 who achieved a major response using the ITT population was generally consistent for subgroups of interest.

The FDA agrees with the presented results from analysis of duration of response, PFS, time to response and OS. FDA considered all the secondary efficacy analysis as exploratory as the study did not meet its primary endpoint.

The FDA does not agree with the Applicant's description of MYD88 mutations in cohorts 1 and 2, as determined by next generation sequencing (NGS). This was not a pre-specified analysis and there is limited data on the impact of CXCR4 mutations assessed by NGS versus the standard Sanger assay. Additionally, the NGS assay was not reviewed by the Agency and the Agency cannot verify the accuracy of the reported mutations or the rates. See Section 6.3.2.3 for additional discussion regarding the FDA's assessment of the mutational analysis of patients enrolled in Study BGB-3111-302.

Dose/Dose Response

Data:
See 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 6.3.2.1** for FDA's assessment of zanubrutinib dose- and exposure-response relationships.

Durability of Response Data:

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Reference ID: 4850271

In further support of durability of response, the first in human BGB-3111-AU-003 study, the median durations of VGPR or CR, major response, and overall response have not been reached for all Waldenström's macroglobulinemia patients who achieved a response to study treatment based on a median follow-up time of 34.1 months for VGPR or CR and 33.4 months for major response.

The estimated event-free rates at 12, 18, and 24 months for Waldenström's macroglobulinemia patients who achieved a major response were 91.6%, 88.1%, and 82.7%, respectively. The event free rate in patients with a major response at 36 months was estimated as 79.0% when 13 patients were still being followed BGB-3111-AU-003.

Median follow-up for the All WM population was 20.2 months. The event free rates for patients who achieved a VGPR or CR at 12, 18 and 24 months were 89.8% 83.3% and 80.9%, respectively. Event-free rates for All WM patients who achieved a major response were 89.2%, 84.0%, and 81.7%, respectively. Event-free rates for All WM patients who achieved an overall response at 12, 18, and 24 months were 89.2%, 83.5% and 80.9%, respectively.

The Applicant's Position:

Efficacy data from the pivotal Phase 3 Study BGB-3111-302 and supportive studies BGB-3111-AU-003 and BGB-3111-210 have demonstrated that zanubrutinib has a clear efficacy benefit in the treatment of patients with Waldenström's macroglobulinemia. Responses achieved with zanubrutinib therapy were durable across the 3 studies. In Study BGB-3111-302, event-free rates were > 90% for patients overall in the ibrutinib and zanubrutinib treatment arms who achieved a major response. In Cohort 1, at both the data cutoffs of 31 August 2019 and 31 March 2020, the median durations of VGPR or CR and major response per overall combined assessment had not been reached for overall or relapsed/refractory patients in either treatment arm who achieved a response to study treatment.

When including patients enrolled on studies BGB-3111-AU-003 and BGB-3111-210, with a median follow-up of 20.2 months for the combined studies represented in the All WM population, the event free rates for patients who achieved a VGPR or CR, MRR, or overall response at 2 years remained >80% indicating durability of response.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of the durability of response. Based on the data cutoff of August 31, 2019, in Cohort 1, the median duration of VGPR or CR and major response per IRC had not been reached for both the relapsed/refractory analysis set and the ITT analysis set in either treatment arm for subjects who achieved a response to study treatment. Nine events occurred in subjects who achieved a major response on the ibrutinib arm, while 8 events occurred in subjects who achieved a major response on the zanubrutinib arm. The event-free rates at 12 and 18 months for patients who achieved a major response per overall combined assessment in the ibrutinib and zanubrutinib arms were 87.9% and 87.9%, and 94.4% and 85.2%, respectively (FDA Table 12).

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Reference ID: 4850271

FDA Table 13: Duration of Major Response (Data Cutoff August 31, 2019)

	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib N=18	Zanubrutinib N=19	Ibrutinib N=81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
MRR event	12 0	14 2 (14.3)	65 9 (13.80	65 6 (9.2)	77 9 (11.7)	79 8 (10.1)
Median DoR	NE	NE	NE	NE	NE	NE
Event-free rate at % (95%)						
12 Months	100	90.9 (50.8, 98.7)	85.6 (73.1, 92.6)	95.1 (85.5, 98.4)	87.9 (77.0, 93.8)	94.4 (85.8, 97.9)
18 Months	100	79.5 (39.3, 94.5)	85.6 (73.1, 92.6)	87.0 (72.5, 94.1)	87.9 (77.0, 93.8)	85.2 (71.7, 92.6)

Source: FDA Statistical Reviewer's Analysis

Persistence of Effect

Data:

Data for duration of response, PFS and OS is presented in the secondary endpoint section for the ASPEN study and for duration of response for the BGB-3111-210 and BGB-3111-AU-003 in the duration of response section above. In the All WM population (N=244), the median follow-up time was 26.0 months and the estimated progression-free survival event free rates at 12, 18, and 24 months were 85.2%, 81.8%, and 77.3%, respectively. In the *MYD88^{MUT}* and *MYD88^{WT}*patients, the median progression-free survival has not been reached in either population based on a median follow-up time of 25.4 (range: 0 to 63.80) months and 25.1 (range: 1.6 to 63.3) months, respectively. The estimated event free rates at 12, 18 and 24 months were longer for MYD88MUT versus MYD88WT as expected.

For OS, in BGB-3111-210, the median overall survival time had not been reached after a median follow-up time of 25.7 months (range: 3.2 to 28.8). The overall survival rate at 12 months was 90.5%. In BGB-3111-AU-003, 11 (15.1%) Waldenström's macroglobulinemia patients died at the time of data cut-off; the median overall survival time was not reached after a median follow-up time of 42.8 months (range: 4.4 to 64.2). The event free rate for all Waldenström's macroglobulinemia patients at 24 months was 93.0%.

In the MYD88^{MUT} and MYD88^{WT}patients the median overall survival had not been reached in in either population based on a median follow-up time of 28.0 months (range: 0.4 to 64.2) and 26.0 months (range 2.3 to 63.9), respectively. The estimated event free rates at 12, 18, and 24

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months were 95.8%, 94.7%, and 90.2%, respectively, for $MYD88^{MUT}$ patients and 95.0%, 89.9%, and 89.9%, respectively, for $MYD88^{WT}$ patients. In the All WM population, the median follow-up time was similar at 27.8 months (range 0.4 to 64.2). The estimated event free rates at 12, 18, and 24 months were 95.8%, 94.1%, and 90.4%, respectively.

The Applicant's Position:
For Study BGB-3111-302, Kaplan-Meier distributions for the time to event endpoints of progression-free survival, overall survival, and duration of response, supported by studies BGB-3111-AU-003 and BGB-3111-210 support zanubrutinib's persistence of effect in patients with Waldenström's macroglobulinemia.

The FDA's Assessment:
In general, persistence of effect over time after treatment was demonstrated by a trend for prolonged progression-free survival and OS. However, the results from these time-to-event endpoints were considered as descriptive. No inference should be made from these analyses.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:

To assess how depth of response could improve quality of life (i.e., attaining a VGPR could result in clinical benefit to the patient) during treatment with zanubrutinib or ibrutinib, changes in quality of life were measured using the EORTC QLQ-C30 questionnaire and the EQ-5D as described in BGB-3111-302 Clinical Study Report Section 9.7.1.3.4.

At the 31 March 2020 data cutoff, in both treatment arms in Cohort 1, most quality of life measures (patient reported outcomes) improved in patients overall. There was no statistically significant difference between the 2 treatment arms for QLQ-C30 global health status/quality of life scale scores (Table 14.2.1.25.1a). However, in most assessments, zanubrutinib trended toward greater improvement, particularly when analyzed over the first year on treatment in patients who achieved a deeper response (best overall response assessment of VGPR). This was most notable for improvements in EQ-5D score and QLQ-C30 subscales including loss of appetite, fatigue, physical and role functioning, and dyspnea. Consistent with the increase in adverse events of diarrhea in patients treated on the ibrutinib arm, the functional scale for diarrhea trended worse for ibrutinib than for zanubrutinib.

The Applicant's Position:

These patient-reported outcome data demonstrated an improvement in quality of life for patients treated with either drug, with a more pronounced effect in patients who received zanubrutinib treatment and with a deeper response (VGPR). Since disease-related symptoms are mostly controlled in patients who achieve a VGPR (≥ 90% IgM reduction) the clearly differentiated patient reported outcomes demonstrated in patients who achieved a VGPR

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Reference ID: 4850271

treated with zanubrutinib versus those treated with ibrutinib suggest a greater tolerability of zanubrutinib due to the characteristics of the drug itself, and further support clinical benefit consistent with the shorter time to VGPR and deeper response

The FDA's Assessment:
The FDA disagrees that these QoL data are informative. The interpretability of results of PRO endpoints is significantly limited by the sample size, study design and completion rate. The study was neither designed, nor powered, to assess these endpoints. In addition, Study BGB-3111-302 is an open-label study. PROs in the context of open-label studies are difficult to interpret because, unlike objective endpoints, they are based on patient assessments which can depend on knowledge of the treatment assignment. Missing data could also prevent the interpretation of the results. Therefore, the results from these PROs analyses should be considered descriptive analyses. (b) (4) (b) (4)

Additional Analyses Conducted on the Individual Trial

Data:
No other analyses were conducted for the ASPEN trial.

The Applicant's Position:
Not applicable

The FDA's Assessment:
Additional analyses using the standard response definition have been included in the FDA's assessment under the efficacy section.

Integrated Review of Effectiveness

The FDA's Assessment:
Since only one Phase 3 randomized controlled study was submitted to support the proposed indication, the integrated review of efficacy was not applicable.

Assessment of Efficacy Across Trials

Primary Endpoints

Data:

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Disease response in the overall WM population in studies BGB-3111-302, BGB-3111-210, and BGB-3111-AU-003, including $MYD88^{MUT}$, $MYD88^{WT}$ and all WM is summarized in BeiGene Table 14. The WM population represents pooled data across studies for patients with Waldenström's macroglobulinemia treated with zanubrutinib.

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Reference ID: 4850271

BeiGene Table 14 Analysis of Disease Response Per Overall Combined Assessment by Investigators (Overall WM Population) (ITT/Efficacy Analysis Set)

	BGB-3111-302			BGB-3111-210	BGB-3111-AU-003	All WM Zanubrutinib		
	Cohort 1 Ibrutinib (N = 99) n (%)	Cohort 1 Zanubrutinib (N = 102) n (%)	Cohort 2 Zanubrutinib (N = 26) n (%)	Zanubrutinib (N = 43) n (%)	Zanubrutinib (N = 73) n (%)	MYD88 MUT [a] (N = 196) n (%)	MYD88 WT [b] (N = 40) n (%)	Total [c] (N = 244) n (%)
Best Overall Response, n (%)								
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (2.5)	1 (0.4)
Very good partial response (VGPR)	19 (19.2)	33 (32.4)	8 (30.8)	12 (27.9)	33 (45.2)	73 (37.2)	10 (25.0)	86 (35.2)
Partial response (PR)	58 (58.6)	47 (46.1)	6 (23.1)	17 (39.5)	26 (35.6)	82 (41.8)	11 (27.5)	96 (39.3)
Minor response (MR)	16 (16.2)	17 (16.7)	7 (26.9)	4 (9.3)	10 (13.7)	26 (13.3)	11 (27.5)	38 (15.6)
Stable disease (SD)	3 (3.0)	3 (2.9)	4 (15.4)	2 (4.7)	3 (4.1)	7 (3.6)	4 (10.0)	12 (4.9)
Progressive disease (PD)	2 (2.0)	1 (1.0)	1 (3.8)	7 (16.3)	0 (0.0)	6 (3.1)	3 (7.5)	9 (3.7)
Not evaluable (NE) [d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Reference ID: 4850271

	BGB-3111-302			BGB-3111-210	BGB-3111-AU-003	All WM Zanubrutinib		
	Cohort 1 Ibrutinib (N = 99) n (%)	Cohort 1 Zanubrutinib (N = 102) n (%)	Cohort 2 Zanubrutinib (N = 26) n (%)	Zanubrutinib (N = 43) n (%)	Zanubrutinib (N = 73) n (%)	MYD88 MUT [a] (N = 196) n (%)	MYD88 WT [b] (N = 40) n (%)	Total [c] (N = 244) n (%)
Ongoing without postbaseline tumor assessment	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)
Discontinued prior to first assessment	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)
VGPR or CR Rate, n (%)	19 (19.2)	33 (32.4)	8 (30.8)	12 (27.9)	34 (46.6)	73 (37.2)	11 (27.5)	87 (35.7)
95% CI [e]	(12.0, 28.3)	(23.4, 42.3)	(14.3, 51.8)	(15.3, 43.7)	(34.8, 58.6)	(30.5, 44.4)	(14.6, 43.9)	(29.6, 42.0)
Risk Difference, % [f]		14.4						
95% CI		(2.4, 26.5)						
p-value [g]		0.0206						
Major Response Rate (PR or Better), n (%)	77 (77.8)	80 (78.4)	14 (53.8)	29 (67.4)	60 (82.2)	155 (79.1)	22 (55.0)	183 (75.0)
95% CI [e]	(68.3, 85.5)	(69.2, 86.0)	(33.4, 73.4)	(51.5, 80.9)	(71.5, 90.2)	(72.7, 84.6)	(38.5, 70.7)	(69.1, 80.3)

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Reference ID: 4850271

	BGB-3111-302			BGB-3111-210	BGB-3111-AU-003	All WM Zanubrutinib		
	Cohort 1 Ibrutinib (N = 99) n (%)	Cohort 1 Zanubrutinib (N = 102) n (%)	Cohort 2 Zanubrutinib (N = 26) n (%)	Zanubrutinib (N = 43) n (%)	Zanubrutinib (N = 73) n (%)	MYD88 MUT [a] (N = 196) n (%)	MYD88 WT [b] (N = 40) n (%)	Total [c] (N = 244) n (%)
Risk Difference, % [f]		0.0						
95% CI		(-11.6, 11.5)						
Overall Response Rate (MR or Better), n (%)	93 (93.9)	97 (95.1)	21 (80.8)	33 (76.7)	70 (95.9)	181 (92.3)	33 (82.5)	221 (90.6)
95% CI [e]	(87.3, 97.7)	(88.9, 98.4)	(60.6, 93.4)	(61.4, 88.2)	(88.5, 99.1)	(87.7, 95.7)	(67.2, 92.7)	(86.2, 93.9)

Data Source: Table 2.7.3.3.1.1
Abbreviations: ITT, Intent-to-treat; NE, Not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; WM, Waldenström's macroglobulinemia
Date of Cut-off: 31Mar2020 for all three studies.
[a] Include Studies BGB-3111-302 Cohort 1, BGB-3111-210, and BGB-3111-AU-003; Only mutation L265P are included.
[b] Include Studies BGB-3111-302 Cohort 2, BGB-3111-210, and BGB-3111-AU-003; Mutations other than L265P, i.e., S243N (from Study BGB-3111-210) are included.
[c] Include MYD88 mutant (MUT), MYD88 wild type (WT), and MYD88 unknown (UNK) patients.
[d] Includes NE, UNK, and disease flare.
[e] 95% CI is calculated using the Clopper-Pearson method.
[f] Mantel-Haenszel common risk difference with the 95% confidence interval calculated using a normal approximation and Sato's standard error stratified by the stratifications factors per IRT (strata CXCR4 WT and UNK are combined) and age group (<=65 and >65). Ibrutinib is the reference group.

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[g] Based on CMH test stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (<=65 and >65)

The Applicant's Position:

Zanubrutinib was effective in terms of disease response in all studies of WM patients, with consistently high response rates (VGPR/CR; major response; overall response) across all studies and subgroups for the overall WM study population

The FDA's Assessment:

The FDA does not agree with the Applicant's statement, "Zanubrutinib was effective in terms of disease response in all studies of WM patients, with consistently high response rates (VGPR/CR; major response; overall response) across all studies and subgroups for the overall WM study population". This statement is broad and subjective.

The FDA's assessment of efficacy for this application was based on the randomized Study BGB-3111-302. The FDA did not conduct additional efficacy analyses using data from the supportive studies. Study BGB-3111-302 did not meet the primary endpoint of a superiority of CR+VGPR rate in relapsed/refractory Waldenström's Macroglobulinemia in patients treated with zanubrutinib compared to those treated with ibrutinib, as assessed by Independent Review Committee (2-sided p=0.116). As a result, all subsequent hypothesis tests and associated p-values are descriptive only.

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Reference ID: 4850271

Secondary and Other Endpoints

Data:

- Time to response:
  - Time to VGPR or CR across the *MYD88^{MUT}*, *MYD88^{WT}* and All WM populations was similar at approximately 5.6 months. The median time to VGPR or CR on the ibrutinib arm of Study BGB-3111-302 was almost double that of the All WM zanubrutinib population at over 10 months.
  - Median time to major response was shorter than median time to VGPR or CR and was similar across all studies, *MYD88^{MUT}*, *MYD88^{WT}* and All WM populations occurring within 3 months of starting therapy.
- Duration of response:
  - *Duration of VGPR or CR*: The median duration of VGPR or CR not been reached for the overall population in any treatment across the 3 studies except for Cohort 2 of Study BGB-3111-302 and *MYD88^{WT}* WM (which is largely driven by Cohort 2) both with an estimated median of 22 months.
- *Duration of major response (PR or better)*: The median durations of major response had not been reached for the overall across treatment arms and across all 3 studies, *MYD88^{MUT}, MYD88^{WT,}* and the All WM population except for Study BGB-3111-302 Cohort 2 which had an estimated median duration of major response of 25.7 months.
- Progression free survival (PFS):
  - *T*he median progression-free survival for the overall WM population by combined assessment has not been reached across treatment groups (with the exception of Study BGB-3111-302, Cohort 2). *MYD88^{WT}* patients have a shorter PFS with 12-months and 24-months progression-free survival at 70.0% and 59.9%, respectively, as compared to 87.8% and 80.6% in *MYD88^{MUT}* patients. The estimated median PFS is 27.5 months in Cohort 2, with 12-months and 24-months event free survival at 69.2% and 61.5%.
- Overall survival:
  - Median overall survival for the overall population has not been reached across treatment arms for all studies, *MYD88^{MUT}*, *MYD88^{WT}*, or the All WM population. Survival rates in the *MYD88^{MUT}* population at 12, 18, and 24 months were similar to slightly higher than survival rates in the *MYD88^{WT}* Waldenström's macroglobulinemia population at 95.8%, 94.7%, 90.2% and 95.0%, 89.9%, and 89.9%

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Reference ID: 4850271

respectively. In the All WM population survival rates at 12, 18, and 24 months were 95.8%, 94.1% and 90.4% respectively.

The Applicant's Position:

Results from the secondary endpoints across trial are consistent with a positive Benefit/risk for zanubrutinib in WM. The ASPEN study provided clear evidence of the efficacy of zanubrutinib relative to ibrutinib in adult patients with WM. The clinical benefit of zanubrutinib was apparent in the totality of the data, both in the depth and durability of responses, with rapid and sustained decreases in IgM and associated resolution of IgM-related symptoms (eg, fatigue, B-symptoms, hyperviscosity, peripheral neuropathy, amyloidosis and disease-related cytopenias) and improvement in quality of life measures.

Several adverse effects have been associated with BTK inhibitors as a drug class, including diarrhea and the events predefined for specific adverse analyses Hemorrhage, Major hemorrhage, Atrial fibrillation and atrial flutter, Hypertension, Second primary malignancies, Tumor lysis syndrome, Infections and Cytopenias. These toxicities have been observed with varying frequency and severity across products, 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). Events of special interest for BTK inhibitors occurred with zanubrutinib but at generally lower rates than with ibrutinib. These lower rates are perhaps most notable because the events can be treatment-limiting with ibrutinib.

The results from ASPEN were supported by efficacy data from single-arm zanubrutinib studies, BGB-3111-AU-003 and BGB-3111-210. Pooled data sets as shown above demonstrate deep and durable responses. Response to zanubrutinib appeared to be agnostic to line of therapy, with high responses seen in both treatment-naive and relapsed/refractory patients. Efficacy was observed independent of mutational status with high response seen in both the *MYD88*^{MUT} and *MYD88*^{WT} subtypes. Collectively, the efficacy results provided in this application demonstrate that zanubrutinib has a clear clinical benefit in the treatment of patients with WM and support use of zanubrutinib for the treatment of patients with WM.

The FDA's Assessment:

The FDA does not agree with the Applicant's conclusion, that the ASPEN study provided "clear evidence of the efficacy of zanubrutinib relative to ibrutinib in adult patients with WM" or the sentence that, "Collectively, the efficacy results provided in this application demonstrate that zanubrutinib has a clear clinical benefit in the treatment of patients with WM". This statement is broad, misleading, and promotional. Only one Phase 3 randomized controlled study, Study BGB-3111-302 (ASPEN) was conducted to support the proposed indication. All other trials did not include a comparator arm to assess efficacy relative to ibrutinib. The ASPEN study failed to demonstrate superiority for zanubrutinib over ibrutinib for the prespecified endpoint of CR/VGPR. Major response rate, the efficacy measure used to support the original ibrutinib approval was numerically similar between the two arms. Based on the available data, there is no evidence to suggest a clear evidence of efficacy of zanubrutinib relative to ibrutinib in adult

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Reference ID: 4850271

patients with WM. FDAs analysis of efficacy is based on the Major response rates reported in the zanubrutinib arm.

The FDA does not agree with the Applicant's inclusion of information regarding adverse events associated with BTK inhibitors in this section. See Section 8.3 for discussion of the relevant safety findings.

Subpopulations

Data:
Please refer to subgroup data presented in Section 8.1.2, Study Results.

The Applicant's Position:
Please refer to subgroup data presented in Section 8.1.2, Study Results.

Additional Efficacy Considerations

The FDA's Assessment:
The FDA's assessment of efficacy focused on the results from the randomized, phase 3 study, BGB-3111-302, which enrolled patients with both newly diagnosed and relapsed/refractory WM. Refer to the FDA's assessment under the efficacy section.

Integrated Assessment of Effectiveness

Data:

The following is a comparison of efficacy results by investigator assessment for zanubrutinib across studies BGB-3111-302, BGB-3111-AU-003 and BGB-3111-210. Studies were compared for response assessment, time to response, duration of response, progression-free survival, and overall survival. All WM population represents pooled data across studies for WM patients treated with Zanubrutinib.

Disease response

Across the All WM population, the rate of VGPR or CR was 35.7%. The All WM population had a major response rate (PR or better) of 75%. Similar to the overall WM population, the *MYD88*^{MUT} population had higher VGPR or CR and higher major response rate than the *MYD88*^{WT} WM population.

Time to Response

In the overall WM population in Study BGB-3111-302, the median times to VGPR or CR in the zanubrutinib-treated patients in Cohort 1 and Cohort 2 were 5.55 months and 6.88 months respectively. In Study BGB-3111-210, the median time to VGPR or CR was 4.24 months. In Study

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Reference ID: 4850271

BGB-3111-AU-003, the median time to VGPR or CR in the overall WM population was 7.80 months. Time to VGPR or CR across the *MYD88^{MUT}*, *MYD88^{WT}* and All WM populations was similar at approximately 5.6 months. The median time to VGPR or CR on the ibrutinib arm of Study BGB-3111-302 was almost double that of the All WM zanubrutinib population at just over 10 months.

Median time to major response was shorter than median time to VGPR or CR and was similar across all studies, *MYD88^{MUT}*, *MYD88^{WT}* and All WM populations occurring within 3 months of starting therapy.

Duration of Response

Duration of VGPR or CR

Most responders remain in remission (32/33 [97.0%], with a median follow-up of 17.5 months in the Study BGB-3111-302 Cohort 1 Zanubrutinib arm. The event rate is higher in Study BGB-3111-302 Cohort 2, and Studies BGB-3111-210 and BGB-3111-AU-003 2/8 (25.0%) patients, 4/12 (33.3%) patients, and 9/34 (26.5%) patients, respectively).

The median duration of VGPR or CR per overall combined assessment has not been reached for the overall population and or relapsed/refractory populations in any treatment group of the studies except for Cohort 2 of Study BGB-3111-302 and *MYD88^{WT}* WM (which is largely driven by Cohort 2) both with an estimated median of 22 months.

Data on duration of VGPR or CR for the relapsed/refractory population is similar to the overall population.

Duration of Major Response

In Study BGB-3111-302 Cohort 1 Zanubrutinib, the arm with the largest size and a median follow-up of 22.1 months, most responders (72, 90.0%) continue to respond. The event rate is higher in Study BGB-3111-302 Cohort 2, and Studies BGB-3111-210 and BGB-3111-AU-003: 7/14 (50.0%) patients, 7/29 (24.1%) patients, and 13/60 (21.7%) patients, respectively.

Progression-Free Survival

Overall Waldenström's Macroglobulinemia Population

The event rate is the lowest in Study BGB-3111-302 Cohort 1 at 13.7%, with most patients censored without documented progressive disease or death (88/102, 86.3%). The event rates for the other studies range from 24.7% in Study BGB-3111-AU-003 to 42.3% in BGB-3111-302 Cohort 2.

With the exception of Study BGB-3111-302, Cohort 2, the median progression-free survival for the overall WM population by combined assessment has not been reached across treatment groups. As expected, *MYD88^{WT}* patients have a shorter PFS with 12-months and 24-months progression-free survival at 70.0% and 59.9%, respectively, as compared to 87.8% and 80.6% in *MYD88^{MUT}* patients. The MYD88 mutational status also explains the lower PFS observed in BGB-

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Reference ID: 4850271

3111-302 Cohort 2, in which 11 (42.3%) of 26 patients had events of progressive disease (n = 10) or death (n = 1). The estimated median PFS is 27.5 months in Cohort 2, with 12-months and 24-months event free survival at 69.2% and 61.5%.

Overall Survival

Overall Waldenström's Macroglobulinemia Population

With a median follow-up of 23.5 months to 26.4 months for zanubrutinib in studies BGB-3111-302 and BGB-3111-210, the death rate ranges from 8.8% to 11.6%. With a longer follow-up of 42.8 months, Study BGB-3111-AU-003 has a higher death rate at 15.1%. Median overall survival for the overall population has not been reached across treatment arms for all studies, $MYD88^{MUT}$, $MYD88^{WT}$, or the All WM population.

In Study BGB-3111-302, the survival rates at 12, 18, and 24 months for patients overall in the zanubrutinib treatment group were 97.0%, 97.0%, and 90.3%, respectively (Cohort 1) and 96.2%, 88.1% and 88.1%, respectively (Cohort 2). In Study BGB-3111-210, the survival rate at 12 months was 90.5%. In Study BGB-3111-AU-003, the survival rates at 12, 18, and 24 months were similar to both zanubrutinib cohorts in BGB-3111-302, with 97.3%, 95.9%, and 93.0%, respectively.

Survival rates in the $MYD88^{MUT}$ population at 12, 18, and 24 months were similar to slightly higher than survival rates in the $MYD88^{WT}$ Waldenström's macroglobulinemia population at 95.8%, 94.7%, 90.2% and 95.0%, 89.9%, and 89.9% respectively. In the All WM population survival rates at 12, 18, and 24 months were 95.8%, 94.1% and 90.4% respectively.

The Applicant's Position:

The comparison of efficacy results for zanubrutinib across studies, specifically looking at response assessment, time to response, duration of response, progression-free survival, and overall survival, are all indicative of a clear clinical benefit in the treatment of patients with WM and support use of zanubrutinib for the treatment of patients with WM.

While the number of zanubrutinib patients in Cohort 2 was significantly smaller than Cohort 1 (n=26 vs n=102), the VGPR or CR rate of Cohort 2 and 1 were similar (30.8% and 32.4%, respectively) and the MRR of Cohort 2 and 1 was 53.8% and 78.4%, respectively. Taken together these data suggest responsiveness of WM to zanubrutinib independent of MYD88 mutational status and that submission of an application for a humanitarian device (HUD) would not be necessary.

The FDA's Assessment:

The assessment of efficacy for this application was based primarily on the results from Study BGB-3111-302. FDA did not independently verify the data listed above by the Applicant regarding efficacy of zanubrutinib across all supportive studies. FDA agrees generally with the Applicant that zanubrutinib efficacy appears to be independent of the MYD88 mutation status. A companion diagnostic is not required for this application. However, the FDA notes that the

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Reference ID: 4850271

number of patients enrolled in Cohort 2 is relatively small. A PMC will be issued with this application to obtain additional efficacy and safety information in the $MYD88^{WT}$ WM population.

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Reference ID: 4850271

8.2. Review of Safety

The Applicant Position:
The safety review of zanubrutinib for this sNDA is primarily based on the results from the ASPEN study, with the supporting safety derived from 5 additional clinical studies across WM and other hematologic malignancy studies. The integrated safety analysis 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 WM.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the safety review for this sNDA. The FDA's safety review is primarily based on the results from Study BGB-3111-302 (ASPEN). An integrated safety analysis was done for particular adverse events of special interest. The FDA agrees with the Applicant's assessment that the safety profile for zanubrutinib in patients with WM is consistent with that observed other studies with zanubrutinib, and there were no new safety concerns identified with zanubrutinib in patients with WM.

Safety Review Approach

Data:

Safety from the following trials are included in the application, with a data cut of 31 March 2020

- Study BGB-3111-302, The study consists of 2 cohorts: Cohort 1 enrolled WM patients with *MYD88*^{MUT} disease and includes a randomized (1:1) comparison of treatment with zanubrutinib (n = 101) or ibrutinib (n = 98); Cohort 2 is an exploratory single-arm evaluation of zanubrutinib in WM patients with *MYD88*^{WT} disease (n = 28).
- Three single-arm studies evaluating the safety and efficacy of zanubrutinib in patients with WM: a Phase 2 study in Chinese patients with R/R WM (BGB-3111-210, n = 44); a Phase 1 dose comparison study in Chinese patients with B-cell malignancies (BGB-3111-1002, n = 44), that included 2 patients with WM; and a Phase 1/2 study in patients with various B-cell malignancies (BGB-3111-AU-003, n = 385 total for all indications) including 78 patients with R/R and treatment-naïve WM.
- Two single-arm, Phase 2 studies evaluating the efficacy and safety of zanubrutinib in Chinese patients with R/R mantle cell lymphoma (BGB-3111-206, n = 86) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (BGB-3111-205, n = 91) provide additional supportive safety data.

The safety data were reviewed according to the following 5 patient subsets. Patients who received more than 1 dose level (ie, as a result of dose escalation, dose reduction, or a protocol amendment) are grouped according to the dose originally assigned.

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Reference ID: 4850271

- **Study BGB-3111-302 Cohort 1**, comparing zanubrutinib (Arm A, n = 101) versus ibrutinib (Arm B, n = 98).
- The **All Zanubrutinib** group (n = 779), comprising data from all patients treated with zanubrutinib monotherapy from all 6 aforementioned studies.
- The **All WM group** (n = 253), comprising all patients with WM treated with zanubrutinib from Studies BGB-3111-302 (Arm A from Cohort 1 and Cohort 2, n = 129), BGB-3111-210 (WM patients, n = 44), BGB-3111-AU-003 (WM patients, n = 78), and BGB-3111-1002 (WM patients, n = 2). A total of 207 patients were enrolled from study sites outside of China while 46 were enrolled to studies conducted exclusively within China.
- The **All China group** (n = 265), comprising patients from Studies BGB-3111-210, BGB-3111-1002, BGB-3111-205, and BGB-3111-206 conducted exclusively in China.
- The **All Non-China group** (n = 514), comprising patients from Studies BGB-3111-302 (Arm A from Cohort 1 and Cohort 2) and BGB-3111-AU-003 conducted outside of China.

There were no prespecified hypotheses in the safety outcomes and all p-values are descriptive.

The FDA's Assessment:
The FDA's assessment of safety focused on the results from the randomized, phase 3 study, BGB-3111-302, which enrolled patients with both newly diagnosed and relapsed/refractory WM. The safety population from the randomized portion of this trial (Cohort 1, $MYD88^{MUT}$) included 101 subjects who received zanubrutinib and 98 patients who received ibrutinib (Total=199). Additionally, there were 28 subjects with $MYD88^{WT}$ who were enrolled in Cohort 2 and received zanubrutinib. The FDA conducted safety analyses for Cohort 1 and Cohort 2 independently. FDAs safety analysis was based on the March 31, 2020 data cutoff.

The FDA also conducted additional safety analyses from the ISS database, which included 779 subjects who received zanubrutinib monotherapy for the treatment of B-cell malignancies including, but not limited to, WM, mantle cell lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma. These analyses were used to inform and update the USPI accordingly.

Review of the Safety Database

Overall Exposure

Data:
The clinical safety data supporting the proposed indication of zanubrutinib in adult patients with WM is based on zanubrutinib treated patients from 6 clinical trials.

BeiGene Table 15 provides the total number of subjects and study details for all studies included in the safety analysis.

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Reference ID: 4850271

BeiGene Table 15 Key Design Features of Clinical Studies

Study Number	Studies Including Patients with Waldenström's Macroglobulinemia				Other B-cell Malignancies	
	BGB-3111-302	BGB-3111-210	BGB-3111-AU-003	BGB-3111-1002	BGB-3111-205	BGB-3111-206
Countries	AU, USA, EU (CZ, DE, ES, FR, UK, GR, IT, NL, PO, SW)	China	AU, NZ, SK, USA, IT, UK	China	China	China
Phase	3	2	1/2	1	2	2
Control Group	Ibrutinib, 420 mg QD (Cohort 1 only)	NA	NA	NA	NA	NA
Disease Type	WM	WM	CLL/SLL, MCL, FL, MZL, DLBCL, WM, HCL, MALT, Richter's Transf.	CLL/SLL, MCL, FL, MZL, WM	CLL/SLL	MCL
Zanubrutinib Dose	160 mg PO BID	160 mg PO BID	40-320 mg PO QD, 160 mg PO BID	160 mg PO BID and 320 mg PO QD	160 mg PO BID	160 mg PO BID
Number of Patients Treated (n)						
Ibrutinib WM	98	0	0	0	0	0
Zanubrutinib WM	129 (101 in Cohort 1, 28 in Cohort 2)	44	78	2	0	0
Zanubrutinib, All	129	44	385	44	91	86

Abbreviations: BID, twice a day; NA, not available; PO, orally; QD, once a day; R/R, relapsed or refractory; TN, treatment-naïve

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Reference ID: 4850271

Countries/Geography: AU, Australia; CZ, Czech Republic; DE, Germany; ES, Spain; EU, European Union; FR, France; GR, Greece; NL, Netherlands; NZ, New Zealand; PO, Poland; SK, South Korea; SW, Sweden; USA, United States of America; UK, United Kingdom
Disease type: CLL/SLL, chronic lymphocytic leukemia/ small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma (sub-diagnosis of NHL); FL, follicular lymphoma (sub-diagnosis of NHL); HCL, hairy cell leukemia; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma (sub-diagnosis of NHL); MZL, marginal zone lymphoma (sub-diagnosis of NHL); NHL, Non-Hodgkin's lymphoma; Richter's transf, Richter's transformation; WM, Waldenström's macroglobulinemia

Most patients included in this integrated safety analysis received zanubrutinib at a dose of 160 mg twice a day (n = 662). A total of 105 patients were assigned a dose of 320 mg once a day. The remaining 12 patients were assigned daily doses ranging from 40 to 160 mg once a day as part of the dose escalation component (Part 1) of Study BGB-3111-AU-003.

Extent of Exposure

In **Study BGB-3111-302 Cohort 1**, the median duration of exposure was 25.22 months and 25.30 months for patients in the ibrutinib and zanubrutinib treatment arms, respectively; 55 (56.1%) and 57 (56.4%) patients had a minimum exposure of 24 months. The total exposures (in patient-months) were 2215.49 and 2397.37, respectively, in the ibrutinib and zanubrutinib arms. Median relative dose intensities for patients in the ibrutinib and zanubrutinib arms were 97.22% (range: 51.6% to 100.0%) and 97.99% (range: 27.9% to 100.0%), respectively. Twenty-two (22.4%) ibrutinib-treated and 15 (14.9%) zanubrutinib-treated patients required 1 or more dose reductions (Table 2.7.4.1.2.1).
For the All Zanubrutinib safety pool, the treatment exposure in presented below:

BeiGene Table 16 Summary of Treatment Exposure (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98)	**Zanubrutinib (N = 101)**
Duration of exposure (months)		
n	98	101
Mean (SD)	22.61 (9.386)	23.74 (8.368)
Median	25.22	25.30
Min, Max	0.3, 37.9	0.8, 38.2
Total exposure (patient-months)[a]	2215.49	2397.37

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

Reference ID: 4850271

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98)	**Zanubrutinib (N = 101)**
Duration of exposure, n (%)		
<3 months	8 (8.2)	6 (5.9)
3 - <6 months	3 (3.1)	1 (1.0)
6 - <9 months	3 (3.1)	3 (3.0)
9 - <12 months	2 (2.0)	1 (1.0)
12 - <18 months	3 (3.1)	5 (5.0)
18 - <24 months	24 (24.5)	28 (27.7)
24 - <30 months	40 (40.8)	39 (38.6)
30 - <36 months	13 (13.3)	17 (16.8)
36 - <48 months	2 (2.0)	1 (1.0)
≥ 48 months	0 (0.0)	0 (0.0)

Source: Table 2.7.4.1.2.1
Abbreviations: max, maximum; min, minimum, N, number of patients who received at least one dose of ibrutinib or zanubrutinib; Q1, first quartile, Q3, third quartile; SD, standard deviation; WM, Waldenström's macroglobulinemia.
Note: Percentages are based on N, unless otherwise specified. Duration of exposure is defined as first dose date to last dose date for patients that discontinued treatment on or before the data cutoff date or until the data cutoff date for ongoing patients.
[a] Total exposure in patient-months is calculated by adding together the duration of exposure of all patients in each respective group.
[b] Relative dose intensity is the ratio of actual daily dose and the assigned daily dose.

The Applicant's Position:
The large number of patients treated for greater than 2 years overall allowed for an adequate assessment of the safety of long term zanubrutinib exposure.

The comprehensive analysis of adverse events reported herein did not reveal any new or unanticipated safety signals. The improved safety profile predicted from its pharmacokinetic and pharmacodynamic profiles as well as its superior selectivity is corroborated by results from Study BGB-3111-302 as well as all available safety data. Thus, zanubrutinib offers the potential for improved safety and tolerability over existing treatment options for adult patients with WM, and therefore, an improved benefit versus risk profile.

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

Reference ID: 4850271

The FDA's Assessment:
The FDA agrees with the Applicant's assessment regarding the overall exposure for patients enrolled in study BGB-3111-302. The median duration of treatment was 25.22 months and 25.30 months for patients in the ibrutinib and zanubrutinib treatment arms, respectively. The FDA agrees that patients received sufficient exposure to evaluate the safety of zanubrutinib.

The FDA does not agree with the Applicant's inclusion of their safety conclusions in this section or the promotional language the Applicant used, including the following statements:

- "The comprehensive analysis of adverse events reported herein did not reveal any new or unanticipated safety signals"
- "The improved safety profile predicted from its pharmacokinetic and pharmacodynamic profiles as well as its superior selectivity is corroborated by results from Study BGB-3111-302 as well as all available safety data. Thus, zanubrutinib offers the potential for improved safety and tolerability over existing treatment options for adult patients with WM, and therefore, an improved benefit risk profile". The safety assessments are all descriptive. The Applicant did not prespecify any meaningful differences between the arms for any adverse events.

See Sections 8.2 and 8.3 for discussion of the FDA's overall assessment of the safety findings, and Section 1.3 for discussion of the benefit/risk profile of zanubrutinib in patients with WM.

Relevant characteristics of the safety population:

Data:

Demographic and baseline characteristics were generally similar across the 5 analysis populations. In **Study BGB-3111-302, Cohort 1**, patients tended to be of relatively advanced age, as expected for a WM population. The median ages were comparable between treatment groups (70.5 years ibrutinib; 70.0 years zanubrutinib); however, a higher proportion of patients randomized to zanubrutinib than ibrutinib were ≥ 75 years old or < 65 years old. In both groups, most patients (> 90%) had an ECOG Performance Status score of 0 or 1.

BeiGene Table 17 Demographic and Baseline Characteristics (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98)	**Zanubrutinib (N = 101)**
Age (years)		
n	98	101
Mean (SD)	70.1 (8.49)	69.1 (10.30)
Median	70.5	70.0

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98)	**Zanubrutinib (N = 101)**
Min, Max	38, 90	45, 87
Age group, n (%)		
< 65 years	23 (23.5)	34 (33.7)
≥ 65 and < 75 years	51 (52.0)	31 (30.7)
≥ 75 years	24 (24.5)	36 (35.6)
Sex, n (%)		
Male	64 (65.3)	68 (67.3)
Female	34 (34.7)	33 (32.7)
Race, n (%)		
Asian	0 (0.0)	4 (4.0)
White	94 (95.9)	87 (86.1)
Black or African American	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Not Reported	4 (4.1)	9 (8.9)
Unknown	0 (0.0)	1 (1.0)
Missing	0 (0.0)	0 (0.0)
Region, n (%) [a]		
Asia	0 (0.0)	0 (0.0)
European Union	58 (59.2)	60 (59.4)
North America	10 (10.2)	9 (8.9)
Australia/New Zealand	30 (30.6)	32 (31.7)
ECOG performance status, n (%)		
0	42 (42.9)	46 (45.5)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98)	**Zanubrutinib (N = 101)**
1	49 (50.0)	50 (49.5)
2	7 (7.1)	5 (5.0)
Viral serology HBcAb positive, n (%)	4 (4.1)	7 (6.9)
Height (cm)		
n	95	99
Mean (SD)	169.73 (9.396)	170.84 (10.284)
Median	170.00	170.00
Min, Max	150.0, 196.0	145.0, 192.0
Weight (kg)		
n	98	101
Mean (SD)	74.43 (15.469)	74.42 (16.757)
Median	72.85	74.00
Min, Max	49.6, 125.7	40.4, 138.4

Source: Table 2.7.4.1.3.1
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; min, minimum; max, maximum; N, number of patients who received at least 1 dose of ibrutinib or zanubrutinib; SD, standard deviation; WM, Waldenström's macroglobulinemia
Note: Percentages are based on N, unless otherwise specified.
[a] Asia includes China and South Korea; European Union includes the Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden and United Kingdom; North America includes the United States.

The Applicant's Position:

There were no noteworthy differences in demographics between the studies aside from what is mentioned above.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the baseline demographic and disease characteristics of patients enrolled in Cohort 1 of Study BGB-3111-302. The FDA notes that in Cohort 1 ($MYD88^{MUT}$), 37 patients were treatment naïve (zanubrutinib: 19; ibrutinib: 18) and 164 were relapsed/refractory (zanubrutinib: 83; ibrutinib: 81). In Cohort 2 ($MYD88^{WT}$), of the 28 patients enrolled, five patients were treatment-naïve and 23 were relapsed refractory. In this

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Reference ID: 4850271

cohort nearly all patients (27/28) were White, and one was race Unknown. The baseline demographic information for patients enrolled in Cohort 2 is provided in FDA Table 13 below.

FDA Table 14: Study BGB-3111-302 (Cohort 2) Baseline Characteristics

	Treatment-Naïve N=5 n(%)	Relapsed/Refractory N=23 n(%)	Total N=28 n(%)
Age			
Mean (SD)	80.4 (6.3)	67.9 (13.8)	70.1 (13.6)
Median (Range)	81 (71-87)	71 (39-87)	72 (39-87)
≤65	0 (0.0)	9 (39.1)	9 (32.1)
>65	5 (100.0)	14 (60.9)	19 (67.9)
>75	4 (80.0)	8 (34.8)	12 (42.9)
Sex			
M	3 (60.0)	11 (47.8)	14 (50.0)
F	2 (40.0)	12 (52.2)	14 (50.)
Race			
White	4 (80.0)	23 (100.0)	27 (96.4)
Unknown	1 (20.0)	0 (0.0)	1 (3.6)

Source: FDA Clinical Reviewer's Analysis

Adequacy of the safety database:

Data:

The **All Zanubrutinib** group (n = 779), comprising data from all patients treated with zanubrutinib from all of 6 studies including 253 WM patients were included in the safety pool (ISS).

The Applicant's Position:
The safety data base as described above represents an acceptable safety data base. The large number of patients treated for greater than 2 years overall allowed for an adequate assessment of the safety of long term zanubrutinib exposure.

The FDA's Assessment:
The FDA's safety analysis focused on the data provided for Study BGB-3111-302. The FDA agrees that, in general, the safety database from Study BGB-3111-302 is adequate to assess the safety of zanubrutinib in patients with WM. However, the FDA notes that there were very few patients who were treatment naïve and received zanubrutinib (Cohort 1: 19; Cohort 2: 5), and few patients with $MYD88^{WT}$ WM (n=28) included in Study BGB-3111-302. Post-marketing commitments (PMCs) will be issued with this application to obtain additional safety and efficacy

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Reference ID: 4850271

data in patients with newly diagnosed WM as well as those with MYD88^{WT} WM (including patients who are both treatment-naïve and relapsed/refractory). An additional PMC will be issued with this application to obtain additional safety and efficacy data in racial and ethnic minorities (see Section 8.1 for additional information).

The FDA agrees with the Applicant's assessment that the overall safety database of patients with hematologic malignancies who have received zanubrutinib (N=779) represents an acceptable database for assessment of safety of zanubrutinib in these patient populations.

Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
N/AP

The Applicant's Position:
There are no issues regarding the data integrity and submission quality.

The FDA's Assessment:
The quality of the submitted safety data was adequate for substantive primary review.

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. Only those adverse events that were treatment-emergent are included in summary tables. For China studies, causality was assessed on a 5-point scale, with adverse events recorded as not related, unlikely related, possibly related, probably related, and related to study treatment, with the last 3 grouped together as treatment-related events (3:2 mapping). For non-China studies, causality was assessed on a 2-point scale, with adverse events recorded as either related or not related to study treatment (1:1 mapping). For analysis of data in this Summary of Clinical Safety, events were remapped, with treatment-related events including those events considered as related, possibly related or probably related to zanubrutinib, or with missing assessment of causal relationship by the investigator (3:2 mapping).

All adverse events were graded for severity using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Peripheral blood cytopenias are graded for severity according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) consensus criteria for patients with CLL/SLL (Hallek et al 2008). Adverse event verbatim

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Reference ID: 4850271

descriptions were coded to the most similar Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 lower level term. The linked preferred term and primary system organ class were also captured in the database.
Summaries of the following categories of safety data are presented:

- Adverse events of all grades
- Grade 3 or higher adverse events
- Serious adverse events
- Adverse events leading to reduction of study drug dose
- Adverse events leading to treatment discontinuation
- Adverse events leading to treatment interruption
- 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, electrocardiograms, and Eastern Cooperative Oncology Group (ECOG) performance status

Adverse events of special interest are those that are known to be associated with the class of BTK inhibitors.
There were no prespecified hypotheses in the safety outcomes and all p-values are descriptive.
Unless otherwise noted, patients enrolled to studies at clinical study sites in China are categorized as "Chinese," while those enrolled at study sites outside of China are categorized as "non-Chinese" regardless of race or ethnicity.

The Applicant's Position:
Adverse events were collected and analyzed as described above.

The FDA's Assessment:
The FDA agrees with the Applicant's description of categorization of adverse events. The categorization of adverse events is appropriate for this application. The FDA conducted additional safety analyses using grouped adverse event terms to better characterize the overall incidence of specific adverse events.

Routine Clinical Tests

Data:
Key assessments included routine clinical laboratory tests (hematology, chemistry), ECGs, vital sign assessments, and pregnancy tests.

The Applicant's Position:
Laboratory assessments were carried out as specified in the ASPEN protocol.

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Reference ID: 4850271

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. In general, the safety assessment methods and time points that were utilized in Study BGB-3111-302 are appropriate for the population, disease and indication being sought.

Safety Results

The Applicant's Position:

Overall, higher proportions of ibrutinib-treated patients had at least 1 adverse event; Grade 3 or higher adverse events; serious adverse events; adverse events leading to death, treatment discontinuation, dose reduction, and dose hold; and treatment-related adverse events compared with zanubrutinib-treated patients. This trend continued with additional follow-up including further separation with over 15% of ibrutinib treated patients discontinuing treatment due to adverse events versus 4% for zanubrutinib treated patients (BeiGene Table 18).

BeiGene Table 18 Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98) n (%)	**Zanubrutinib (N = 101) n (%)**
Patients with at least one TEAE	98 (100.0)	98 (97.0)
Grade 3 or higher	66 (67.3)	65 (64.4)
Serious	46 (46.9)	44 (43.6)
Leading to death	4 (4.1)	1 (1.0)
Leading to treatment discontinuation	15 (15.3)	4 (4.0)
Leading to dose reduction	25 (25.5)	15 (14.9)
Leading to dose interruption [a]	54 (55.1)	52 (51.5)
Treatment-related	86 (87.8)	83 (82.2)
Patients with at least one AESI	83 (84.7)	89 (88.1)
Grade 3 or higher AESI	51 (52.0)	53 (52.5)
Serious AESI	32 (32.7)	29 (28.7)

Source: Table 2.7.4.2.1.1, Table 2.7.4.1.2.1

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Reference ID: 4850271

Abbreviations: AESI, adverse event of special interest; eCRF, electronic case report form; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinemia.
Notes: Percentages are based on N, unless otherwise specified.
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. Adverse event grades are evaluated based on National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03).
[a] Any interruption due to an adverse event with duration > 1 day derived from drug administration eCRF in BGB-3111-AU-003; from drug administration eCRF in BGB-3111-205, BGB-3111-206, BGB-3111-210 and BGB-3111-302 (interruption due to an adverse event); and from adverse event eCRF in BGB-3111-1002 (action taken = drug held).
Data cutoff: 31MAR2020

The FDA's Assessment:

FDA does not agree with the Applicant's statement, "overall, higher proportions of ibrutinib-treated patients had at least 1 adverse event; Grade 3 or higher adverse events; serious adverse events; and adverse events leading to death…compared with zanubrutinib-treated patients." This statement is broad and misleading. Overall, the number of subjects in each treatment arm who experienced at least 1 adverse event (zanubrutinib: n=98; ibrutinib: n=98) Grade 3 or higher adverse events (zanubrutinib: n=65; ibrutinib: n=66), serious adverse events (zanubrutinib: n=44; ibrutinib: n=46) and Grade 5 adverse events (zanubrutinib: n=1; ibrutinib: n=2) were nearly identical in the two treatment arms. The FDA does not agree with the Applicant's assessment of adverse events leading to death (see Section below for additional discussion of the deaths on Study BGB-3111-302). The FDA also notes that the overall number of deaths was numerically higher in the zanubrutinib arm (zanubrutinib: n=9; ibrutinib: n=8), though the numbers were small. While numerically higher, there may have been slight differences between the two arms. Overall, the numbers were similar, and the differences were not sufficient to make generalized conclusions.
A summary of the FDA's major safety findings for Cohort 1 ($MYD88^{MUT}$) and Cohort 2 ($MYD88^{WT}$) is provided in the tables below.

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Reference ID: 4850271

FDA Table 15: Study BGB-3111-302 (Cohort 1) - Summary of Safety Results

	Treatment Naive		Relapsed/ Refractory		Overall	
	Ibrutinib (N=18) n(%)	Zanubrutinib (N=19) n(%)	Ibrutinib (N=80) n(%)	Zanubrutinib (N=82) n(%)	Ibrutinib (N=98) n(%)	Zanubrutinib (N=101) n(%)
Total Deaths	0 (0.0)	3 (15.8)	8 (10.0)	6 (7.3)	8 (8.1)	9 (8.9)
Subjects with ≥1 TEAE	18 (100.0)	19 (100.0)	80 (100.0)	79 (96.3)	98 (100.0)	98 (97.0)
Subjects with ≥1 Grade 3 or higher TEAE	12 (66.7)	15 (78.9)	54 (67.5)	50 (61.0)	66 (67.3)	65 (64.4)
SAE (Any)	9 (50.0)	11 (57.9)	37 (46.3)	33 (40.2)	46 (46.9)	44 (43.6)
TEAE leading to treatment discontinuation	4 (22.2)	0 (0.0)	11 (13.8)	4 (4.9)	15 (15.3)	4 (4.0)

Source: FDA Clinical Reviewer's Analysis

FDA Table 16: Study BGB-3111-301 (Cohort 2) - Summary of Safety Results

	Zanubrutinib N=28 n(%)
Deaths	4 (14.3)
Subjects with ≥1 TEAE	24 (85.7)
Subjects with ≥1 Grade 3 or higher TEAE	18 (64.3)
SAE (Any)	11 (39.3)
TEAE leading to treatment discontinuation	2 (7.1)

Source: FDA Clinical Reviewer's Analysis

Deaths

Data:

In **Study BGB-3111-302 Cohort 1**, 8 (8.2%) patients in the ibrutinib arm and 9 (8.9%) patients in the zanubrutinib arm died while on study. The most common cause of death was progressive disease (4 patients in each arm). Five patients in the ibrutinib arm and 1 patient in the zanubrutinib arm died within 30 days of last study treatment.

BeiGene Table 19 Summary of all deaths (safety analysis set)

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Total number of deaths	8 (8.2)	9 (8.9)

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

Reference ID: 4850271

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98) n (%)	**Zanubrutinib (N = 101) n (%)**
Cause of death		
Progressive disease	4 (4.1)	4 (4.0)
Adverse event	2 (2.0)	1 (1.0)
Unknown	2 (2.0)	1 (1.0)
Other	0 (0.0)	3 (3.0)
Deaths within 30 days of last dose date	5 (5.1)	1 (1.0)
Cause of death		
Adverse event	2 (2.0)	1 (1.0)
Progressive disease	1 (1.0)	0 (0.0)
Unknown	2 (2.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Deaths > 30 days of last dose date	3 (3.1)	8 (7.9)
Cause of death		
Progressive disease	3 (3.1)	4 (4.0)
Adverse event	0 (0.0)	1 (1.0)
Unknown	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (3.0)

Source: Table 2.7.4.2.16
Abbreviations: N, number of patients who received at least one dose of ibrutinib or zanubrutinib; WM, Waldenström macroglobulinaemia.
Notes: Patients with multiple events for a given preferred term are counted only once for that preferred term. Events are sorted by decreasing frequency of preferred terms and then alphabetically in the All Zanubrutinib group.
Percentages are based on N, unless otherwise specified.
Data in this table are based on End-of-Study/End-of-Treatment CRFs.

The following Grade 5 (fatal) events were reported for each group:

- **In Study BGB-3111-302 Cohort 1:** Fatal AEs were reported for 4 ibrutinib-treated patients and 1 zanubrutinib-treated patient. Adverse events leading to death among ibrutinib-

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Reference ID: 4850271

treated patients were sepsis, bacterial sepsis, death (cause unspecified), and acute cardiac failure. There was a single Grade 5 event (treatment-related) of cardiomegaly in the zanubrutinib arm, that occurred in an 84-year-old male with R/R WM (b) (6) who died after plasmapheresis in the setting of progressive disease, approximately 3 months after initiating zanubrutinib.

The Applicant's Position:
Zanubrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other zanubrutinib clinical trials.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the deaths that occurred in Cohort 1 of Study BGB-3111-302. Overall, a similar number of subjects died in both treatment arms (zanubrutinib: n=9, ibrutinib: n=8). Of these, there were four subjects who died due to disease progression in both treatment arms. There were slightly more subjects who died due to Grade 5 adverse events in the ibrutinib arm (zanubrutinib: n=1; ibrutinib: n=4), and who died within 30 days of the last dose (zanubrutinib: n=1; ibrutinib: n=5). However, the numbers were small and conclusions regarding the relative risk of death between the two treatments should be made with caution.

The FDA does not agree with the Applicant's inclusion of the following statement in this section: "Zanubrutinib was well-tolerated and showed an acceptable safety profile". This statement is broad and promotional. See Section 1.3 for the FDA's discussion of the overall benefit/risk of zanubrutinib in patients with WM.

FDA's summary of the deaths that occurred in Cohort 2 ($MYD88^{WT}$) is provided in FDA Table 16 below. A summary of the Grade 5 Adverse events that occurred in Study BGB-3111-302 is provided in FDA Table 17 below.

FDA Table 17: Study BGB-3111-302 (Cohort 2) - Summary of Deaths

	Cohort 2 (N=28) n(%)
Total Deaths	4 (14.3)
Death Within 30 Days	2 (7.1)
Cause of Death	
Disease Progression	2 (7.1)
Adverse Event	1 (3.6)
Other	1 (3.6)

Source: FDA Clinical Reviewer's Analysis

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

Reference ID: 4850271

FDA Table 18: Study BGB-3111-302 - Summary of Grade 5 Adverse Events

Patient ID	Treatment	Age/Sex	Disease Status (TN/RR)	Grade 5 AE Study Day	Fatal AE Term
Cohort 1					
(b) (6)	Zanubrutinib	(b) (6)	RR	88	Cardiomegaly
	Ibrutinib		RR	372	Death
	Ibrutinib		RR	118	Bacterial sepsis
	Ibrutinib		RR	10	Cardiac failure acute
	Ibrutinib		RR	168	Sepsis
Cohort 2					
(b) (6)	Zanubrutinib	(b) (6)	RR	666	Lymphoma transformation

Source: FDA Clinical Reviewer's Analysis

Serious Adverse Events

Data:

In **Study BGB-3111-302 Cohort 1**, serious adverse events reported in > 1 patient (> 1%) were as follows:

- Ibrutinib: pneumonia (11.2%); atrial fibrillation (5.1%); sepsis (4.1%); pyrexia, syncope, and pericarditis (3.1% each); and urinary tract infection, upper respiratory tract infection, pleural effusion, loss of consciousness, acute myocardial infarction, and cholecystitis (2.0% each)
- Zanubrutinib: influenza, febrile neutropenia, neutropenia, and pyrexia (3.0% each); and lower respiratory tract infection, sepsis, pleural effusion, anaemia, thrombocytopenia, and basal cell carcinoma (2.0% each)

Serious adverse events reported at a ≥ 2% higher frequency among ibrutinib than zanubrutinib patients were pneumonia, upper respiratory tract infection, sepsis, acute myocardial infarction, cholecystitis, syncope, loss of consciousness, pericarditis, urinary tract infection, and atrial fibrillation. Conversely, serious adverse events reported at a ≥ 2% higher frequency among zanubrutinib-treated patients were influenza, febrile neutropenia, neutropenia, lower respiratory tract infection, thrombocytopenia, and basal cell carcinoma.

Twenty-four (24.5%) patients on the ibrutinib arm reported serious infections compared with 16 (15.8%) on the zanubrutinib arm. Eleven patients (11.2%) on the ibrutinib arm reported a serious adverse event of pneumonia compared with 1 (1.0%) on the zanubrutinib arm. Eight (7.9%) patients on the zanubrutinib arm reported a serious blood and lymphatic system disorder compared with 4 (4.1%) on the ibrutinib arm, with neutropenia or febrile neutropenia each reported in 3 (3.0%) zanubrutinib-treated patients compared to none in ibrutinib-treated patients.

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BeiGene Table 20 Serious Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2% of Patients in Any Patient Group (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Patients with at least one serious TEAE	46 (46.9)	44 (43.6)
Infections and infestations	24 (24.5)	16 (15.8)
Pneumonia	**11 (11.2)**	**1 (1.0)**
Cellulitis	1 (1.0)	0 (0.0)
Urinary tract infection	**2 (2.0)**	**0 (0.0)**
Upper respiratory tract infection	**2 (2.0)**	**0 (0.0)**
Lower respiratory tract infection	**0 (0.0)**	**2 (2.0)**
Sepsis	**4 (4.1)**	**2 (2.0)**
Influenza	**1 (1.0)**	**3 (3.0)**
Blood and lymphatic system disorders	4 (4.1)	8 (7.9)
Anaemia	1 (1.0)	2 (2.0)
Febrile neutropenia	**0 (0.0)**	**3 (3.0)**
Neutropenia	**0 (0.0)**	**3 (3.0)**
Thrombocytopenia	**0 (0.0)**	**2 (2.0)**
Respiratory, thoracic and mediastinal disorders	4 (4.1)	5 (5.0)
Pleural effusion	2 (2.0)	2 (2.0)
General disorders and administration site conditions	4 (4.1)	5 (5.0)
Pyrexia	3 (3.1)	3 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	4 (4.0)
Basal cell carcinoma	**0 (0.0)**	**2 (2.0)**
Nervous system disorders	5 (5.1)	2 (2.0)
Syncope	**3 (3.1)**	**1 (1.0)**

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Loss of consciousness	**2 (2.0)**	**0 (0.0)**
Cardiac disorders	13 (13.3)	7 (6.9)
Atrial fibrillation	**5 (5.1)**	**0 (0.0)**
Acute myocardial infarction	**2 (2.0)**	**0 (0.0)**
Pericarditis	**3 (3.1)**	**0 (0.0)**
Hepatobiliary disorders	3 (3.1)	0 (0.0)
Cholecystitis	**2 (2.0)**	**0 (0.0)**

Source: Table 2.7.4.2.2.3
Abbreviations: N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event;
Notes: 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 for the All Zanubrutinib group. Percentages are based on N, unless otherwise specified.
Differences in adverse events of 2% or more between ibrutinib and zanubrutinib arms in Study BGB-3111-302 Cohort 1 are **bolded**.
Data cutoff: 31MAR2020

The Applicant's Position:

Serious adverse events were rare overall occurring in less than half the patients. As expected for patients with hematologic malignancies, infections were the most commonly seen serious events. The incidences of serious adverse events remained comparable between the ibrutinib and zanubrutinib arms. The incidence of serious adverse events remained slightly higher overall for the ibrutinib arm versus zanubrutinib arms.

The FDA's Assessment:
The FDA agrees with the Applicant's presentation of the serious adverse events that occurred in study BGB-3111-302. Overall, the percentage of patients who experienced an SAE was slightly higher in the ibrutinib arm (zanubrutinib: 43.6%; ibrutinib: 46.9%). The FDA conducted additional analyses of serious adverse events by grouped terms, which is presented along with the FDA's analysis of serious adverse events in FDA Table 18.

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In Cohort 1, serious adverse events that occurred with at least 2% greater incidence in the zanubrutinib arm included influenza (zanubrutinib: 3.0%; ibrutinib: 1.0%), neutropenia (zanubrutinib: 4.0%; ibrutinib: 0.0%), febrile neutropenia (zanubrutinib: 4.0%; ibrutinib: 0.0%), and thrombocytopenia (zanubrutinib: 2.0%; ibrutinib: 0.0%). Serious adverse events that occurred with at least 2% greater incidence in the ibrutinib arm include pneumonia (zanubrutinib: 4.0%; ibrutinib: 12.2%), atrial fibrillation (zanubrutinib: 0.0%; ibrutinib: 5.0%), sepsis (zanubrutinib: 3.0%; ibrutinib: 7.1%), syncope (zanubrutinib: 1.0%; ibrutinib: 3.1%), pericarditis (zanubrutinib: 0.0%; ibrutinib: 3.1%), upper respiratory tract infection (zanubrutinib: 0.0%; ibrutinib: 2.0%), acute myocardial infarction (zanubrutinib: 0.0%; ibrutinib: 2.0%), and loss of consciousness (zanubrutinib: 0.0%; ibrutinib: 2.0%).

FDA Table 19: Study BGB-3111-302 - Serious Adverse Events (SAEs)

	Cohort 1		Cohort 2
	Ibrutinib N=98 n(%)	**Zanubrutinib N=101 n(%)**	**Zanubrutinib N=28 n(%)**
Subject with ≥1 SAE	**46 (46.9)**	**44 (43.6)**	**11 (39.3)**
Infections and Infestations	**24 (24.5)**	**16 (15.8)**	**7 (25.0)**
Pneumonia[1]	12 (12.2)	4 (4.0)	5 (17.9)
Sepsis[2]	7 (7.1)	3 (3.0)	1 (3.6)
Cellulitis	1 (1.0)	0 (0.0)	2 (7.1)
Upper Respiratory Tract Infection	2 (2.0)	0 (0.0)	0 (0.0)
Urinary Tract Infection[3]	2 (2.0)	1 (1.0)	0 (0.0)
Influenza	1 (1.0)	3 (3.0)	0 (0.0)
Cardiac Disorders	**13 (13.3)**	**7 (7.0)**	**0 (0.0)**
Atrial Fibrillation	5 (5.1)	0 (0.0)	0 (0.0)
Pericarditis	3 (3.1)	0 (0.0)	0 (0.0)
Acute myocardial infarction	2 (2.0)	0 (0.0)	0 (0.0)
Blood and Lymphatic System Disorders	4 (4.1)	8 (8.0)	1 (3.6)
Anemia	2 (2.0)	2 (2.0)	0 (0.0)
Neutropenia	0 (0.0)	4 (4.0)	0 (0.0)
Febrile Neutropenia	0 (0.0)	4 (4.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	2 (2.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	**4 (4.1)**	**5 (5.0)**	**4 (14.3)**
Pleural Effusion	2 (2.0)	2 (2.0)	0 (0.0)
General Disorders and Administration Site Conditions	**4 (4.1)**	**5 (5.0)**	**2 (7.1)**
Pyrexia	3 (3.1)	3 (3.0)	1 (3.6)
Nervous System Disorders	**5 (5.1)**	**2 (2.0)**	**0 (0.0)**
Syncope	3 (3.1)	1 (1.0)	0 (0.0)
Loss of Consciousness	2 (2.0)	0 (0.0)	0 (0.0)
Neoplasms Benign, Malignant and Unspecified	1 (1.0)	4 (4.0)	1 (3.6)
Basal Cell Carcinoma	0 (0.0)	2 (2.0)	0 (0.0)

[1]Includes preferred terms: all terms containing "pneumonia", lower respiratory infection, lung infection

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Reference ID: 4850271

[2]Includes preferred terms: Escherichia sepsis, streptococcal sepsis, bacterial sepsis, neutropenic sepsis, post procedural sepsis, sepsis, septic shock, urosepsis
[3]Includes preferred terms: urinary tract infection, urinary tract infection bacterial
Source: FDA Clinical Reviewer's Analysis

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

BeiGene Table 21 Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
Adverse Event Category, n (%)	**Ibrutinib (N = 98)**	**Zanubrutinib (N = 101)**
Patients with at least one TEAE	98 (100.0)	98 (97.0)
Grade 3 or Higher	66 (67.3)	65 (64.4)
Serious	46 (46.9)	44 (43.6)
Leading to Death	4 (4.1)	1 (1.0)
Leading to Treatment Discontinuation	**15 (15.3)**	**4 (4.0)**
Leading to Dose Reduction	**25 (25.5)**	**15 (14.9)**
Leading to Dose Interruption a	**54 (55.1)**	**52 (51.5)**
Treatment-Related	86 (87.8)	83 (82.2)
Patients with at least one AESI	83 (84.7)	89 (88.1)
Grade 3 or Higher AESI	51 (52.0)	53 (52.5)
Serious AESI	32 (32.7)	29 (28.7)

Source: Table 10 in Module 2.7.4
Abbreviations: AESI, adverse event of special interest; eCRF, electronic case report form; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinemia.
Notes: Percentages are based on N, unless otherwise specified.
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. Adverse event grades are evaluated based on National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03).

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Reference ID: 4850271

a Any interruption due to an adverse event with duration > 1 day derived from the drug administration eCRF for BGB-3111-302 (interruption due to an adverse event)

In **Study BGB-3111-302 Cohort 1**, 15 (15.3%) ibrutinib-treated patients and 4 (4.0%) zanubrutinib-treated patients discontinued study treatment due to an adverse event. Events leading to treatment discontinuation were as follows:

- Ibrutinib: atrial fibrillation (2 patients); pneumonia, bacterial sepsis, sepsis, chronic myeloid leukaemia, acute myocardial infarction, pericardial haemorrhage, interstitial lung disease, pneumonitis, pulmonary fibrosis, death (cause unspecified), haemolytic anaemia, drug-induced liver injury, and hepatitis (1 patient each)
- Zanubrutinib: plasma cell myeloma, cardiomegaly, subdural haemorrhage, and neutropenia (1 patient each)

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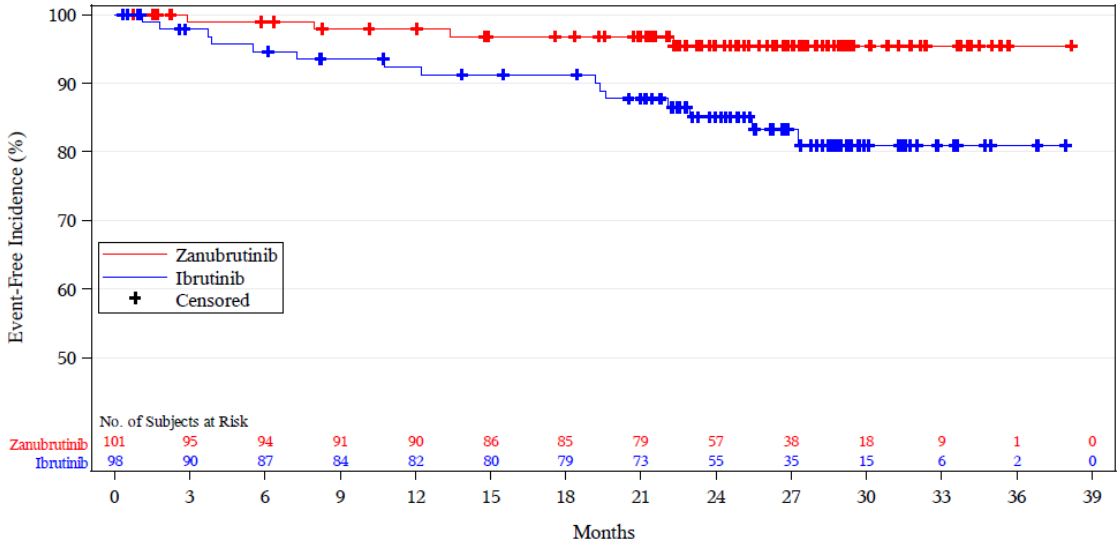
BeiGene Figure 10 Time to Treatment Discontinuation due to Adverse Event



BeiGene Table 22 Patient Disposition and Reasons for Treatment/Study Discontinuation (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98) n (%)	**Zanubrutinib (N = 101) n (%)**
Number of patients treated	98	101
Patients discontinued from treatment	29 (29.6)	22 (21.8)
Reason for discontinuation		
Progressive disease	6 (6.1)	9 (8.9)
Adverse event	15 (15.3)	4 (4.0)
Withdrawal by subject	0 (0.0)	5 (5.0)
Investigator's discretion	5 (5.1)	2 (2.0)
Protocol deviation	0 (0.0)	0 (0.0)
Other	3 (3.1)	2 (2.0)
Patients remained on treatment	69 (70.4)	79 (78.2)
Patients discontinued from study	14 (14.3)	15 (14.9)
Reason for discontinuation		
Death	8 (8.2)	9 (8.9)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
	Ibrutinib (N = 98) n (%)	**Zanubrutinib (N = 101) n (%)**
Withdrawal by subject	6 (6.1)	6 (5.9)
Lost to follow-up	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Patients remained in study	84 (85.7)	86 (85.1)
Study follow-up time (months)[a]		
n	98	101
Mean (SD)	25.30 (7.270)	25.36 (6.781)
Median	26.35	25.79
Min, Max	0.5, 38.1	1.6, 38.2

Source: Table 2.7.4.1.2.2
Abbreviations: max, maximum; min, minimum; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; SD, standard deviation; WM, Waldenström's macroglobulinemia.
Note: Percentages are based on N, unless otherwise specified.
[a] In Study BGB-3111-AU-003, three patients were transitioned to the long-term extension study (LTE1 study).
[b] Study follow-up time is defined as the time from the first dose date (randomization date for Study BGB-3111-302) to the end of study or death date (whichever is earlier) for patients discontinued from the study, or the database cutoff date for ongoing patients.

The Applicant's Position:
In the ASPEN trial, fewer patients on the zanubrutinib treatment arm discontinued due to an AE than on the ibrutinib arm on ASPEN. Comparisons of the incidence and type of adverse events in **Study BGB-3111-302, Cohort 1**, including Grade 3 or higher, serious, treatment-related events, and adverse events leading to treatment discontinuation, suggest that the adverse event profile for zanubrutinib among patients with WM is safer than that for ibrutinib.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the overall incidence of treatment discontinuation due to adverse events in Cohort 1 of Study BGB-3111-302. Overall, more subjects in the ibrutinib arm discontinued treatment due to an adverse event (zanubrutinib:

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Reference ID: 4850271

4.0%; ibrutinib: 15.3%). The FDA agrees with the Applicant's description of the TEAEs that led to treatment discontinuation.

The FDA does not agree with the Applicant's statement, "Comparisons of the incidence and type of adverse events in Study BGB-3111-302, Cohort 1, including Grade 3 or higher, serious, treatment-related events, and adverse events leading to treatment discontinuation, suggest that the adverse event profile for zanubrutinib among patients with WM is safer than that for ibrutinib". This statement is overly generalized, misleading and promotional. See corresponding sections in this review for discussion of TEAEs, Grade 3 or higher TEAEs, and serious adverse events. Section 1.3 for additional discussion of the benefit/risk profile.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In **Study BGB-3111-302 Cohort 1**, 25 (25.5%) ibrutinib-treated patients and 15 (14.9%) zanubrutinib-treated patients required at least 1 dose reduction due to an AE. Those leading to dose reduction in > 1 patient in the ibrutinib treatment arm were diarrhoea, neutropenia, contusion, and atrial fibrillation (2 patients each); and in the zanubrutinib treatment arm, were neutropenia (3 patients) and diarrhoea (2 patients) (Source: Table 2.7.4.2.2.6).

BeiGene Table 23 Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term (Cohort 1) (Safety Analysis Set) (Data Cutoff 31 March 2020)

System Organ Class/ Preferred Term [a]	Overall	
	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with at least 1 AE leading to treatment discontinuation	15 (15.3)	4 (4.0)
Blood and lymphatic system disorders		
Neutropenia	0 (0.0)	1 (1.0)
Haemolytic anaemia	1 (1.0)	0 (0.0)
Cardiac disorders		
Cardiomegaly	0 (0.0)	1 (1.0)
Acute myocardial infarction	1 (1.0)	0 (0.0)
Atrial fibrillation	2 (2.0)	0 (0.0)
Pericardial haemorrhage	1 (1.0)	0 (0.0)
Injury, poisoning and procedural complications		

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System Organ Class/ Preferred Term [a]	Overall	
	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Subdural haemorrhage	0 (0.0)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Plasma cell myeloma	0 (0.0)	1 (1.0)
Chronic myeloid leukaemia	1 (1.0)	0 (0.0)
General disorders and administration site conditions		
Death	1 (1.0)	0 (0.0)
Hepatobiliary disorders		
Drug-induced liver injury	1 (1.0)	0 (0.0)
Hepatitis	1 (1.0)	0 (0.0)
Infections and infestations		
Bacterial sepsis	1 (1.0)	0 (0.0)
Pneumonia	1 (1.0)	0 (0.0)
Sepsis	1 (1.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease	1 (1.0)	0 (0.0)
Pneumonitis	1 (1.0)	0 (0.0)
Pulmonary fibrosis	1 (1.0)	0 (0.0)

Source: Table 14.3.1.2.2.9a
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MYD88, myeloid differentiation factor 88.
Cohort 1 includes patients with activating mutations in MYD88.
Patients with multiple events for a given preferred term and system organ class are counted only once for each preferred term and system organ class, respectively.
MedDRA Version 23.0.
[a] Within each system organ class, preferred terms are sorted by most common incidence in Overall Zanubrutinib column.
Data cutoff 31 March 2020

The Applicant's Position:
Fewer zanubrutinib recipients in Study BGB-3111-302, Cohort 1 required dose reductions for adverse events compared with ibrutinib.

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The FDA's Assessment:
The FDA agrees with the Applicant's assessment that in Study BGB-3111-302, Cohort 1, more subjects in the ibrutinib arm (n=25; 25.5%) required at least one dose reduction due to an adverse event compared to the zanubrutinib arm (n=15; 14.9%). In Cohort 2, 2 subjects (7.1%) required a dose reduction due to an adverse event.

Significant Adverse Events

Data:

Adverse events of special interest are those that are known to be associated with the class of BTK inhibitors. The search criteria that define events within each category of adverse events of special interest are detailed in the table below:

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BeiGene Table 24 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

Abbreviations: CMQ, Company MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, Standardized MedDRA Query; SOC, system organ class.

In **Study BGB-3111-302 Cohort 1**, approximately equal numbers of patients in each treatment arm reported at least 1 adverse event of special interest (84.7% in ibrutinib-treated patients and 88.1% in zanubrutinib-treated patients), events reported more frequently among ibrutinib-treated patients compared with zanubrutinib-treated patients were in the categories of haemorrhage (60.2% versus 52.5%), hypertension (20.4% versus 13.9%), and atrial fibrillation/flutter (18.4% versus 4.0%). Conversely, neutropenia was reported more frequently

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Reference ID: 4850271

in zanubrutinib-treated patients compared with ibrutinib-treated patients (31.7% versus 16.3%, respectively). Overall rates of adverse events of special interest that met the criteria for seriousness and/or were ≥ Grade 3 in severity were comparable between treatment arms.

BeiGene Table 25 Overview of Treatment-Emergent Adverse Events of Special Interest by Category (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
AESI Category	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Patients with at least one AESI	83 (84.7)	89 (88.1)
Patients with at least one serious AESI	32 (32.7)	29 (28.7)
Patients with at least one Grade 3 or higher AESI	51 (52.0)	53 (52.5)
Anemia	13 (13.3)	12 (11.9)
Serious	1 (1.0)	2 (2.0)
Grade 3 or higher	5 (5.1)	6 (5.9)
Atrial fibrillation and flutter	18 (18.4)	4 (4.0)
Serious	6 (6.1)	0 (0.0)
Grade 3 or higher	7 (7.1)	0 (0.0)
Hemorrhage (inclusive of major haemorrhage)	59 (60.2)	53 (52.5)
Major hemorrhage[a]	10 (10.2)	6 (5.9)
Serious	7 (7.1)	5 (5.0)
Grade 3 or higher	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	14 (13.9)
Serious	0 (0.0)	0 (0.0)
Grade 3 or higher	15 (15.3)	9 (8.9)
Infections	71 (72.4)	73 (72.3)
Serious	24 (24.5)	16 (15.8)
Grade 3 or higher	24 (24.5)	19 (18.8)
Opportunistic infections	3 (3.1)	2 (2.0)
Serious	0 (0.0)	2 (2.0)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
AESI Category	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Grade 3 or higher	0 (0.0)	2 (2.0)
Neutropenia	16 (16.3)	32 (31.7)
Serious	0 (0.0)	6 (5.9)
Grade 3 or higher	9 (9.2)	23 (22.8)

Source: Table 2.7.4.2.6.1.1, Table 2.7.4.2.6.2.1, Table 2.7.4.2.6.3.1
Abbreviations: AESI, adverse event of special interest; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; WM, Waldenström's macroglobulinemia.
a Major haemorrhage is defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade. The search criteria are defined in Table 2.
Notes: Percentages are based on N, unless otherwise specified.
Adverse events are graded for severity based on National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03).

The Applicant's Position:

Comparisons of the incidence and type of adverse events suggest that the adverse event profile for zanubrutinib among patients with WM is safer than that for ibrutinib. Further, zanubrutinib had lower risk of specific events known to be associated with ibrutinib therapy, specifically atrial fibrillation, hypertension, major bleeding and diarrhoea. Despite the higher frequency of neutropenia reported with zanubrutinib treatment, rates of infection were similar between the treatment arms and the incidence of grade 3 or higher and serious infections was higher on the ibrutinib arm compared with the zanubrutinib arm.

The FDA's Assessment:
The FDA disagrees with the Applicant's conclusions that comparisons of adverse events suggests that the adverse event profile for zanubrutinib among patients with WM is safer than that for ibrutinib. Cytopenias were numerically higher in the zanubrutinib arm. Additionally, certain adverse events were reported in only a small number of patients in both arms, precluding any conclusions regarding comparative safety benefit.

However, FDA agrees with the Applicant's selection of adverse events of special interest associated with the use of zanubrutinib and BTK inhibitors. The FDA conducted safety analyses for specified adverse events of special interest including hemorrhage, atrial fibrillation and flutter, infections and second primary malignancies. The occurrence of these events in Study BGB-3111-302 was compared to the overall safety database of zanubrutinib in B-cell malignancies (N=779). The FDA notes the Applicant's approach of using SMQ narrow search

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Reference ID: 4850271

criteria for assessment of the incidence of adverse events of special interest. The FDA's analysis differs from the Applicant's and was based on System Organ Class (SOC) and preferred adverse event terms.

Hemorrhage and Bruising

FDA's analysis of the hemorrhage events differs from the Applicant's. The FDA's analysis is based on grouped preferred terms. The FDA also separated hemorrhage and bruising events. The incidence of hemorrhage was similar in the two treatment arms in Cohort 1 (zanubrutinib: n=41; 40.6%; ibrutinib: n=41; 42.9%). The incidence of Grade 3-4 hemorrhage was slightly higher in the ibrutinib arm (zanubrutinib: n=4; 4.0%; ibrutinib: n=9; 9.2%). In Cohort 2, 11 patients (39.3%) experienced a hemorrhage event. Of these, 3 (10.7%) were Grade 3-4. In general, hemorrhage events occurred slightly more frequently in Study BGB-3111-302 than in the overall zanubrutinib B-cell malignancy population. Overall, more subjects in the ibrutinib arm experienced bruising events (zanubrutinib: n=20; 19.8%; ibrutinib: n=33; 33.7%). In Cohort 2, 35.7% of subjects experienced a bruising event. There were no Grade 3-4 bruising events in Study BGB-3111-302.

A summary of the FDA's analysis of hemorrhage events and bruising events that occurred in Study BGB-3111-302 as well as in the pooled zanubrutinib patient population, as well as the list of preferred terms included in this analysis, is provided in FDA Table 19 below.

FDA Table 20: FDA's Analysis of Hemorrhage Events in Study BGB-3111-302 and Pooled Population

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)		Cohort 2 N=28 N(%)		ISS Dataset Zanubrutinib N=779 n(%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Hemorrhage[1]	42 (42.9)	9 (9.2)	41 (40.6)	4 (4.0)	11 (39.3)	3 (10.7)	271 (34.8)	25 (3.2)
Bruising[2]	33 (33.7)	0	20 (19.8)	0	10 (35.7)	0	198 (25.4)	1 (0.1)

[1]Includes Preferred Terms: Epistaxis, hematuria, hemoptysis, hematoma, hemothorax, , hematochezia, melena, all PTs that included "hemorrhage" "hematoma" "hemorrhagic".
[2]Includes Preferred Terms: Contusion, ecchymosis, eye contusion, increased tendency to bruise, infusion site bruising, oral contusion
Source: FDA Clinical Reviewer's Analysis

Atrial Fibrillation and Atrial Flutter

The FDA's analysis of atrial fibrillation and atrial flutter was based on the relevant preferred terms, and was consistent the Applicant's analysis. Overall, more subjects in the ibrutinib arm experienced atrial fibrillation and atrial flutter (zanubrutinib: n=4; 4.0%; ibrutinib: n=19; 19.4%). The incidence of atrial fibrillation in Study BGB-3111-302 was similar to the incidence in the overall zanubrutinib pooled safety population. A summary of the FDA's analysis of atrial

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Reference ID: 4850271

fibrillation and atrial flutter that occurred in Study BGB-3111-302 as well as in the pooled zanubrutinib patient population, is included in FDA Table 20 below.

FDA Table 21: FDA's Analysis of Atrial Fibrillation and Atrial Flutter in Study BGB-3111-302 and Pooled Population

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)		Cohort 2 N=28 N(%)		ISS Dataset Zanubrutinib N=779 n(%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Atrial Fibrillation	17 (17.3)	6 (6.1)	4 (4.0)	0 (0.0)	1 (3.6)	0 (0.0)	38 (4.9)	11 (1.4)
Atrial Flutter	2 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	2 (0.3)

Source: FDA Clinical Reviewer's Analysis

Hypertension

The FDA's analysis of hypertension was based on grouped terms including the following: blood pressure increased, high blood pressure and hypertension. Overall, slightly more subjects in the ibrutinib arm experienced hypertension, as well as Grade 3-4 hypertension. The incidence of hypertension in subjects who received zanubrutinib in Study BGB-3111-302 was slightly higher than the pooled zanubrutinib safety population. A summary of the FDA's analysis of hypertension that occurred in Study BGB-3111-302 as well as in the pooled zanubrutinib patient population, is included in FDA Table 21 below.

FDA Table 22: FDA's Analysis of Hypertension in Study BGB-3111-302 and Pooled Population

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)		Cohort 2 N=28 N(%)		ISS Dataset Zanubrutinib N=779 n(%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Hypertension[1]	20 (20.4)	15 (15.3)	14 (13.7)	9 (8.8)	3 (10.7)	3 (10.7)	67 (8.6)	25 (3.2)

[1]Includes Preferred Terms: blood pressure increased, high blood pressure, hypertension
Source: FDA Clinical Reviewer's Analysis

Infections

FDA's analysis of Infections was based on the SOC Infections and Infestations and grouped preferred terms. Overall, the number of subjects who experienced an infection was similar in the two treatment arms (zanubrutinib: n=73, 72.3%; ibrutinib: n=71; 72.4%). There were slightly more subjects in the ibrutinib arm who experienced Grade 3-4 infection compared to the zanubrutinib arm (zanubrutinib: n=19, 18.8%; ibrutinib: n=24; 24.5%). Overall, the types of infections were balanced between the two treatment arms, with the exception of pneumonia,

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Reference ID: 4850271

which occurred in more subjects in the ibrutinib arm (zanubrutinib: n=12, 11.8%; ibrutinib: n=25, 25.5%). A summary of the Infections that occurred in ≥10% of subjects in either treatment arm in Cohort 1 or in Cohort 2 of Study BGB-3111-302 is provided in FDA Table 22 below.

FDA Table 23: FDA's Analysis of Infections in Study BGB-3111-302

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)		Cohort 2 N=28 N(%)	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Infections and Infestations	71 (72.4)	24 (24.5)	73 (72.3)	19 (18.8)	22 (78.6)	8 (28.6)
Upper Respiratory Tract Infection[1]	39 (39.8)	2 (2.0)	44 (43.6)	0 (0.0)	9 (32.1)	0 (0.0)
Pneumonia[2]	25 (25.5)	10 (10.2)	12 (11.8)	4 (4.0)	8 (28.6)	3 (10.7)
Urinary Tract Infection	13 (13.1)	2 (2.0)	11 (10.8)	0 (0.0)	4 (14.3)	0 (0.0)
Lower Respiratory Tract Infection	10 (10.1)	0 (0.0)	10 (9.8)	0 (0.0)	2 (7.1)	0 (0.0)
Localized Infection	10 (10.1)	0 (0.0)	1 (1.0)	0 (0.0)	1 (3.6)	0 (0.0)
Herpes Zoster	1 (1.0)	1 (1.0)	4 (3.9)	1 (1.0)	3 (10.7)	0 (0.0)

[1]Includes Preferred Terms: laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract congestion, upper respiratory tract infection, viral upper respiratory tract infection
[2]Includes Preferred Terms: lower respiratory tract infection, lung infiltration, organizing pneumonia, pneumonia, pneumonia aspiration, pneumonia viral
Source: FDA Clinical Reviewer's Analysis

Second Primary Malignancies

Second primary malignancies has been identified as a risk with the use of BTK inhibitors and is included in the Warnings and Precautions section of the USPI. The FDA conducted an analysis of the incidence of second primary malignancies in patients who received zanubrutinib in Study BGB-3111-302, as well as in the updated pooled zanubrutinib patient population, using the Neoplasms SOC. Section 5.4 of the USPI was updated to include the results of this analysis. A summary of the FDA's analysis of second primary malignancies is provided in FDA Table 23 below.

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Reference ID: 4850271

FDA Table 24: FDA Analysis of Second Primary Malignancies in Study BGB-3111-302 and the Pooled Population

	Cohort 1 Ibrutinib (N=98) n(%)	Cohort 1 Zanubrutinib (N=101) n(%)	Cohort 2 (N=28) n(%)	ISS Dataset N=779 n(%)
Patients with SPM	12 (12.2)	15 (14.9)	4 (14.3)	105 (13.5)
Non-Melanoma Skin Cancer	8 (8.2)	6 (6.0)	3 (10.7)	66 (8.5)
Basal cell carcinoma	2 (2.0)	4 (4.0)	3 (10.7)	37 (4.7)
Squamous cell carcinoma	6 (6.1)	2 (2.0)	0 (0.0)	27 (3.5)
Skin Cancer[1]	2 (2.0)	2 (2.0)	0 (0.0)	10 (1.3)
Malignant Melanoma[2]	0 (0.0)	2 (2.0)	0 (0.0)	11 (1.4)
Malignant Solid Tumors[3]	2 (2.0)	3 (3.0)	0 (0.0)	30 (3.9)
Hematologic Malignancies[4]	1 (1.0)	2 (2.0)	1 (3.6)	9 (1.2)

[1]Includes Preferred Terms: skin Cancer, lentigo maligna, keratoacanthoma
[2]Includes Preferred Terms: malignant melanoma, malignant melanoma in situ, malignant melanoma stage I, malignant melanoma stage II
[3]Includes Preferred Terms: Adenocarcinoma gastric, bladder cancer, bladder transitional cell carcinoma, breast cancer, colon cancer, colorectal cancer metastatic, endometrial adenocarcinoma, external ear neoplasm malignant, invasive ductal breast carcinoma, laryngeal cancer, lung neoplasm malignant, neoplasm malignant, neoplasm prostate, neuroendocrine carcinoma metastatic, ocular surface squamous neoplasm, pleomorphic malignant fibrous histiocytoma, prostate cancer, renal cell carcinoma, sarcomatoid carcinoma of the lung, small cell lung cancer, soft tissue neoplasm, squamous cell carcinoma of head and neck, squamous cell carcinoma of the parotid gland
[4]Includes Preferred Terms: acute myeloid leukemia, anaplastic large cell lymphoma T- and null-cell types, B-cell lymphoma, chronic myelomonocytic leukemia, cutaneous T-cell lymphoma, myelodysplastic syndrome, plasma cell myeloma, Waldenström's macroglobulinemia
Source: FDA Clinical Reviewer's Analysis

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Adverse reactions of any grade reported in > 20% of patients were as follows:

Study BGB-3111-302 Cohort 1:

- Ibrutinib: diarrhoea (33.7%), upper respiratory tract infection (31.6%), muscle spasms (27.6%), contusion (24.5%), epistaxis and peripheral oedema (20.4% each)
- Zanubrutinib: upper respiratory tract infection (29.7%), neutropenia (25.7%), fatigue (22.8%), diarrhoea (21.8%)

Adverse events reported at a ≥ 5% higher frequency among ibrutinib- than zanubrutinib-treated patients were diarrhoea, contusion, muscle spasms, epistaxis, peripheral oedema, hypertension, atrial fibrillation, localised infection, and pneumonia.

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Reference ID: 4850271

Conversely, adverse events reported at a ≥ 5% higher frequency among zanubrutinib- than ibrutinib-treated patients were neutropenia, constipation, dyspnoea, and back pain.

BeiGene Table 26 Adverse Events Reported in ≥ 10% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Patients with at least one TEAE	98 (100.0)	98 (97.0)
Infections and infestations	71 (72.4)	73 (72.3)
Upper respiratory tract infection	31 (31.6)	30 (29.7)
Pneumonia	**15 (15.3)**	**3 (3.0**)
Urinary tract infection	13 (13.3)	11 (10.9)
Nasopharyngitis	7 (7.1)	11 (10.9)
Lower respiratory tract infection	10 (10.2)	10 (9.9)
Localised infection	**10 (10.2)**	**1 (1.0)**
Gastrointestinal disorders	59 (60.2)	63 (62.4)
Diarrhoea	**33 (33.7**)	**22 (21.8**)
Constipation	**7 (7.1)**	**16 (15.8)**
Nausea	13 (13.3)	18 (17.8)
Vomiting	14 (14.3)	12 (11.9)
Skin and subcutaneous tissue disorders	49 (50.0)	51 (50.5)
Rash	17 (17.3)	14 (13.9)
Purpura	6 (6.1)	3 (3.0)
Pruritus	6 (6.1)	11 (10.9)
Respiratory, thoracic and mediastinal disorders	50 (51.0)	43 (42.6)
Cough	18 (18.4)	16 (15.8)
Epistaxis	**20 (20.4)**	**14 (13.9)**

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Dyspnoea	**7 (7.1)**	**14 (13.9)**
Investigations	21 (21.4)	19 (18.8)
Neutrophil count decreased	3 (3.1)	7 (6.9)
Platelet count decreased	2 (2.0)	1 (1.0)
White blood cell count decreased	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	3 (3.1)	2 (2.0)
Aspartate aminotransferase increased	2 (2.0)	1 (1.0)
General disorders and administration site conditions	55 (56.1)	56 (55.4)
Fatigue	19 (19.4)	23 (22.8)
Pyrexia	13 (13.3)	16 (15.8)
Oedema peripheral	**20 (20.4)**	**12 (11.9)**
Musculoskeletal and connective tissue disorders	59 (60.2)	55 (54.5)
Back pain	**9 (9.2)**	**17 (16.8)**
Arthralgia	18 (18.4)	16 (15.8)
Muscle spasms	**27 (27.6)**	**10 (9.9)**
Pain in extremity	7 (7.1)	12 (11.9)
Metabolism and nutrition disorders	25 (25.5)	28 (27.7)
Hypokalaemia	5 (5.1)	1 (1.0)
Hyperglycaemia	1 (1.0)	1 (1.0)
Hyperuricaemia	7 (7.1)	4 (4.0)
Blood and lymphatic system disorders	32 (32.7)	44 (43.6)
Anaemia	13 (13.3)	12 (11.9)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Neutropenia	**14 (14.3)**	**26 (25.7)**
Thrombocytopenia	12 (12.2)	13 (12.9)
Injury, poisoning and procedural complications	42 (42.9)	43 (42.6)
Contusion	**24 (24.5)**	**15 (14.9)**
Nervous system disorders	45 (45.9)	46 (45.5)
Headache	14 (14.3)	18 (17.8)
Dizziness	12 (12.2)	13 (12.9)
Renal and urinary disorders	22 (22.4)	20 (19.8)
Haematuria	12 (12.2)	8 (7.9)
Vascular disorders	28 (28.6)	21 (20.8)
Hypertension	**19 (19.4)**	**14 (13.9)**
Cardiac disorders	35 (35.7)	25 (24.8)
Atrial fibrillation	**17 (17.3)**	**4 (4.0)**

Source: Table 2.7.4.2.2.1
Abbreviations: N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinemia.
Notes: 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 for the All Zanubrutinib group. Differences in adverse event frequency of 5% or more among patients in the ibrutinib and zanubrutinib arms in Study BGB-3111-302 Cohort 1 are **bolded**; differences of 5% or more between the All China and All Non-China groups are *italicized*.
Percentages are based on N, unless otherwise specified.
Data cutoff: 31MAR2020

Grade 3 or Higher Adverse Events

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Reference ID: 4850271

Study BGB-3111-302 Cohort 1: ≥ Grade 3 adverse events reported in ≥ 3% of patients were as follows:

- Ibrutinib: hypertension (14.3%); neutropenia and pneumonia (9.2% each); atrial fibrillation (6.1%); anaemia, syncope and thrombocytopenia (5.1% each); and sepsis (4.1%)
- Zanubrutinib: neutropenia (17.8%); hypertension (8.9%); thrombocytopenia (6.9%); anemia (5.9%); back pain and decreased neutrophil count (5.0% each); febrile neutropenia, pyrexia, and syncope (4.0% each); and diarrhoea and arthralgia (3.0% each)

Grade 3 or higher adverse events reported at ≥ 3% higher frequency among ibrutinib- than zanubrutinib-treated patients were pneumonia, hypertension, and atrial fibrillation. Conversely, adverse events reported at a ≥ 3% higher frequency among zanubrutinib patients were neutropenia, decreased neutrophil count, back pain, febrile neutropenia, and arthralgia.

BeiGene Table 27 Grade 3 or Higher Adverse Events Reported in ≥ 3% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
Patients with at least one grade 3 or higher TEAE	66 (67.3)	65 (64.4)
Infections and infestations	24 (24.5)	19 (18.8)
Pneumonia	**9 (9.2)**	**1 (1.0)**
Upper respiratory tract infection	1 (1.0)	0 (0.0)
Sepsis	4 (4.1)	2 (2.0)
Blood and lymphatic system disorders	17 (17.3)	28 (27.7)
Neutropenia	9 (9.2)	18 (17.8)
Anaemia	5 (5.1)	6 (5.9)
Thrombocytopenia	5 (5.1)	7 (6.9)
Febrile neutropenia	0 (0.0)	4 (4.0)
Investigations	4 (4.1)	5 (5.0)
Neutrophil count decreased	1 (1.0)	5 (5.0)
Platelet count decreased	0 (0.0)	0 (0.0)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
System Organ Class Preferred Term	**Ibrutinib (N = 98) n (%)**	**Zanubrutinib (N = 101) n (%)**
White blood cell count decreased	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (4.1)	6 (5.9)
Diarrhoea	2 (2.0)	3 (3.0)
Metabolism and nutrition disorders	3 (3.1)	5 (5.0)
Hypokalaemia	0 (0.0)	1 (1.0)
Vascular disorders	14 (14.3)	10 (9.9)
Hypertension	14 (14.3)	9 (8.9)
General disorders and administration site conditions	4 (4.1)	7 (6.9)
Pyrexia	2 (2.0)	4 (4.0)
Nervous system disorders	8 (8.2)	7 (6.9)
Syncope	5 (5.1)	4 (4.0)
Musculoskeletal and connective tissue disorders	3 (3.1)	11 (10.9)
Arthralgia	0 (0.0)	3 (3.0)
Back pain	1 (1.0)	5 (5.0)
Cardiac disorders	14 (14.3)	7 (6.9)
Atrial fibrillation	6 (6.1)	0 (0.0)

Source: Table 2.7.4.2.2.2
Abbreviations: N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinemia.
Notes: 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 for the All Zanubrutinib group. Differences in adverse event frequency of 3% or more between ibrutinib and zanubrutinib arms in Study BGB-3111-302 Cohort 1 are **bolded**; differences of 3% or more between All China and All Non-China groups are *italicized*.
Percentages are based on N, unless otherwise specified.

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Reference ID: 4850271

Adverse event grades are graded for severity National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03).
Data cutoff: 31MAR2020

The Applicant's Position:

Zanubrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other zanubrutinib clinical trials.

Several adverse effects have been associated with BTK inhibitors as a drug class, including diarrhea and the events predefined for specific adverse analyses hemorrhage, major hemorrhage, atrial fibrillation and atrial flutter, hypertension, second primary malignancies, tumor lysis syndrome, infections and cytopenias. These toxicities have been observed with varying frequency and severity across products, in part due to differences in the specificity for BTK inhibition and off-target effects. Events of special interest for BTK inhibitors occurred with zanubrutinib but at generally lower rates than with ibrutinib. These lower rates are perhaps most notable because these events can be treatment-limiting with ibrutinib as demonstrated by the higher rate of treatment discontinuation due to AE in the ibrutinib arm 15% vs 4%.

The FDA's Assessment:
In general, The FDA agrees with the Applicant's presentation of the most common treatment-emergent adverse events (TEAEs) in Cohort 1 of Study BGB-3111-302. The FDA's analysis of the most common TEAEs was based on SOCs, preferred terms, and several grouped terms.

The most common adverse events in both treatment arms included the following:
- Musculoskeletal pain (zanubrutinib: 44.6%; ibrutinib: 38.8%)
- Upper respiratory tract infection (zanubrutinib: 43.6%; ibrutinib: 39.8%)
- Hemorrhage (zanubrutinib: 40.6%; ibrutinib: 42.9%)
- Fatigue (zanubrutinib: 30.7%; ibrutinib: 24.5%)
- Neutropenia (zanubrutinib: 30.7%; ibrutinib: 16.3%)
- Rash (zanubrutinib: 26.5%; ibrutinib: 30.6%)
- Diarrhea (ibrutinib: 33.3%; zanubrutinib: 21.6%)

Adverse events that occurred with ≥5% greater incidence in the zanubrutinib arm compared to the ibrutinib arm include the following:
- Musculoskeletal pain (zanubrutinib: 44.6%; ibrutinib: 38.8%)
- Neutropenia (zanubrutinib: 30.7%; ibrutinib: 16.3%)
- Fatigue (zanubrutinib: 30.7%; ibrutinib: 24.5%)
- Dyspnea (zanubrutinib: 15.8%; ibrutinib: 9.1%)
- Constipation (zanubrutinib: 15.7%; ibrutinib: 7.1%)

The FDA does not agree with the Applicant's statement, "Zanubrutinib was well tolerated", as

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Reference ID: 4850271

this is subjective, broad and promotional. Nearly all subjects who received zanubrutinib experienced a TEAE, and 64% experienced a Grade 3 or higher TEAE. The FDA does not agree with the Applicant's statement, "Events of special interest for BTK inhibitors occurred with zanubrutinib but at generally lower rates than with ibrutinib". While several adverse events of special interest (i.e., atrial fibrillation and diarrhea), did occur at lower rates with zanubrutinib, the ASPEN trial was not designed to assess a comparative safety benefit of zanubrutinib relative to ibrutinib. Overall adverse events of special interest occurred at low rates in both treatment arms, precluding conclusions regarding comparative safety benefit. There were several adverse events of special interest that occurred more frequently in subjects who received zanubrutinib (i.e., neutropenia), and several that were very similar in the two treatment arms (i.e., hemorrhage).

A summary of the FDA's analysis of the most common TEAEs that occurred in ≥10% of subjects in the zanubrutinib arm by treatment and Grade, as well as the FDA's analysis of Grade 3-4 TEAEs is presented in FDA Table 24 below.

FDA Table 25: FDA's Analysis of Treatment-Emergent Adverse Events Reported in ≥ 10% of Patients in the Zanubrutinib arm in Cohort 1 by System Organ Class and Preferred Term

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Any TEAE	**98 (100.0)**	**66 (67.3)**	**98 (97.0)**	**65 (64.4)**
Infections and Infestations	**71 (72.4)**	**24 (24.5)**	**73 (72.3)**	**19 (18.8)**
Upper Respiratory Tract Infection[1]	39 (39.8)	2 (2.0)	44 (43.6)	0 (0.0)
Pneumonia[2]	25 (25.5)	10 (10.2)	12 (11.8)	4 (4.0)
Urinary Tract Infection	13 (13.1)	2 (2.0)	11 (10.8)	0 (0.0)
Gastrointestinal Disorders	**59 (60.2)**	**4 (4.1)**	**63 (62.4)**	**6 (5.9)**
Diarrhea	33 (33.7)	2 (2.0)	22 (21.6)	3 (2.9)
Nausea	13 (13.1)	1 (1.0)	18 (17.6)	0 (0.0)
Constipation	7 (7.1)	0 (0.0)	16 (15.7)	0 (0.0)
Vomiting	14 (14.1)	1 (1.0)	12 (11.8)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	**59 (60.2)**	**3 (3.1)**	**55 (54.5)**	**11 (10.9)**
Musculoskeletal pain[3]	38 (38.8)	1 (1.0)	45 (44.6)	9 (9.0)
Muscle spasms	27 (27.6)	1 (1.0)	10 (9.8)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	**49 (50.0)**	**0 (0.0)**	**51 (50.5)**	**1 (1.0)**
Bruising[4]	33 (33.7)	0 (0.0)	20 (19.8)	0 (0.0)
Rash[5]	30 (30.6)	0 (0.0)	27 (26.7)	0 (0.0)
Pruritis	6 (6.1)	0 (0.0)	11 (10.8)	1 (1.0)
Respiratory, Thoracic and Mediastinal Disorders	**50 (51.0)**	**3 (3.1)**	**43 (42.6)**	**6 (5.9)**
Cough[6]	24 (24.5)	0 (0.0)	20 (19.8)	0 (0.0)

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Reference ID: 4850271

	Cohort 1 Ibrutinib N=98 N(%)		Cohort 1 Zanubrutinib N=101 N(%)	
Dyspnea[7]	9 (9.1)	0 (0.0)	16 (15.8)	0 (0.0)
General Disorders and Administration Site Conditions	**55 (56.1)**	**3 (3.1)**	**56 (55.4)**	**7 (6.9)**
Fatigue[8]	24 (24.5)	1 (1.0)	31 (30.7)	1 (1.0)
Pyrexia	13 (13.1)	2 (2.0)	16 (15.7)	4 (3.9)
Peripheral Edema	20 (20.2)	0 (0.0)	12 (11.8)	0 (0.0)
Blood and Lymphatic System Disorders	**32 (32.7)**	**17 (17.3)**	**44 (43.6)**	**28 (27.7)**
Neutropenia[9]	16 (16.3)	9 (9.1)	31 (30.7)	22 (21.8)
Thrombocytopenia[10]	14 (14.1)	5 (5.1)	14 (13.9)	7 (6.9)
Anemia	13 (13.1)	5 (5.1)	12 (11.8)	6 (5.9)
Vascular Disorders	**28 (28.6)**	**14 (14.1)**	**21 (20.8)**	**10 (10.0)**
Hemorrhage[11]	42 (42.9)	9 (9.2)	41 (40.6)	4 (4.0)
Hypertension	19 (19.2)	14 (14.1)	14 (13.7)	9 (8.8)
Nervous System Disorders	**45 (45.9)**	**8 (8.2)**	**46 (45.5)**	**7 (6.9)**
Headache	14 (14.1)	1 (1.0)	18 (17.6)	1 (1.0)
Dizziness	12 (12.1)	0 (0.0)	13 (12.7)	1 (1.0)

[1]Includes Preferred Terms: laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract congestion, upper respiratory tract infection, viral upper respiratory tract infection
[2]Includes Preferred Terms: lower respiratory tract infection, lung infiltration, organizing pneumonia, pneumonia, pneumonia aspiration, pneumonia viral
[3]Includes Preferred Terms: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
[4]Includes Preferred Terms: contusion, ecchymosis, eye contusion, increased tendency to bruise, infusion site bruising, oral contusion
[5]Includes Preferred Terms: dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, erythema, photodermatosis, photosensitivity reaction, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, skin toxicity, urticaria, vasculitic rash
[6]Includes Preferred Terms: cough, productive cough, allergic cough, upper-airway cough syndrome
[7]Includes Preferred Terms: dyspnea, dyspnea exertional
[8]Includes Preferred Terms: asthenia, fatigue, lethargy
[9]Includes Preferred Terms: neutropenia, neutrophil count decreased
[10]Includes Preferred Terms: thrombocytopenia, platelet count decreased
[11]Includes Preferred Terms: Epistaxis, hematuria, hemoptysis, hematoma, hemothorax, , hematochezia, melena, all PTs that included “hemorrhage” “hematoma” “hemorrhagic
Source: FDA Clinical Reviewer’s Analysis

Laboratory Findings

Data:

Incidence of Abnormal Laboratory Values

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Reference ID: 4850271

Hematology

Study BGB-3111-302 Cohort 1: ibrutinib- compared with zanubrutinib-treated patients had a lower incidence of any grade (40.2% and 56.4%, respectively) and ≥ Grade 3 (9.3% and 23.8%, respectively) of decreased neutrophil counts (Table X). There were no meaningful baseline or postbaseline differences between treatment arms for other hematology parameters of interest (ie, hemoglobin concentrations, platelet and lymphocyte counts).

Chemistry

For **Study BGB-3111-302 Cohort 1**, the following differences were observed when comparing laboratory abnormalities in selected serum chemistry analytes between ibrutinib- and zanubrutinib-treated patients:

Ibrutinib-treated patients exhibited a higher frequency of postbaseline, any grade increase in serum AST, bilirubin, serum urate concentrations and increased serum glucose at *baseline* than zanubrutinib-treated patients. Zanubrutinib-treated patients exhibited a higher frequency of postbaseline, any grade increases in serum creatinine than ibrutinib-treated patients and increased glucose than ibrutinib-treated patients. There were no clinically meaningful differences for any of the aforementioned comparisons in the frequencies of ≥ Grade 3 abnormalities (all of which were observed in < 5% of patients in either treatment arm) (Table X).Finally, ibrutinib-treated patients exhibited a higher frequency of postbaseline, any grade, increased serum urate concentrations than zanubrutinib-treated patients (50.5% and 26.5%). There were no clinically meaningful differences for any of the aforementioned comparisons in the frequencies of ≥ Grade 3 abnormalities (all of which were observed in < 5% of patients in either treatment arm).

BeiGene Table 28 Incidence of Baseline and Postbaseline Hematology Parameter Abnormalities and Serum Chemistry Analytes of Interest (Safety Analysis Set)

	BGB-3111-302 Cohort 1	
Analyte	**Ibrutinib (N = 98)**	**Zanubrutinib (N = 101)**
Neutrophils (10^9/L) (low abnormal)		
Baseline		
n	98	100
Patients with Grade ≥ 1 toxicity (%)	16 (16.3)	18 (18.0)
Patients with Grade ≥ 3 toxicity (%)	3 (3.1)	3 (3.0)
Any postbaseline		

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
Analyte	**Ibrutinib (N = 98)**	**Zanubrutinib (N = 101)**
n	97	101
Patients with Grade ≥ 1 toxicity (%)	39 (40.2)	57 (56.4)
Patients with Grade ≥ 3 toxicity (%)	9 (9.3)	24 (23.8)
Aspartate Aminotransferase (U/L)		
Baseline		
n	96	100
Patients with Grade ≥ 1 toxicity (%)	0 (0.0)	3 (3.0)
Patients with Grade ≥ 3 toxicity (%)	0 (0.0)	0 (0.0)
Any postbaseline		
n	97	101
Patients with Grade ≥ 1 toxicity (%)	18 (18.6)	13 (12.9)
Patients with Grade ≥ 3 toxicity (%)	2 (2.1)	0 (0.0)
Bilirubin (µmol/L)		
Baseline		
n	98	100
Patients with Grade ≥ 1 toxicity (%)	4 (4.1)	3 (3.0)
Patients with Grade ≥ 3 toxicity (%)	0 (0.0)	0 (0.0)
Any postbaseline		
n	97	101
Patients with Grade ≥ 1 toxicity (%)	36 (37.1)	14 (13.9)

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
Analyte	**Ibrutinib (N = 98)**	**Zanubrutinib (N = 101)**
Patients with Grade ≥ 3 toxicity (%)	1 (1.0)	1 (1.0)
Creatinine (µmol/L)		
Baseline		
n	98	101
Patients with Grade ≥ 1 toxicity (%)	12 (12.2)	17 (16.8)
Patients with Grade ≥ 3 toxicity (%)	0 (0.0)	0 (0.0)
Any postbaseline		
n	98	101
Patients with Grade ≥ 1 toxicity (%)	29 (29.6)	41 (40.6)
Patients with Grade ≥ 3 toxicity (%)	1 (1.0)	1 (1.0)
Glucose (mmol/L)		
Baseline		
n	87	89
Patients with Grade ≥ 1 toxicity (%)	24 (27.6)	17 (19.1)
Patients with Grade ≥ 3 toxicity (%)	1 (1.1)	1 (1.1)
Any postbaseline		
n	90	92
Patients with Grade ≥ 1 toxicity (%)	43 (47.8)	56 (60.9)
Patients with Grade ≥ 3 toxicity (%)	2 (2.2)	2 (2.2)
Urate (µmol/L)		

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Reference ID: 4850271

	BGB-3111-302 Cohort 1	
Analyte	**Ibrutinib (N = 98)**	**Zanubrutinib (N = 101)**
Baseline		
n	90	94
Patients with Grade ≥ 1 toxicity (%)	19 (21.1)	15 (16.0)
Patients with Grade ≥ 3 toxicity (%)	1 (1.1)	1 (1.1)
Any postbaseline		
n	97	98
Patients with Grade ≥ 1 toxicity (%)	49 (50.5)	26 (26.5)
Patients with Grade ≥ 3 toxicity (%)	6 (6.2)	4 (4.1)

Source: Table 2.7.4.3.3.1 (Hematology) and Table 2.7.4.3.3.2 (Chemistry)

The Applicant's Position:
Zanubrutinib was well tolerated and showed an acceptable safety profile that is consistent with the other zanubrutinib clinical trials. Mean hemoglobin concentrations increased from baseline and remained increased over time in both treatment arms, which is consistent with improved bone marrow function and no clinically meaningful changes from baseline were observed in the median values for serum chemistry analytes of interest.

The FDA's Assessment:
In general, The FDA agrees with the Applicant's description of the laboratory findings in Cohort 1 of Study BGB-3111-302.

However, the FDA's analysis for Neutrophils Decreased varies slightly from the Applicant's (zanubrutinib: 50%; ibrutinib: 34%). The FDA notes that more subjects in the zanubrutinib arm experienced decreased neutrophils (zanubrutinib: 50%; ibrutinib: 34%), as well as Grade 3-4 decreased neutrophils (zanubrutinib: 24%; ibrutinib: 9%). The incidence of the other changes in hematologic parameters, including platelets decreased (zanubrutinib: 39%; ibrutinib: 35%) and hemoglobin decreased (zanubrutinib: 20%; ibrutinib: 20%), were similar in the two treatment arms.

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Reference ID: 4850271

The FDA disagrees with the Applicant's conclusion that there were no clinically meaningful changes from baseline in the median values for serum chemistry analytes of interest. The FDA notes that more subjects in the zanubrutinib arm had an increase in glucose (zanubrutinib: 45%; ibrutinib: 33%), an increase in creatine (zanubrutinib: 31%; ibrutinib: 21%), and an increase in potassium (zanubrutinib: 24%; ibrutinib: 12%), all of which may be clinically meaningful. Vital Signs

Data:
For the **All Zanubrutinib** patient group, there were no noteworthy changes from baseline in median values for systolic or diastolic blood pressures, pulse rate, respiratory rate, temperature or weight

The Applicant's Position:
For the **All Zanubrutinib** patient group, there were no noteworthy changes from baseline in median values for systolic or diastolic blood pressures, pulse rate, respiratory rate, temperature or weight

The FDA's Assessment:
The FDA agrees with the Applicant's assessment that there were no noteworthy changes from baseline median values for vital signs with the exception of blood pressure, as discussed above.

Electrocardiograms (ECGs)

Data:
For the **All Zanubrutinib** group, 13 (1.8%) patients had at least 1 postbaseline QTcF interval measurement of > 500 msec and 35 (4.9%) patients had a maximum increase from baseline in QTcF of > 60 msec (Table 2.7.4.4.2). Of these patients, 2 patients reported treatment-emergent adverse events in the system organ class of Cardiac disorders within 2 weeks of the electrocardiogram QTcF prolonged event (Listing 2.7.4.4.5).

The Applicant's Position:
Overall, zanubrutinib showed an acceptable safety and tolerability profile which is consistent with the other zanubrutinib clinical trials.

The FDA's Assessment:
The FDA agrees with the Applicant's description of ECGs. The reported values are accurate and consistent with observations at the time of the original NDA approval (4% of zanubrutinib-treated patients at any dose level had maximum increase from baseline in QTcF >60 msec). The FDA does not agree with the Applicant's statement, "overall zanubrutinib showed an acceptable safety and tolerability profile, which is consistent with the other zanubrutinib clinical trials". This statement is broad and does not belong in this section that describes ECG findings.

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Reference ID: 4850271

QT
Data:

All Zanubrutinib group:

- One patient in Study BGB-3111-205 (Patient (b) (6)) treated with zanubrutinib had electrocardiogram QT prolongation on 29 March 2018 (Day 113), coincident with an adverse event of wandering pacemaker on the same day. The event was Grade 1 and was considered possibly related to zanubrutinib by the investigator. The event was ongoing as of the data cutoff date.
- One patient in Study BGB-3111-AU-003 (Patient (b) (6)) experienced a QT prolongation on 04 January 2019 (Day 358), coincident with an adverse event of congestive cardiac failure on the same day. The event was serious, Grade 3, and considered not related to zanubrutinib by the investigator. This event was also ongoing as of the data cutoff date.

The Applicant's Position:
No WM patients treated with zanubrutinib have been found to be associated with QT prolongation.

The FDA's Assessment:
The Applicant's position statement, "No WM patients treated with zanubrutinib have been found to be associated with QT prolongation" is misleading. Among all zanubrutinib-treated patients, 13 (1.8%) patients had at least 1 postbaseline QTcF interval measurement of >500 msec and 35 (4.9%) patients had a maximum increase from baseline in QTcF of >60 msec. However, FDA notes that there were no clinical events of prolonged QT in the WM population in Study BGB-3111-302.

The two patients reported here are those patients with a cardiac AE reported within 2 weeks of a QTcF prolongation event. Both had underlying disease of CLL.

Immunogenicity

Data:
Not applicable

The Applicant's Position:
N/Ap

The FDA's Assessment:
Not applicable.

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Reference ID: 4850271

Analysis of Submission-Specific Safety Issues

8.2.5.1 [Name Safety Issue]

Data:
N/AP

The Applicant's Position:
N/AP

The FDA's Assessment:
Not applicable.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

To assess how depth of response could improve quality of life (ie, attaining a VGPR could result in clinical benefit to the patient) during treatment with zanubrutinib or ibrutinib, changes in quality of life were measured using the EORTC QLQ-C30 questionnaire and the EQ-5D as described in BGB-3111-302 Clinical Study Report Section 9.7.1.3.4.

The Applicant's Position:
Discussion in found in section 8.1.2.

The FDA's Assessment:
See Section 8.1 for the FDA's assessment of the Clinical Outcome Assessment (COA) analyses.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
Age
In the **All Zanubrutinib** group, > 97% of patients in all age categories (< 65 years, ≥ 65 years to < 75 years, and ≥ 75 years) experienced at least 1 adverse event. Not unexpectedly, with increasing age there was a clear trend toward higher incidences of ≥ Grade 3 adverse events (63.2%, 64.3%, and 76.3%, respectively), serious adverse events (37.9%, 48.4%, and 60.5%, respectively), adverse events leading to treatment discontinuation (6.7%, 13.5%, and 13.8% respectively), dose reduction (5.9%, 8.3%, and 11.2%, respectively), and death (2.9%, 5.2%, and 9.9% respectively). Similar age-related trends were also observed in the **All WM** group.
Sex

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Reference ID: 4850271

In the **All Zanubrutinib** group, > 98% of patients of both sexes reported at least 1 adverse event. One or more ≥ Grade 3 events were reported in 64.4% of males and 69.7% of females; serious adverse events were reported in 45.6% and 45.8%, respectively. Adverse events leading to treatment discontinuation were reported in 10.4% of males and 10.0% of females, and adverse events leading to dose reduction were reported in 7.4% of males and 8.4% of females. More male than female patients experienced Grade 5 events (5.9% and 3.2%, respectively). Comparable frequencies of ≥ Grade 3 and serious adverse events as well as those leading to treatment discontinuation were observed between male and female patients in the **All WM** group. As was noted for the **All Zanubrutinib** group, there were more males than females with Grade 5 events (5.3% and 1.3%, respectively) in the **All WM** group as well

Weight

In the **All Zanubrutinib** group, > 98% of patients with baseline weight below or at/above the median weight for the patient group (70.70 kg) reported at least 1 adverse event. The frequency of ≥ Grade 3 adverse events was slightly higher among patients below the median baseline weight than those at/above 70.70 kg (69.5% and 62.7%, respectively). Adverse events that met the criteria for seriousness (46.1% and 45.3%) as well as events that led to death (5.3% and 4.7%), treatment discontinuation (10.9% and 9.6%), and dose reduction (6.9% and 8.5%) were comparable for both weight groups.

Patients in the **All WM** group with baseline weights below the median had higher frequencies of ≥ Grade 3 (74.6% and 59.1%, respectively) and serious (54.0% and 40.9%) adverse events, as well as those that led to death (5.6% and 2.4%) and treatment discontinuation (11.1% and 7.1%) compared to those at or above the median weight at baseline. The frequencies of adverse events leading to dose reduction were comparable (9.5% and 11.0%)

Race

As the number of patients in the "Other" race category was small (N = 39 for the **All Zanubrutinib** group), including 10 for whom race was not reported the comparisons below are mostly limited to White and Asian race categories. Patients from China accounted for approximately 5/6 of all Asian patients in the **All Zanubrutinib** group. In the **All Zanubrutinib** group, > 97% of patients in each race category experienced at least 1 adverse event. Comparable frequencies of ≥ Grade 3 adverse events (64.7% and 67.4%) as well as those leading to treatment discontinuation (10.1% and 10.2%) were observed between White and Asian groups, respectively. More patients experienced at least 1 serious adverse event (48.0% and 40.1%, respectively) and adverse events leading to dose reduction (10.1% and 5.0%) in the White group than in the Asian group. While adverse events leading to death were comparable between White and Asian groups (4.8% and 4.7%, respectively), they were notably higher in the "Other" group (10.3%). This comparison must be interpreted with caution due to the small sample size and heterogeneity of the "Other" group.

In the **All WM** group, more patients in the Asian than in the White group experienced ≥ Grade 3 adverse events (73.7% and 64.6%, respectively), while more patients in the White than in the Asian group experienced adverse events leading to dose reduction (12.7% and 3.5%, respectively). Comparable frequencies of serious adverse events as well as those leading to

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Reference ID: 4850271

treatment discontinuation were observed between the White and Asian groups. There was a comparable frequency of events leading to death in the Asian and White groups (5.3% and 3.9%, respectively) with no deaths reported in the "Other" group (N = 15).

Region

The incidence of adverse events in zanubrutinib-treated patients can be compared for studies conducted in China and outside of China by examining the **All China** versus the **All Non-China** groups.

The rate of adverse events for patients in the **All China** group was comparable to that for patients in the **All Non-China** group (98.5% and 98.1%, respectively); the rates of ≥ Grade 3 adverse events (66.8% and 65.8%, respectively) and deaths (5.3% and 4.9%, respectively) were also comparable. For the **All China** group, lower rates of serious adverse events (38.5%) were reported compared with the **All Non-China** group (49.4%). However, in the **All China** group, treatment-related adverse events (94.3%) were reported at higher rates than in the **All Non-China** group (75.7%).

The Applicant's Position:

Zanubrutinib treatment was generally well tolerated in all patient groups and the safety profile was consistent across patient groups. The spectrum of adverse events observed across all patient groups is consistent with the known toxicity profile for the BTK inhibitor class as well as those intrinsic to B-cell malignancy patient populations. The safety profile of zanubrutinib is comparable across demographical subgroups (age, sex, weight, race and region).

The FDA's Assessment:

The FDA agrees with the Applicant's description of the safety analyses in different demographic subgroups. The FDA notes that in Study BGB-3111-302, the number of racial and ethnic minorities was small and there were no Black or African American subjects. The overall safety population of patients with Waldenström's Macroglobulinemia treated with zanubrutinib on clinical trials includes 253 patients. Of these, 181 (71.5%) were White, 57 (22.5%) were Asian, one (0.4%) was Black or African American and the remainder of patients where categorized as "other", "not reported" or "missing". A PMC will be issued with this application to obtain additional safety and efficacy data with zanubrutinib in racial and ethnic minorities with WM.

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.

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Reference ID: 4850271

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:

See Section 8.2 for discussion of the occurrence of second primary malignancies in Study BGB-3111-302 and in the overall pooled zanubrutinib safety population.

Human Reproduction and Pregnancy

Data:

No new information is provided in the current submission

The Applicant's Position:

Not applicable

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that this is not applicable. The USPI includes a Warning and Precaution for embryo-fetal toxicity.

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 FDA agrees that this is not applicable.

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.

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Reference ID: 4850271

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 FDA agrees with the Applicant's assessment.

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 02 June 2020, BRUKINSA 80 mg was approved in China for the treatment of adult patients with MCL who have received at least one prior therapy, and for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy.

Cumulatively, as of 13 November 2020, approximately (b) (4) capsules of zanubrutinib have been supplied to the market worldwide (equivalent to (b) (4) daily doses based on the recommended daily dose of four 80 mg capsules per day; 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 FDA agrees with the Applicant's statement that there are no safety-related issues arising from post-marketing data that need to be addressed in the current product labeling.

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.

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Reference ID: 4850271

The FDA's Assessment:
The FDA agrees that the safety information collected in the post-market setting is expected to be consistent with the safety profile of zanubrutinib observed in clinical trials.

8.2.11. Integrated Assessment of Safety

Data:
The safety profile of zanubrutinib in patients with WM and other B-cell malignancies is derived from 6 clinical studies involving 877 patients, including 779 patients treated with zanubrutinib and 98 patients treated with ibrutinib. Approximately 98% of zanubrutinib-treated patients in these studies received the approved dose of 320 mg, either once a day (n = 105, 13.5%) or as 160 mg twice a day (n = 662, 85.0%). Among 779 patients receiving zanubrutinib, 55% were exposed for 24 months or longer and 16% were exposed for 36 months or longer, including 43 patients exposed for 48 months or longer. Patients included in the safety summary and analyses are for the most part representative of the general WM and B-cell malignancy patient populations. Key exceptions include the lower proportion of black patients exposed to zanubrutinib (0.6%) and exclusion of patients with severe renal or hepatic impairment. **All Zanubrutinib** group were male; 53.5% of patients were white and 41.3% were Asian.
Zanubrutinib was generally well tolerated across all patient groups, and the overall safety profile was consistent across patient groups.
The most common adverse reactions in > 20% of patients who received zanubrutinib were neutrophil count decreased (56%), platelet count decreased (44%), upper respiratory tract infection (40%), hemoglobin decreased (28%), rash (27%), bruising (25%), diarrhea (23%), pneumonia (21%) and cough (21%).

Adverse Events of Interest
Predefined adverse events of special interest based on the types of events known to be associated with the class of BTK inhibitors are described below. Important differences in the incidence of toxicities between zanubrutinib and ibrutinib are noted.
In the **All Zanubrutinib** group, 718 (92.2%) patients reported at least 1 adverse event of special interest. Events within the categories of infections (75.7%), haemorrhage (54.9%), and neutropenia (35.6%) were reported most frequently. Events that met the criteria for seriousness and/or were ≥ Grade 3 were reported in 248 (31.8%) and 425 (54.6%) patients, respectively

Hemorrhage/Major Hemorrhage
In **Study BGB-3111-302 Cohort 1**, the incidence of haemorrhage of any grade was higher among ibrutinib-treated patients compared with zanubrutinib-treated patients (59, [60.2%] versus 53 [52.5%] patients, respectively).

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Reference ID: 4850271

In the All Zanubrutinib group, 428 patients (54.9%) had at least 1 occurrence of haemorrhage. The most frequently reported events were petechiae, purpura, and/or contusion (31.7%) and haematuria (14.0%).
In **Study BGB-3111-302 Cohort 1**, major haemorrhage was reported in 10 (10.2%) ibrutinib-treated patients compared with 6 (5.9%) zanubrutinib-treated patients
In the **All Zanubrutinib** group, 31 patients (4.0%) reported at least 1 occurrence of major haemorrhage . The most frequently reported events were haematuria (4 patients), gastrointestinal haemorrhage, purpura, and upper gastrointestinal haemorrhage (in 3 patients each), and intracranial haemorrhage, haemothorax, periorbital haematoma, and subdural haemorrhage (in 2 patients each).

Atrial Fibrillation/Flutter
Ibrutinib was associated with a higher incidence of atrial fibrillation/flutter than zanubrutinib.
In **Study BGB-3111-302, Cohort 1**, ibrutinib-treated patients had a more than 5-fold higher incidence of treatment-emergent atrial fibrillation/flutter than zanubrutinib-treated patients on an exposure-adjusted basis (0.90 and 0.17 persons/100 person-months for ibrutinib and zanubrutinib, respectively). The incidence of all grade atrial fibrillation in ibrutinib-treated patients was generally consistent with prior experience in patients with WM (Gustine et al 2016; Treon et al 2017; Dimopoulos et al 2017). Neither age nor a history of atrial fibrillation/flutter were confounding variables for the observed difference in atrial fibrillation between arms, and risk factors for atrial fibrillation were balanced across the ibrutinib and zanubrutinib arms in Cohort 1.
In the **All Zanubrutinib** group, 22 patients (2.8%) reported at least 1 occurrence of atrial fibrillation /flutter. A majority of patients with atrial fibrillation/flutter had known risk factors including a prior history of atrial fibrillation, hypertension, pre-existing cardiovascular disease, or concurrent infection. Serious and ≥ Grade 3 events were reported in 5 and 6 patients, respectively.

Hypertension
Ibrutinib was associated with a higher incidence of hypertension adverse events compared with zanubrutinib in **Study BGB-3111-302, Cohort 1**, (20.4% and 13.9%, respectively).In the **All Zanubrutinib** group, 95 (12.2%) patients reported at least 1 occurrence of treatment emergent hypertension. Serious and ≥ Grade 3 events were reported in 3 (0.4%) and 41 (5.3%) patients, respectively.

In the **All Zanubrutinib** group, the overall incidence of all grade and ≥ Grade 3 hypertension was consistent with the larger data pool. Likewise, the rates were comparable across other zanubrutinib data pools.

Second primary malignancies and infections
In **Study BGB-3111-302, Cohort 1**, second primary malignancies and infections were reported at comparable rates among ibrutinib- and zanubrutinib-treated patients. In the **All Zanubrutinib**

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Reference ID: 4850271

group, 102 (13.1%) patients reported second primary malignancies. Consistent with prior experience, the most frequently reported events were in the subcategory of skin cancers (8.9%), and included basal skin carcinomas (4.7%), squamous cell carcinomas of the skin (3.1%), and malignant melanoma (1.0%); all other events were reported in < 1% of patients.

Tumor Lysis Syndrome
In **Study BGB-3111-302 Cohort 1**, no occurrences of tumour lysis syndrome were reported in either treatment arm. A total of three patients reported tumour lysis syndrome (Study BGB3111-AU-003); none had WM.

Peripheral Blood Cytopenias
Neutropenia was the most common cytopenia adverse event reported across all integrated analysis subsets, and Grade 3 or higher neutropenia was relatively common. The events were typically nonserious and effectively managed without significant compromise to the study treatment regimen. In **Study BGB-3111-302, Cohort 1**, neutropenia of all grades and of Grade 3 or higher was reported more commonly among zanubrutinib than ibrutinib recipients. Febrile neutropenia was less common. The higher incidence of ≥ Grade 3 neutropenia did not result in a higher infection incidence for zanubrutinib recipients, and the incidence of pneumonia was notably higher among ibrutinib- than zanubrutinib-treated patients. Results were consistent in the **All Zanubrutinib** group.

The rate of anaemia and thrombocytopenia adverse events was comparable between the ibrutinib and zanubrutinib groups in **Study BGB-3111-302, Cohort 1.**

Quality of Life
It is notable that the favorable safety findings with zanubrutinib were accompanied by improvements in daily life, including both overall testing as well as symptom-scale scores. Both BTK inhibitors improved most quality-of-life measures over baseline; however, in most assessments, zanubrutinib trended toward greater improvement even when disease is controlled to a similar extent (ie, patients with VGPR).

<u>The Applicant's Position:</u>
The zanubrutinib project began with the hypothesis that pharmacologic improvements could be made upon ibrutinib that would result in better clinical efficacy and safety, and the safety data in this submission support that hypothesis. Zanubrutinib treatment was generally well tolerated in all patient groups and the safety profile was consistent across patient groups. The spectrum of adverse events observed across all patient groups is consistent with the known toxicity profile for the BTK inhibitor class as well as those intrinsic to B-cell malignancy patient populations; these could be readily monitored with conventional safety assessments, were manageable, and for the most part, were reversible. For toxicities such as diarrhoea and cardiovascular adverse events, including atrial fibrillation/flutter and hypertension, the incidence among zanubrutinib-treated patients appears appreciably lower than for the first

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Reference ID: 4850271

generation and less selective BTK inhibitor, ibrutinib. The comprehensive analysis of adverse events reported herein did not reveal any new or unanticipated safety signals. The improved safety profile predicted from its pharmacokinetic and pharmacodynamic profiles, as well as from its superior selectivity, is corroborated by results from Study BGB-3111-302 as well as all available safety data. The favorable safety findings with zanubrutinib were accompanied by improvements in daily life, with greater improvements seen overall for zanubrutinib over ibrutinib even when disease is controlled to a similar extent.

Taken together these results demonstrate that zanubrutinib offers the potential for improved safety and tolerability and an improved benefit versus risk profile over existing treatment options for patients with WM.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the studies that were used to determine the safety profile of zanubrutinib in patients with WM and other B-cell malignancies. The pooled safety database includes 779 patients treated with zanubrutinib. With this application, the FDA conducted safety analyses using the pooled population of patients who have received zanubrutinib (n=779). Based on the FDA's analysis, the most common adverse reactions, including laboratory abnormalities, in ≥ 20% of patients who received zanubrutinib were neutrophil count decreased (56%), upper respiratory tract infection (49%), platelet count decreased (44%), rash (35%), hemorrhage (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), bruising (25%), diarrhea (23%), pneumonia (22%), and cough (21%). The USPI was updated accordingly.

The FDA agrees with the Applicant's selection of predefined adverse events of special interest based on previous studies with zanubrutinib and BTK inhibitors. See Section 8.2 for additional discussion of the adverse events of special interest that occurred in Study BGB-3111-302.

The FDA does not agree with the Applicant's conclusions regarding quality-of-life assessments including the Applicant's statement, "in most assessments, zanubrutinib trended toward greater improvement even when disease is controlled to a similar extent". This statement is overly generalized and promotional. See Section 8.1 for additional discussion of the exploratory COA (PRO) endpoints.

The FDA does not agree with the Applicant's statement, "zanubrutinib treatment was generally well tolerated". This is subjective and overly broad. Nearly all patients treated with zanubrutinib, experience an adverse event.

The FDA also does not agree with the Applicant's conclusion that states, "The improved safety profile predicted from its pharmacokinetic and pharmacodynamic profiles, as well as from its superior selectivity, is corroborated by results from Study BGB-3111-302 as well as all available

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Reference ID: 4850271

safety data. The favorable safety findings with zanubrutinib were accompanied by improvements in daily life, with greater improvements seen overall for zanubrutinib over ibrutinib even when disease is controlled to a similar extent." In Study BGB-3111-302, nearly all patients in both treatment arms experienced a treatment-related adverse event. While there were slightly fewer patients who experienced serious adverse events in the zanubrutinib arm (44% vs. 47%), and slightly fewer patients with Grade 3 or higher treatment-emergent adverse events (64% vs. 67%), overall the differences were small. In addition, while some adverse events did occur in fewer patients who were treated with zanubrutinib compared to those treated with ibrutinib (i.e. bruising, diarrhea, muscle spasms, pneumonia and atrial fibrillation) , several adverse events occurred more frequently with zanubrutinib (i.e, musculoskeletal pain, neutropenia, fatigue, dyspnea and constipation). Taken together, the Applicant's statement regarding the improved safety profile of zanubrutinib is broad, not accurate and is misleading.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The primary study to support the evaluation of efficacy is BGB-3111-302 ASPEN. The ASPEN study is an ongoing, Phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of zanubrutinib and ibrutinib in patients with WM who required therapy according to the consensus panel criteria from the 6th International Workshop on Waldenström's Macroglobulinemia (IWWM-6). The primary efficacy endpoint was proportion superior CR + VGPR as determined by the IRC using an adaptation of the response criteria updated at the Sixth IWWM in the RR population. The following statistical caveats should be considered in interpreting the clinical efficacy of zanubrutinib in patients with WM:

Cohort 1:

- The study did not meet the primary endpoint of superiority of VGPR/CR rate in the RR patient population. As of the data cutoff of August 31, 2019, the rate of CR+VGPR in the zanubrutinib and ibrutinib arms were 28.9% and 19.8%, respectively, for the relapsed/refractory patient population by IRC assessment. Using stratified CMH method, the risk difference was 10.7 with 95% CI of (-2.5, 23.9), with a p-value of 0.116. As a result, all subsequent sequential hypothesis tests and associated p-values are descriptive only.
- As of the data cutoff of August 31, 2019, the major response rates (PR or better) for the relapsed/refractory analysis set by IRC at the time of primary efficacy analysis were generally comparable between the zanubrutinib and ibrutinib arms (78.3%, 80.2% respectively), with a slightly higher response rate in the ibrutinib arm. The result did not demonstrate non-inferiority with the margin of -8%.

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Reference ID: 4850271

- The major response rate in the ITT analysis set by IRC at the time of primary efficacy analysis were generally comparable between the zanubrutinib and ibrutinib arms (77.5%, 77.8% respectively). However, no comparative claims can be made as the study failed the primary endpoint.
- The Applicant's primary efficacy analysis set (all endpoints) was based on the relapsed refractory analysis set, a subset of the ITT analysis set. However, the FDAs analysis and the USPI was based on the ITT population including 18% treatment naïve patients.
- The number of patients within the subgroups were small, with only 19 US patients, and in general the estimates are unstable for small sample size. Therefore, the results should be interpreted with caution.
- The Applicant originally proposed (b) (4) The efficacy results based on pre-specified data cutoff will be included in the label.
- The interpretability of results of PRO endpoints are limited by the sample size, study design and completion rate. The study was neither designed nor powered to assess these endpoints. In addition, the ASPEN study is open-label study, PROs in the context of open-label studies are difficult to interpret because unlike objective endpoints, they are based on patient assessment which can depend on knowledge of the treatment assignment. Missing data could also prevent the interpretation of the results. Therefore, the results from these PROs analyses should be considered as exploratory.

Cohort 2:

Cohort 2 study was a single arm exploratory study. The study enrolled patients with MYD88 wildtype (*MYD88^{WT}*) or MYD88 mutation unknown WM (N = 26 and 2, respectively) and received BRUKINSA 160 mg twice daily. In Cohort 2, MRR as assessed by IRC was 50% (13 out of 26 response evaluable patients). Given the small sample size of the study and descriptive nature of the analysis, caution should be taken for the interpretation of the results for Cohort 2.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the totality of the evidence and the favorable benefit-risk profile of zanubrutinib, the clinical and statistical reviewers recommend regular approval for the following indication:

BRUKINSA is indicated for the treatment of adult patients with Waldenström's Macroglobulinemia (WM).

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X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

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9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
Not applicable.

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10 Pediatrics

The Applicant's Position:
Reasons for Requesting Waiver
Zanubrutinib was granted orphan drug designation (ODD) status by the FDA for the treatment of Waldenström's macroglobulinemia (WM) on 29 June 2016 (#16-5276).
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 claims to be exempt from this requirement.
Applicant Certification
Because zanubrutinib drug product was granted orphan drug designation (#16-5276) for this indication (WM), BeiGene claims to be exempt from this requirement.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Zanubrutinib has orphan drug status for the treatment of Waldenström's macroglobulinemia (Orphan Drug Designation #16-5276, granted June 29, 2016). Because zanubrutinib has orphan drug designation for this indication, it is exempt from PREA requirements. The Applicant submitted a Request for Waiver of Pediatric Studies with this application.

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11 Labeling Recommendations

Data: The table below summarizes changes to the proposed United States Prescribing Information (USPI). See the final approved USPI for BRUKINSA (zanubrutinib) accompanying the approval letter for more information.

FDA Table 26 Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling Labeling**	**FDA's proposed**
1 Indication and Usage	BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).	FDA agrees.
2 Dosage and Administration	N/A	Dosage modifications for adverse reactions table reformatted to present dosage modifications for nonhematologic toxicities separately from hematologic toxicities. A qualifier was added as a footnote advising prescribers to evaluate the benefit: risk of zanubrutinib before resuming treatment for a grade 4 nonhematologic toxicity.
5 Warnings and Precautions (W&P)	W&P updated to include safety data from the WM safety population.	FDA generally agrees but updated W&P 5.1 to describe "hemorrhage" (b) (4) [redacted] W&P 5.4 updated to describe that malignancies reported other than non-melanoma skin cancer include melanoma, solid tumors, and hematologic malignancies.
6 Adverse Reactions	Updated with data from ASPEN	This section was updated based on current labeling practices for presentation of

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Reference ID: 4850271

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling Labeling**	**FDA's proposed**
		adverse reaction data, including the adverse reactions table which reflects adverse reactions occurring in ≥ 10% in the investigational arm and in the laboratory abnormalities table in 20% in the investigational arm. Because some adverse reactions observed in the investigational arm and control arm are due to similar pharmacologic class or mechanism of action, omission of adverse reactions in the investigational arm that occur at a lower rate compared to the control arm may obscure the description of the adverse reactions observed in the investigational arm.
12.3 Clinical Pharmacology Specific Populations	Updated pharmacokinetic numbers.	Based on clinical pharmacology review of data submitted with this supplement, severe renal impairment has no clinically significant effect on zanubrutinib and the label was updated to reflect this.
14 Clinical Studies	14.2 Waldenström's Macroglobulinemia (b) (4)	Major efficacy endpoint presented in the results table for Cohort 1 is ORR, defined as CR+VGPR+PR as assessed by IRC based on response criteria from the IWWM-6.

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Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling Labeling**	**FDA's proposed**
		DOR was an additional efficacy endpoint. FDA agreed to include data in the efficacy table based on modified IWWM-6 criteria alongside the standard IWWM-6 criteria. Race/ethnicity data added per FDA guidance Collection of Race and Ethnicity Data in Clinical Trials FDA does not agree with (b) (4)

The Applicant's Position:
The USPI has been updated to include the WM indication and (Indication and 14.2). Warning and Precautions was updated with the new Patient pool.

The FDA's Assessment:
The FDA modified sections of the USPI as described in the table above.

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
Not applicable.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following clinical PMR will be required:

1. Conduct an integrated safety analysis of patients with lymphoid malignancies and Waldenström's Macroglobulinemia enrolled in clinical trials and from post-marketing reports to further characterize the risk of second primary malignancies with extended follow-up in patients receiving zanubrutinib. Submit interim reports after 2 years and 3 years containing cumulative safety updates. Include incidence rates, time to onset, predisposing factors including coexisting mutations and outcomes in the interim and final reports.

The following clinical PMCs will be required:

1. Conduct a study to further characterize the clinical benefit and safety of zanubrutinib for the treatment of patients with newly diagnosed Waldenström's Macroglobulinemia with MYD88 mutation. This should include an assessment of the CXCR4 mutation status. In addition, the study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

2. Conduct a study to further characterize the clinical benefit and safety of zanubrutinib in patients with newly diagnosed and relapsed/refractory Waldenström's Macroglobulinemia with MYD88WT. This study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

3. Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of zanubrutinib in racial and ethnic minorities with Waldenström's Macroglobulinemia.

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14 Division Director (DHOT) (NME ONLY)

X

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15 Division Director (OCP)

X

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16 Division Director (OB)

X

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17 Division Director (Clinical)

X

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18 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 _____

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19 Appendices

19.1. References

The Applicant's References:

American Cancer Society website: Learn About Waldenstrom macroglobulinemia, http://www.cancer.org/cancer/waldenstrommacroglobulinemia/detailedguide/waldenstrommacroglobulinemia-key-statistics-w-m 2016. Accessed on 29 November 2020.

Anderson KC, Alsina M, Bensinger W, et al. Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma, version 2.2013. J Natl Compr Canc Netw. 2012;10:1211-9.

Castillo J, Moreno D, Arbelaez M, et al. CXCR4 mutations affect presentation and outcomes in patients with Waldenström macroglobulinemia: A systematic review. 2019. Expert Rev of Hematol.

Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood. 2014;124:1404-11.

Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. Lancet Oncol. 2017;18(2):241-50.

Dreyling M, Williams ME. Rare Lymphomas. Springer-Verlag Berlin Heidelberg. 2014.

Garcia-Sanz R. WM, MYD88, and CXCR4: following the thread. Blood. 2016;128(6):746-8.

Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. J Clin Oncol. 1993;11(5):914-20.

Gertz MA. Waldenström macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017;92(2):209-17.

Ghobrial IM, Gertz MA, Fonseca R. Waldenström macroglobulinaemia. Lancet Oncol. 2003;4(11):679-85.

Greenwood M. The natural duration of cancer. Reports of public health and medical subjects. H.M.S.O. 1926;33:iv-26.

Gustine JN, Meid K, Dubeau TE, et al. Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia. Am J Hematol. 2016;91:E312-3.

Gustine JN, Meid K, Dubeau TE, et al. Ibrutinib discontinuation in Waldenström macroglobulinemia: etiologies, outcomes, and IgM rebound. Am J Hematol. 2018;93:511-17.

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Reference ID: 4850271

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 (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood. 2008;111(12):5446-56.

Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;13;123:1637-46.

Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADPmediated platelet aggregation. Leukaemia. 2015;29(4):783-7.

Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol. 2017;3(9):1257-1265.

Kastritis E, Leblond V, Dimopoulos MA, et al. Waldenström's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv270.

Leblond V, Kastritis E, Advani R, et al. Treatment Recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia. Blood. 2016;128:1321-28.

Leukemia and Lymphoma Society. Waldenström macroglobulinemia. No. 20. https://www.lls.org/sites/default/files/file_assets/FS20_Waldenstrom_2018_FINAL.pdf. Accessed 13 July 2020.

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.

Mantel N, Haenszel W. Statistical aspects of analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-48.

Moreau P, Attal M, Pégourié B, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood. 2011;117(11): 3041–4.

National Comprehensive Cancer Network Guidelines (NCCN). NCCN Clinical Practice Guidelines in Oncology. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 2.2020.
https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/ph ysician_gls/pdf/waldenstroms.pdf. Accessed 13 July 2020.

National Comprehensive Cancer Network Guidelines, Lymphoplasmacytic Lymphoma/ Waldenström's Macroglobulinemia 2015: v2.

Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinemia: Update from the VIth International Workshop. Br J Haematol. 2013;160(2):171-6.

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

Reference ID: 4850271

Paludo J, Abeykoon J, Gertz M, et al. Depth of response in Waldenström macroblobulinemia. Poster presented at: International Workshop on Waldenström's Macroblogulinemia; October 12, 2018; New York, NY.

RITUXAN/RUXIENCE (rituximab) [Product Monograph]. Mississauga, Ontario. Hoffmann-La Roche Ltd; 2019.

Sato T. On the variance estimator of the Mantel-Haenszel risk difference. Biometrics. 1989;45:1323-24.

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(11):851-9.

Tang CPS, McMullen J, Tam C. Cardiac side effects of Bruton tyrosine kinase (BTK) inhibitors. Leuk Lymphoma. 2018;59(7):1554-64.

Treon SP, Castillo JJ. What should be the goal of therapy for Waldenström macroglobulinemia patients? Complete response should be the goal of therapy. Blood Adv. 2017;1: 2486–90.

Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. J Clin Oncol. 2018;36(27):2755-61.

Treon SP, Meid K, Gustine J. Yang G, Xu L, Liu X, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenström macroglobulinemia. J Clin Oncol 2020a:38.

Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015a;372:1430-40.

Treon SP, Xu L, Guerrera ML, et al. Genomic landscape of Waldenström macroglobulinemia and its impact on treatment strategies. J Clin Oncol. 2020b;38:1198-1208.

Treon SP, Xu L, Hunter Z. MYD88 Mutations and Response to Ibrutinib in Waldenström's Macroglobulinemia. N Engl J Med. 2015b;73:584-5.

Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367:826-33.

Treon SP, Yang G, Hanzis C, et al. Attainment of complete/very good partial response following rituximab-based therapy is an important determinant to progression-free survival and is impacted by polymorphisms in FCGR3A in Waldenström macroglobulinaemia. Br J Haematol. 2011;154:223-8.

Treon SP. How I treat Waldenström macroglobulinemia. Blood. 2015c;126(6):721-32.

Trotman J, Opat S, Gottlieb D, et al. Zanabrutinib for the treatment of patients with Waldenstrom macroglobulinemia: 3 years of follow-up. Blood. 2020;136(18):2027-2037.

Varettoni M, Zibellini S, Defrancesco I, et al. Pattern of somatic mutations in patients with Waldenström macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica. 2017;102:2077-85.

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Reference ID: 4850271

Weber D, Treon SP, Emmanouilides C, et al. Uniform response criteria in Waldenstrom's macroglobulinemia: Consensus panel recommendations from the second international workshop on Waldenstrom's macroglobulinemia. 2003;30(2):127-31.

Zheng YH, Xu L, Cao C, et al. Rituximab-based combination therapy in patients with Waldenström macroglobulinemia: a systematic review and meta-analysis. Onco Targets Ther. 2019;12:2751-66.

The FDA's References:

Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood. 2014;124:1404-11.

Sekhar J, Sanfilippo K, Zhang Q, Trinkaus K, Vij R, Morgensztern D. Waldenstrom macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. Leukemia Lymphoma. 2012; 53(8):1265-1626.

Castillo JJ, Gustine JN, Meid K, Dubeau TE, Severns P, Xu L, Yang G, Hunter Z, Treon SP. Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenstrom macroglobulinaemia. Br J Haematol. 2018; 181(1):77-85.

Kaiser LM, Hunter ZR, Treon SP, Busked C. CXCR4 in Waldenström's Macroglobulinema: chances and challenges. Leukemia. 2021 Feb;35(2):333-45.

Wang Y, Gali VL, Xu-Monette ZY, Sano D, Thomas SK, Weber DM, Zhu F, Fang X, Deng M, Zhang M, Hagemeister FB. Molecular and genetic biomarkers implemented from next-generation sequencing provide treatment insights in clinical practice for Waldenström macroglobulinemia. Neoplasia. 2021 Apr 1;23(4):361-74.

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Reference ID: 4850271

19.2. Financial Disclosure

The Applicant's Position:
Financial disclosure are included in section m.1.3.4

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

Covered Clinical Study (Name and/or Number):* BGB-3111-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 755		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
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)

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Reference ID: 4850271

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
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.

19.3. Nonclinical Pharmacology/Toxicology

Data:
No new information is provided in the current submission

The Applicant's Position:
N/AP

The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Pharmacometrics Review

19.4.1.1. Applicant's Population Pharmacokinetics Analysis

Objectives: To update the previous population pharmacokinetic (PPK) model of zanubrutinib and to estimate typical values and inter-subject variability of pharmacokinetic (PK) parameters in healthy subjects and cancer patients. To determine the effects of demographic, pathophysiologic, and disease-related covariates on the PK of zanubrutinib to better understand clinical factors that might affect exposure in individual subjects.

Data: This PPK analysis evaluated data from 9 clinical studies listed in **FDA Table 26**.

FDA Table 27: Summary of Studies Included in the PPK Analysis		
Study (Region)	**Title**	**Dose & Data Type**
BGB-3111-AU-003 (Global)	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 mg, 80 mg, 160 mg, and 320 mg QD 160 mg BID. Data cut on 04 Nov 2019
BGB-3111-1002 (China)	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. Data cut on 14 Dec 2017

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Reference ID: 4850271

BGB-3111-205 (China)	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 data cut on 15 Jun. 2018
BGB-3111-206 (China)	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 data cut on 27 Mar. 2018
BGB-3111-103 (Australia)	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 PPK and food effect
BGB-3111-104 (USA)	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 (USA)	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 (USA)	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 mg, 480 mg. PK and QTc
BGB-3111-302 (Global)	A Phase 3 Study Comparing BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)	160 mg BID. Sparse PK data cut on 09 Dec. 2019
Source: Table 2 of Applicant's PPK analysis report		

Methods: Measurement of zanubrutinib concentrations in plasma were performed using a validated high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) assay with a lower limit of quantitation (LLOQ) of 1 ng/mL. The final PPK model was developed from a dataset of 4,925 observed plasma concentrations from 632 subjects enrolled in 9 clinical studies to quantitatively describe the clinical PK of zanubrutinib and identify sources of interindividual variability. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4.0 (ICON, Maryland) was used for the PPK analysis. Inter-occasion variability (IOV) represented the variability between occasions (OCC, defined as different scheduled visits and associated dose/sampling times). OCC=1 represented time <7 days and OCC=2 for time ≥7 days.

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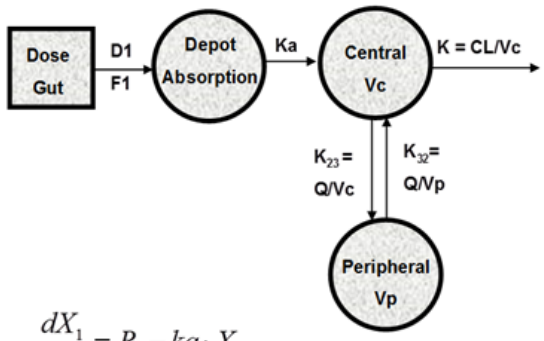
The impact of baseline age, body weight, sex, race (Caucasian, Asian, and Other), creatinine clearance (CRCL), bilirubin (BIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), tumor type (TUMTP, mantle cell lymphoma [MCL], chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL], Waldenström's macroglobulinemia [WM], and other B-cell malignancies), health status (healthy volunteers [HV] or patients with B-cell malignancies), and use of acid-reducing agents (proton-pump inhibitors [PPI], H2-Receptor Antagonists [H2RA) on the PK of zanubrutinib were investigated. Covariates were selected using a forward addition and backward elimination method (based on the significance levels of $p<0.01$ and $p<0.001$, respectively).

Results: The PK of zanubrutinib in the dose range (20 mg - 320 mg) tested was best described by a two-compartment model with first-order elimination from the central compartment and redistribution from the peripheral compartment. Zanubrutinib absorption was characterized using sequential zero-order (D1) then first-order (ka) absorption rate constant. as illustrated in **FDA Figure 4**. The PPK model was parameterized in terms of apparent oral clearance (CL/F), apparent volume of the central compartment (Vc/F), apparent clearance of distribution from the central to the peripheral compartment (Q/F), apparent volume of the peripheral compartment (Vp/F), absorption rate constant (ka), and the duration (D1).
The final PPK model was developed by incorporating the effect of relevant covariates on key structural model parameters of the base model. Covariates were selected based on statistical evaluation, clinical judgment, mechanistic plausibility and prior knowledge. The following statistically significant parameter-covariate relationships were identified as:

$$CL_i(L/hr) = \exp(5.13 \text{ if patient, } 4.77 \text{ if HV} - 0.189 \times \log(ALT/18) + \eta_{CL,i})$$

FDA Figure 4: PPK model diagram for zanubrutinib



$$\frac{dX_1}{dt} = R_1 - ka \cdot X_1$$

$$\frac{dX_2}{dt} = ka \cdot X_1 - (k + k_{23}) \cdot X_2 + k_{32} \cdot X_3$$

$$\frac{dX_3}{dt} = k_{23} \cdot X_2 - k_{32} \cdot X_3$$

D1 = duration for depot compartment
F1 = bioavailability
R1 = rate for depot compartment = Dose/D1
Ka = absorption rate constant
K = elimination rate constant
K_{23} = rate constant from central to peripheral
K_{32} = rate constant from peripheral to central
CL = clearance
Q = inter-compartmental clearance
Vc = central volume
Vp = peripheral volume
X1= the quantity of drug in the absorption compartment
X2 = the quantity of drug in the central compartment
X3 = the quantity of drug in the peripheral compartment
t = time

Source: Figure 1 of Applicant's PPK report

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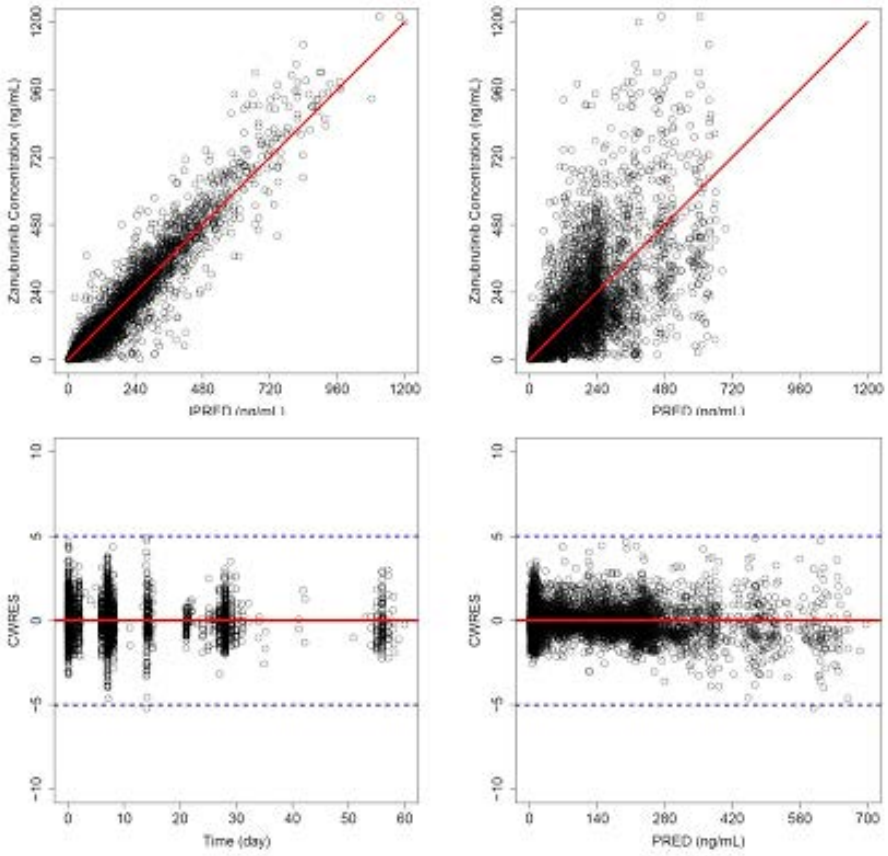
Reference ID: 4850271

The goodness-of-fit plots for the final PPK model are presented in **FDA Figure 5**.

FDA Figure 5: Goodness-of-fit of final PPK model for zanubrutinib



Source: Figures 4 and 5 of Applicant's PPK model

FDA Table 28: Key PK parameters and covariate effects for representative subjects

PK Parameters and Baseline Covariates		Estimate	Change from Typical
Typical CL/F (L/hr, ALT=18 U/L, patient)		170	—
ALT (U/L) on CL/F	10^{th} percentile (10	190	+11.8%
	90^{th} percentile (37	148	-12.8%
Health status on	HV	118	-30.4%
Typical V_c/F (L, patient)		112	—
Typical Q/F (L/hr)		26.5	—
Typical V_p/F (L)		345	—
Typical k_a (hr^{-1})		0.526	—
Typical D_1 (hr)		1.13	—

Source: Table 1 of Applicant's PPK report

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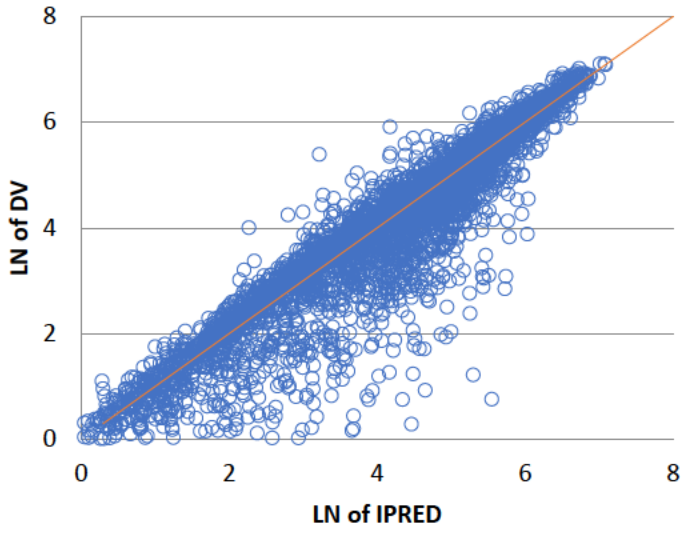
Reference ID: 4850271

Baseline ALT and health status were identified as significant covariates on CL/F. For a typical patient with ALT of 18 U/L, the estimated CL/F was 170 L/hr, Vc/F was 112 L, Q/F was 26.5 L/hr, Vp/F was 345 L, ka was 0.526 hr^{-1}, and D1 was 1.13 hr. Interindividual variability on CL/F, Vc/F, Vp/F, Q/F, and D1 were 36.7%, 37.1%, 102%, 86.4%, and 62.3%, respectively. A summary of key PPK parameters and covariate effects is presented in **Table 28**. The geometric mean elimination half-life was 3.44 hours with a CV of 40.0%. Other covariates, including baseline age, body weight, AST, BIL, CRCL, sex, tumor type, and use of acid-reducing agents did not show statistically significant impact on the PK of zanubrutinib.

***FDA's Comment on Applicant's PPK analysis*:** *The Applicant's PPK model reasonably captured the observed zanubrutinib concentration data in general. However, the rationale for including zero-order transition of zanubrutinib from depot to the absorption site and the time-dependent inter-occasion variability (IOV) were not provided in the report. These may have contributed to over-prediction for some observations in the zanubrutinib concentration range of 1-100 (e^0-$e^{4.6}$) ng/mL (**FDA Figure 6**). These issues can be visualized in GOF plots in natural log scale for Applicant's final PPK model as represented by **FDA Figure 6**. Therefore, the reviewer conducted independent analysis by evaluating an alternative absorption model: first-order transition from depot to the absorption site without time-dependent IOV. See details of reviewer's analysis in **Section 19.4.1.3**.*

FDA Figure 6: Goodness-of-fit plots in log scale for applicant's final PPK model



Source: FDA Clinical Pharmacology Reviewer's analysis

19.4.1.2. Applicant's Exposure-Response Analysis

OBJECTIVES: To explore whether there is an exposure-response (ER) relationship between zanubrutinib exposure metrics (model predicted steady-state trough concentration $C_{min,ss}$, maximal concentration $C_{max,ss}$ and area under the curve $AUC_{0-24,ss}$) and efficacy endpoints

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Reference ID: 4850271

including complete response (CR) or very good partial response (VGPR) rate, major response rate (MRR), and objective response rate (ORR) in patients with Waldenström's macroglobulinemia (WM) from the pivotal Phase 3 study BGB-3111-302 and study BGB-3111-AU-003.
To explore whether there is an E-R relationship between zanubrutinib exposure metrics (model predicted Cmin,ss, Cmax,ss and AUC0-24,ss) and adverse event (AE) of interests safety endpoints (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) using data collected from BGB-3111-1002, BGB-3111-205, BGB- 3111-206, BGB-3111-302 and BGB-3111-AU-003 studies.

DATA: The PPK model-predicted exposure metrics at steady state ($AUC_{0-24,ss}$, $C_{max,ss}$ and $C_{min,ss}$) from Section **Error! Reference source not found.** were computed and merged into the efficacy and safety datasets for E-R analysis.
The efficacy endpoints analyzed in the report were CR/VGPR, MRR (CR + VGPR + partial response [PR]), and ORR (CR + VGPR + PR + minor response [MR]). This E-R analysis for efficacy endpoints evaluated data obtained from study BGB-3111-302 based on independent review committee (IRC) assessment and pooled data from studies BGB-311-AU-003 and BGB- 3111-302 based on investigator assessment. For BGB-3111-302, all zanubrutinib treated subjects including both treatment naïve and relapsed/refractory WM in the efficacy evaluable set of Cohort 1 were included in the analysis. Subjects with MYD88WT WM (Cohort 2) were not included in the analysis.
The safety endpoints were grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections/infestations, grade ≥ 3 anemia, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events and any bleeding events. These endpoints were characterized by incidence only, and data from studies BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-302, and BGB-3111-AU-003 were used in the analysis.

METHOD: The E-R relationships for efficacy endpoints were explored based on the data from studies BGB-3111-AU-003 (N=62) and BGB-3111-302 (N=100). Patients with both efficacy data and PK data were included in the efficacy E-R analysis (N=162). The E-R relationships for safety endpoints were explored based on the data from five studies (BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-302 and BGB-3111-AU-003). The total number of patients with both safety data and PK measurement included in safety analysis was 542.
The final zanubrutinib population PK model predicted $AUC_{0-24,ss}$, $C_{max,ss}$ and $C_{min,ss}$ were used as PK endpoints in this E-R analysis. The model-predicted exposure metrics at steady state ($AUC_{0-24,ss}$, $C_{max,ss}$ and $C_{min,ss}$) were computed using the Bayesian *post-hoc* PK parameters following administration of zanubrutinib and merged into the efficacy and safety datasets for E-R analysis.
All efficacy and safety endpoints were binary responses (yes/no). Boxplots of exposures stratified by each endpoint were generated. The probability of response versus exposure in

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Reference ID: 4850271

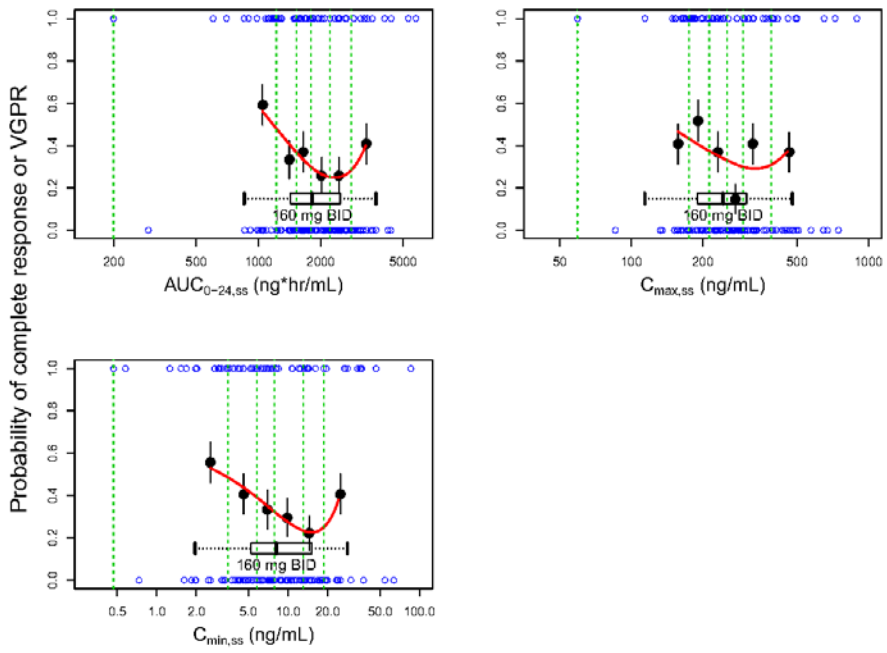
zanubrutinib treated patients were plotted, with probabilities calculated across sets of patients binned by exposure quantile. The E-R analysis was performed with R 3.6.1.

RESULTS

Exposure-Efficacy Results: For efficacy results (CR/VGPR, MRR and ORR) from investigator assessment, over a range of exposures observed in both responders and non-responders across the dose range of 40 mg to 320 mg (based on pooled data from studies BGB-3111-302 and BGB-3111-AU-003), the median $AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{min,ss}$ values were similar between responders and non-responders. The probability plots of CR/VGPR, MRR or ORR versus model-predicted exposures showed no apparent trend for $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0\text{-}24,ss}$ as shown in **FDA Figure 7** to **FDA Figure 9**. Similar results are obtained for these efficacy results from IRC.

Exposure-Safety Results: Based on data collected from BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-302, and BGB-3111-AU-003, no E-R relationship was observed between zanubrutinib exposure metrics (model predicted $AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{min,ss}$) and adverse event (AE) of interests or safety endpoints (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). Example relationship is shown in **FDA Figure 10**.

FDA Figure 7: Probability of CR/VGPR versus exposure for WM patients in studies BGB-3111-302 and BGB-3111-AU-003



Source: Figure 2 of Applicant's exposure-response analysis report

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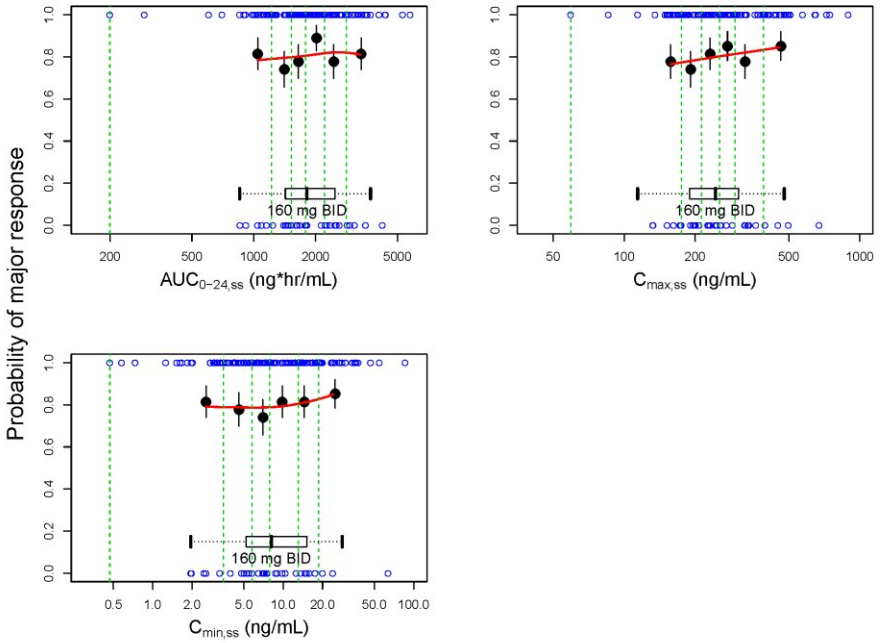
FDA Figure 8: Probability of major response versus exposure for WM patients in studies BGB-3111-302 and BGB-3111-AU-003



Source: Figure 4 of Applicant's exposure-response analysis report

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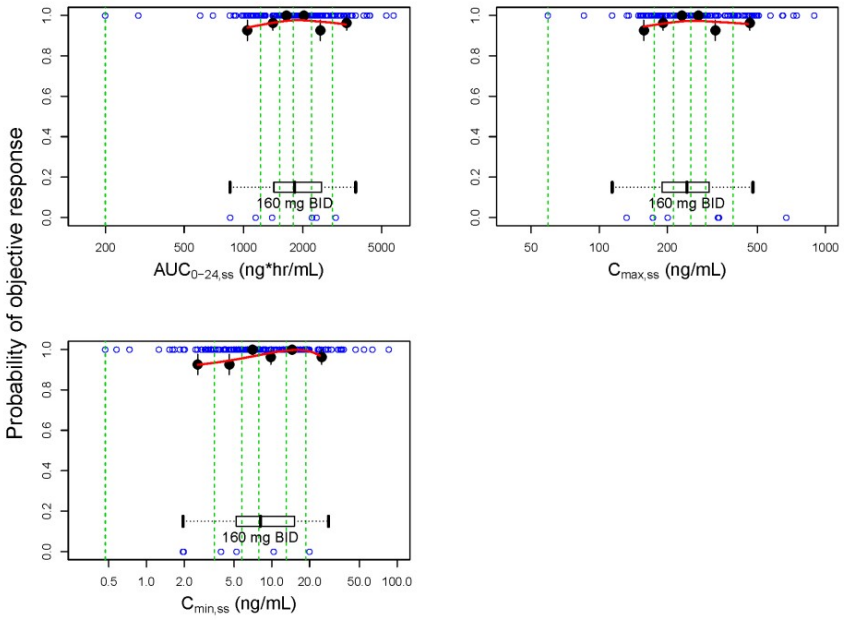
FDA Figure 9: Probability of Objective response versus exposure for WM patients in studies BGB-3111-302 and BGB-3111-AU-003



Source: Figure 6 of Applicant's exposure-response analysis report

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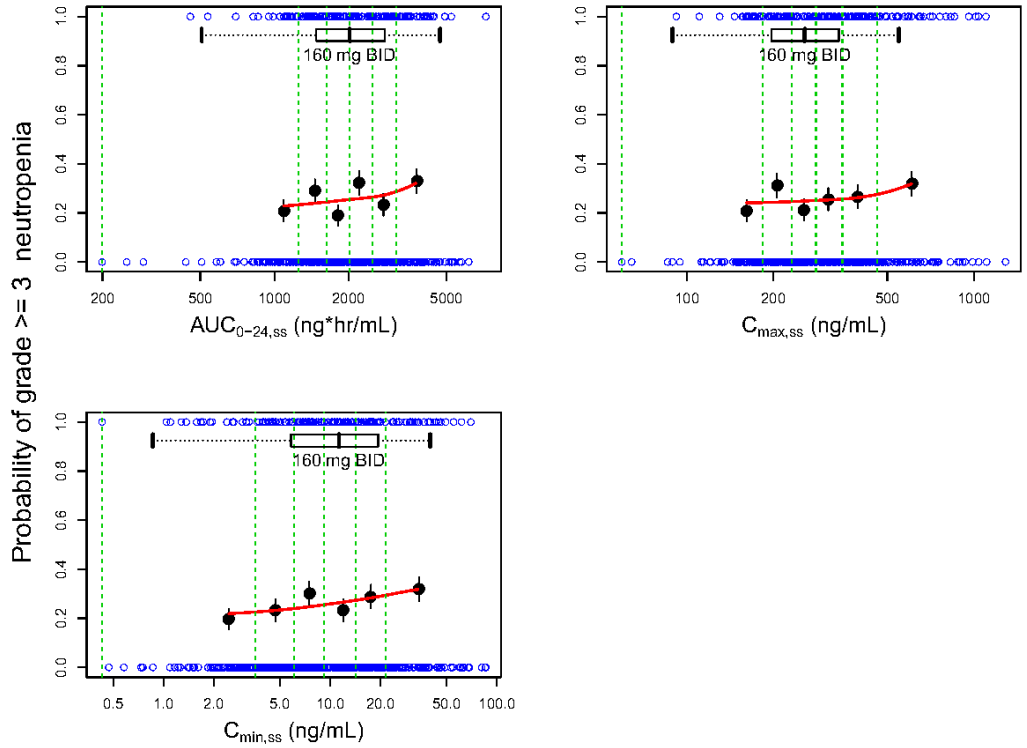
FDA Figure 10: Probability of grade ≥ 3 neutropenia versus steady state exposures



Source: Figures 14 of Applicant's exposure-response analysis report

FDA's Comment on Applicant's E-R analysis: *The Applicant's E-R analyses appear to support the proposed dosage regimen of 160 mg BID and 320 mg QD. Given the uncertainty in PK prediction described above, the reviewer conducted independent E-R analyses for efficacy and safety using data from Study BGB-3111-302.*

19.4.1.3. FDA Reviewer's Exploratory PPK Analysis

Background: The Applicant's final PPK model included zero-order transition of zanubrutinib from depot to the absorption site and the time-dependent inter-occasion variability (IOV). However, the rationale was not provided in the report.

Objectives:

- To evaluate an alternative absorption model, first-order transition of zanubrutinib from depot to the absorption site without time-dependent IOV and compare to the Applicant's final model.
- Use the updated PPK model to evaluate the effect of renal impairment (RI) on zanubrutinib clearance.

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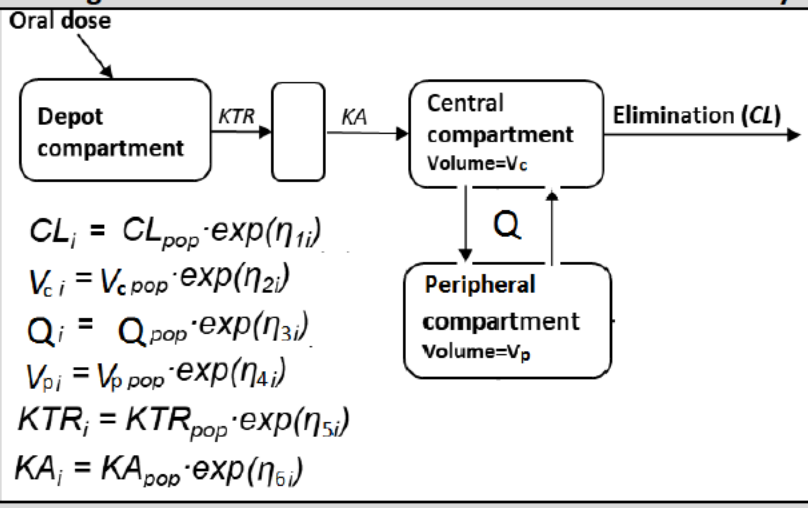
Method: Applicant's PPK dataset was fitted to a simplified PPK model by NONMEM v7.3 (Icon, Ellicott City, Maryland) and R v3.5.0 was used to generate analysis plots.

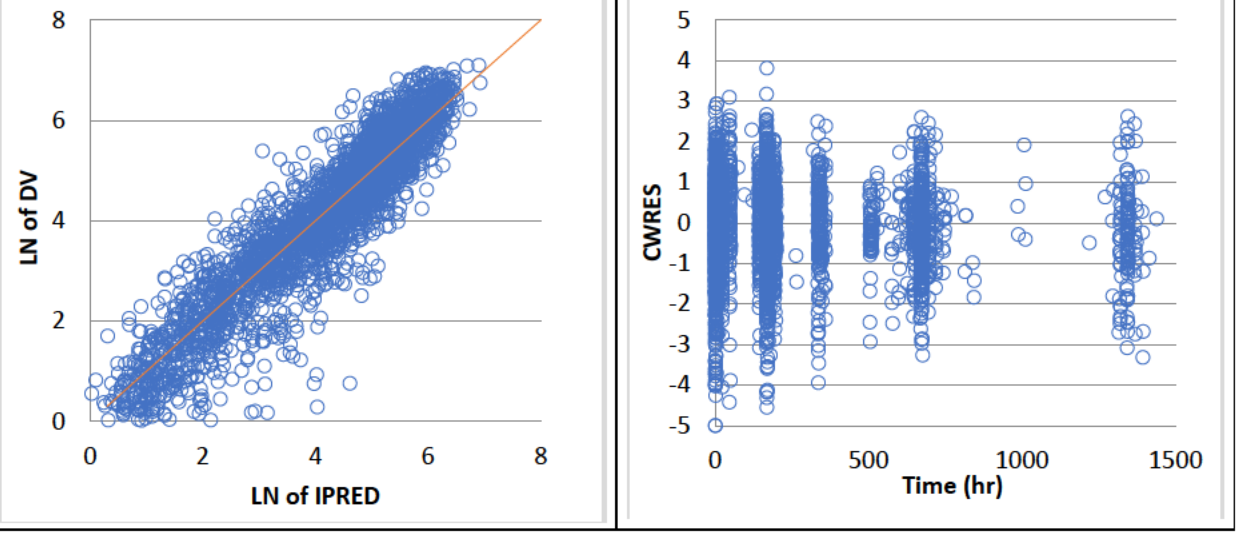
PPK Results: Two-compartment with one absorption transit compartment was found to be a stable base model in fitting the PPK data (**FDA Figure 11**). This FDA's base model resulted in reduction in objective function value (OBJV) of 2897 points from the Applicant's base model. After including the same covariates (patient vs HV, and baseline ALT level) for CL, the OBJV of the FDA's final model further reduced to 37726, which is 5994 points lower compared to Applicant's final model. The GOF plots of FDA's final model suggest improved fitting as shown in **FDA Figure 12**. The parameter estimates for FDA's final model are listed in **FDA Table 28**.

FDA Figure 11: The base model of FDA reviewer's PPK analysis



Source: FDA Clinical Pharmacology Reviewer's analysis

FDA Figure 12: Goodness-of-fit plots for FDA reviewer's final PPK model



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Source: FDA Clinical Pharmacology Reviewer's analysis

FDA Table 29: Parameter estimates for FDA reviewer's final PPK model including health status and baseline ALT level as covariates

Parameter (unit)	Population Estimates			Variability	
	Mean	SE	RSE%	IIV% (SE%)	RSE% of ETA
CL/F (L/h)	116	6.31	5.4	39.8 (1.64)	4.12
V/F (L)	256	26.2	10.2	38.5 (4.55)	11.8
Q/F (L/h)	34.0	1.97	5.8	0 FIXED	
Vp/F (L)	265	17.1	6.5	52.4 (6.46)	12.3
Ktr (1/h)	1.69	0.194	11.5	86.4 (7.23)	8.4
Ka (1/h)	0.795	0.0813	10.2	0 FIXED	
ALT on CL	-0.174	0.0268	-15.4		
Patient vs HV on CL	1.59	0.087	5.5		

Source: FDA Clinical Pharmacology Reviewer's analysis

CRCL was not a statistically significant covariate on zanubrutinib CL/F. To assess the impact of renal function on zanubrutinib PK, the following 4 categories of renal impairment were generated based on patients' estimated CRCL (Normal: CRCL≥90 mL/min; Mild: CRCL=60-89 mL/min; Moderate: CRCL=30-59 mL/min; Severe: CRCL=15-29 mL/min). The final PPK model-estimated CL values for each subject were compared by different renal function categories including normal renal function and mild to severe RI (**FDA Figure 13**). Results from both Applicant's and FDA's final PPK models show consistent trend of comparable CL values across the 4 groups. The estimated CL values based on FDA's final PPK model were slightly higher compared to the Applicant's model for all renal function categories. The more notable change in median CL value for severe RI group was likely due to the small sample size (n=11) but the range was overlapping. The geometric mean of CL in normal, mild, moderate, and severe RI groups were 162, 184, 187, and 186, respectively, based on FDA's analysis.

FDA Figure 13: Comparison of zanubrutinib clearance in patients stratified by renal function (left: Applicant's final model; right: FDA's final model)

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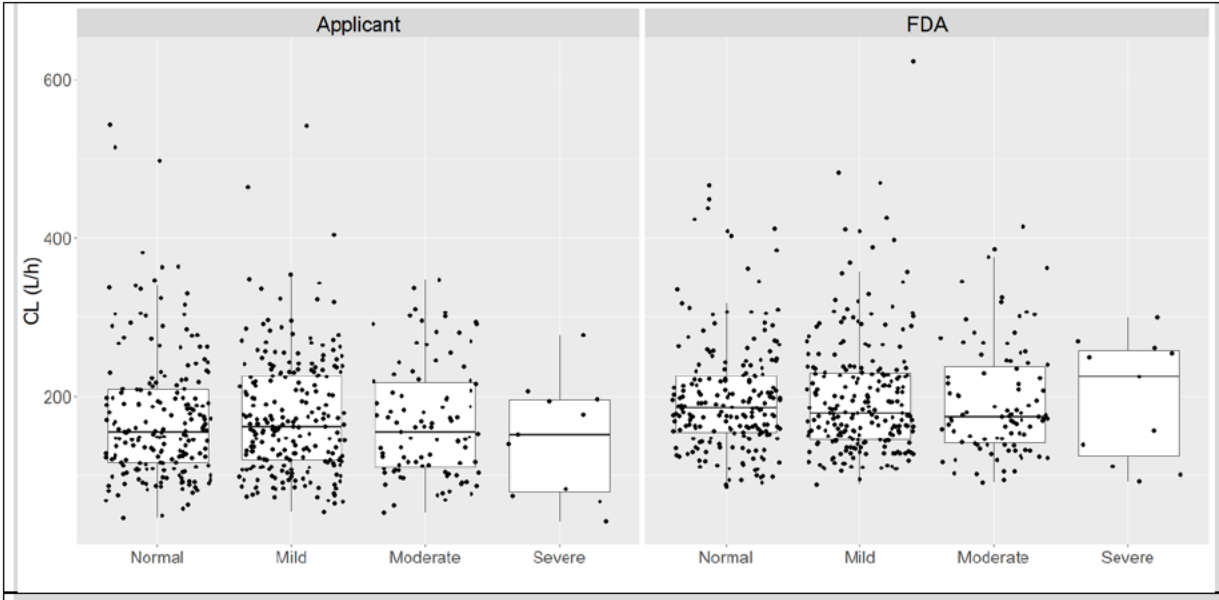
Reference ID: 4850271



Source: FDA Clinical Pharmacology Reviewer's analysis

19.4.1.4. FDA Reviewer's Exploratory Exposure-Response Analysis

Objectives: To conduct E-R analysis for zanubrutinib efficacy and safety using data from Study BGB-3111-302 and FDA's PPK output.

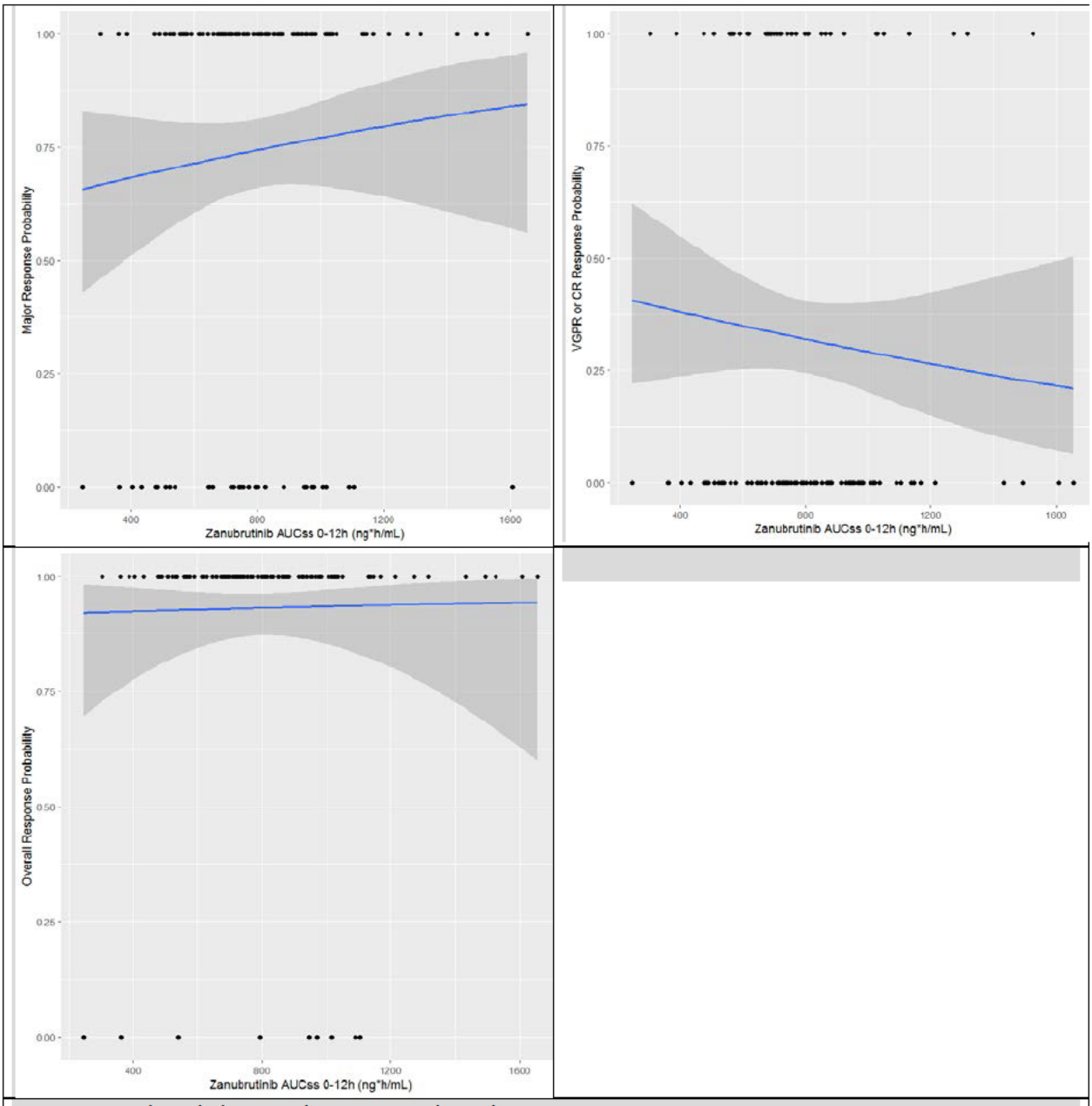
Method: R v3.5.0 was used to generate analysis plots for major efficacy data (adrs.xpt provided by the FDA Statistics reviewer) and safety data (adae.xpt submitted on March 24th, 2021) of Study BGB-3111-302. Zanubrutinib AUC 0-12 hr at steady state (160000/CL) for each patient was derived from FDA's final PPK model and used as the exposure metric for this analysis.

Results: The E-R analysis included 128 patients with WM from Study BGB-3111-302 who received zanubrutinib dose of 160 mg BID. The E-R relationships for VGPR/CR, MRR, and ORR by investigator are shown in **FDA Figure 14**, showing generally flat trend for all three efficacy endpoints. The relationship between exposure and treatment related ≥ Grade 3 neutropenia is shown in **FDA Figure 15**, suggesting a shallow but non-significant trend.

FDA Figure 14: The relationship between exposure and major efficacy endpoints in WM patients of Study BGB-3111-302 based on FDA reviewer's final PPK model

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

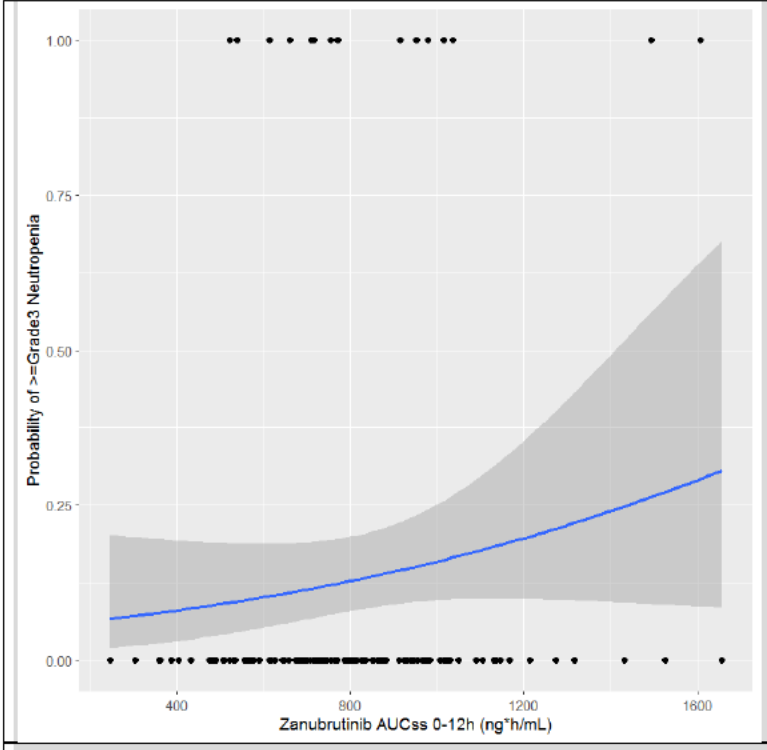
Reference ID: 4850271



Source: FDA Clinical Pharmacology Reviewer's analysis

FDA Figure 15: The relationship between exposure and ≥ Grade 3 neutropenia in WM patients of Study BGB-3111-302 based on FDA reviewer's final PPK model

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



Source: FDA Clinical Pharmacology Reviewer's analysis

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

Reference ID: 4850271

[NDA 213217 S-004 BRUKINSA (zanubrutinib)WM, Beigene USA, Inc.]		

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lauren Price, PharmD	OCP/DCPI	Sections: 6	Select one: ☑ Authored ☐ Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lauren Price -S, 0.9.2342.19200300.100.1.1=2001978474 Date: 2021.08.20 15:30:13 -04'00'			
Clinical Pharmacology Team Leader	Xiling Jiang, PhD	OCP/DCPI	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2021.08.20 15:39:03 -04'00'			
Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections: 6	Select one: ☑ Authored ☐ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hongshan Li -S, 0.9.2342.19200300.100.1.1=2001098258 Date: 2021.08.21 04:28:18 -04'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.08.20 16:13:08 -04'00'			
Genomics Reviewer	Oluseyi Adeniyi, PhD	OCP/DTPM	Sections: 6	Select one: ☑ Authored ☐ Approved
	Signature: Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001901490, cn=Oluseyi Adeniyi -S Date: 2021.08.21 12:25:36 -04'00'			
Genomics Team Leader	Rosane Charlab Orbach, PhD	OCP/DTPM	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2021.08.21 07:45:54 -04'00'			
Clinical Pharmacology Deputy Division Director	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6	Select one: ☐ Authored ☑ Approved
	Signature: Olanrewaju Okusanya -S Digitally signed by Olanrewaju Okusanya -S Date: 2021.08.23 09:35:03 -04'00'			

Clinical Reviewer	Rachel Ershler, MD	OOD/DHM2	Sections: 7, 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Rachel E. Ershler -S Digitally signed by Rachel E. Ershler -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000729909, cn=Rachel E. Ershler -S Date: 2021.08.21 08:38:00 -04'00'			
Statistical Reviewer	Qing Xu, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Qing Xu -S Digitally signed by Qing Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Qing Xu -S, 0.9.2342.19200300.100.1.1=1300431183 Date: 2021.08.20 14:16:34 -04'00'			
Statistical Team Leader/Deputy Director	Lisa Rodriguez, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001011155, cn=Lisa R. Rodriguez -S Date: 2021.08.21 06:36:19 -04'00'			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☐ Authored ☑ Approved
	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2021.08.21 14:41:24 -04'00'			
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ☑ Authored ☑ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.08.20 14:37:02 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHM2	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Bindu Kanapuru -S Digitally signed by Bindu Kanapuru -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bindu Kanapuru -S, 0.9.2342.19200300.100.1.1=0012593628 Date: 2021.08.26 14:20:48 -04'00'			
Division Director (Clinical)	Nicole Gormley, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature:			

OOD: Office of Oncologic Diseases			
OCP: Office of Clinical Pharmacology			
DPM: Division of Pharmacometrics			
DCPI: Division of Cancer Pharmacology I			
OB: Office of Biostatistics			
DBIX: Division of Biometrics IX			
DHM2: Division of Hematologic Malignancies 2			

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/s/

BERNETTA L LANE
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NICOLE J GORMLEY
08/31/2021 08:41:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s004

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 30, 2021

To: Bernetta Lane, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Elizabeth Everhart, Associate Director for Labeling, DHM2

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRUKINSA® (zanubrutinib) capsules, for oral use

NDA: 213217/S-004

In response to DHM2's consult request dated January 13, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for BRUKINSA® (zanubrutinib) capsules, for oral use (Brukinsa). This supplement (S-004) provides for a new indication for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling accessed from SharePoint on July 21, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on July 23, 2021.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Product Labeling

Section	Statement from draft	Comment
14 Clinical Studies, 14.2 Waldenström's Macroglobulinemia	In Cohort 2, **response** (b) (4) (b) (4)	Does "response" here consistent of "CR+VGPR+PR"? If so, please consider including this information to provide context for "response." Additionally, should PR rate be included? Please consider including any additional contextual information (e.g., exploratory) that is needed to make the results interpretable to healthcare providers as results from Cohort 2 will most likely be used in promotional materials for Brukinsa.

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

NISHA PATEL
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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:	July 23, 2021
To:	Bernetta L. Lane, DHS(c), MBA, RN Regulatory 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)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, 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-004
Applicant:	BeiGene USA, Inc.

1 INTRODUCTION

On December 18, 2020, BeiGene USA, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their New Drug Application (NDA) 213217/S-004 for BRUKINSA (zanubrutinib) capsules. With this supplement, the Applicant proposes an additional indication for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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 Hematology Products (DHP) on January 13, 2021, 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 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2021.
- Draft BRUKINSA (zanubrutinib) capsules Prescribing Information (PI) received on December 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2021.
- Approved BRUKINSA (zanubrutinib) capsules labeling dated November 14, 2019.

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.

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/s/

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NISHA PATEL
07/23/2021 09:07:16 AM

BARBARA A FULLER
07/23/2021 09:16:12 AM

LASHAWN M GRIFFITHS
07/23/2021 09:49:48 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	June 2, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 213217/S-004 and S-005
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. (BeiGene)
FDA Received Date:	December 18, 2020, December 23, 2020 and March 19, 2021
OSE RCM #:	2021-578
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

Reference ID: 4805129

1 REASON FOR REVIEW

BeiGene USA, Inc. (BeiGene) submitted supplemental NDA 213217/S-004 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 Waldenstrom macroglobulinemia and NDA 213217/S-005 for the treatment of adult patients with Marginal Zone Lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. We reviewed the proposed Brukinsa PI 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.

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

Reference ID: 4805129

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

BeiGene USA, Inc. (BeiGene) proposed changes to the PI, to support the addition for a new indications for Brukinsa for the treatment of adult patients with Waldenstrom macroglobulinemia and Marginal Zone Lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. We performed a risk assessment of the proposed PI and Patient Information to determine if they are acceptable from a medication error perspective. We find the Patient Information acceptable from a medication error perspective. We identified an area of concern in the PI that should be revised to improve the clarity of the information presented. Specifically, we note that the PI lacks clarity on the recommended dosage and recommended dose modification for adverse reaction, which may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 to address this deficiency.

4 CONCLUSION & RECOMMENDATIONS

We find the Patient Information acceptable from a medication error perspective. We identified areas in the proposed PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Dosage and Administration Section

a. Recommended Dosage

i. We recommend revising the statement, (b) (4) (b) (4) (b) (4) " to "The recommended dose of BRUKINSA is 320 mg taken orally once daily or 160 mg taken orally twice daily until disease progression or unacceptable toxicity."

b. Dosage Modifications for Adverse Reactions

i. In Table 2 Recommended Dose Modification for Adverse Reaction, we recommend retaining the statement, “Starting Dose: 160 mg twice daily or 320 mg once daily” for clarity.

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brukinsa received on March 19, 2021 from BeiGene USA, Inc. (BeiGene).

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* • *For the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.*
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 (b) (4) 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 May 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Brukinsa. Our search identified two previous reviews[a,b], 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.

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,[c] along with postmarket medication error data, we reviewed the following Brukinsa labels and labeling submitted by BeiGene USA, Inc. (BeiGene).

- Prescribing Information (Image not shown) received on December 23, 2020 and March 19, 2021, available from
  \\CDSESUB1\evsprod\nda213217\0056\m1\us\brukinsa-uspi-wm-draft-redlined-word.docx
  \\CDSESUB1\evsprod\nda213217\0063\m1\us\brukinsa-uspi-mzl-draft-redline.pdf
- Patient Information received on December 23, 2020 and March 19, 2021, available from
  \\CDSESUB1\evsprod\nda213217\0056\m1\us\brukinsa-ppi-wm-redline-word.docx
  \\CDSESUB1\evsprod\nda213217\0063\m1\us\brukinsa-ppi-mzl-redlined.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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